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A Review of the Development of Companion Diagnostic Assays and their Relationship to Public Health

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A Review of the Development of Companion Diagnostic Assays and their Relationship to Public Health

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The University of North Carolina at Charlotte
2013

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2017

Abstract

Bringing a companion diagnostic (CDx) to market is a complex process involving several stakeholders including the pharmaceutical industry, regulatory bodies, health financing entities (payers) and healthcare providers. In order to capitalize on synergies between public health policy makers and CDx developers, both groups should better understand the motivations of the other. Policy makers interested in maximizing the public health impact of CDxs through increased development, adoption and use should take into account financial and investment decisions affecting CDx development.

This SSP presents a synthesis of existing literature to educate/inform public health policy makers about the motivations of developers responsible for CDx generation. This information can assist public health decision makers responsible for guidelines and public finance to make such decisions with an appreciation of the dynamic environment in which developers of companion diagnostics operate in the private sector.

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CHAPTER ONE: INTRODUCTION

1.1 CONTEXT

The increasing efficacy and safety standards expected by patients, physicians and payers (PPP) have served as a catalyst for the era of precision medicine and one of its most important tools, companion diagnostic assays (CDxs). As the understanding of the genomic impact on treatment and disease detection has progressed the one-size fits all model of therapeutic treatment has decreased.

Increasing demand for precision medicine has prompted the pharmaceutical industry to produce more efficacious and safe treatments in order to remain competitive in the marketplace. It is estimated that "42% of all drugs in the pipeline have a companion diagnostic" and that a 69% increase will be seen within the next 5 years[1]. The percentage of national health expenditures allocated to prescription drugs increased by 3.3% between 2000 and 2013[2], and in 2015 were 10% of national health expenditures. This review will document the strategic synergies between the pharmaceutical industry and public health through the lens of CDx development.

Companion diagnostics are in vitro diagnostic devices that increase the safety and efficacy of a corresponding therapeutic or drug. The Food and Drug Administration (FDA) defines

three ways in which CDxs are essential: "1) to identify patients who are most likely to benefit from a particular therapeutic product; (2) to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with a particular therapeutic product; and (3) to monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness"[3]. A CDx can be used both to predict outcomes (efficacy and safety) and to monitor the response.

CDxs are genetic sequencing assays that are programmed to detect the presence or absence of relevant biomarkers. They differ from other genetic tests in that they are paired with a particular therapeutic, usually during the pharmaceutical research and development stage. The understanding, importance and utilization of genomics for improving treatment outcomes has seen steady growth in the last two decades. The first CDx was developed by Genentech in partnership with Roche's breast cancer therapeutic Herceptin. Since that time, CDx presence in oncology has outpaced CDx application in other specialty areas; however, the applications are now expanding beyond oncology to other relevant specialty areas[3].

A key factor influencing the implementation and development of CDxs is the regulatory climate in the U.S., with particular attention on the role of the FDA. Despite complex regulatory policy, the market for CDxs is expected to experience a compound annual growth rate (CAGR) of 18.1%; by 2019 the market value of CDxs is projected to be between $5.6B and $5.8B[4,5].

1.2 PURPOSE / PROBLEM STATEMENT

Companion diagnostics for selected pharmaceuticals are a relatively new business strategy for pharmaceutical companies. As more CDxs are developed and marketed, there are potential benefits for the emerging field of predictive public health/medicine. Bringing a CDx to market is a lengthy process that requires navigating among several key stakeholders, including the pharmaceutical industry, regulatory bodies, health financing entities (payers) and healthcare providers. The public health effects are often not obvious but if public health policy makers are to be advocates for CDx innovation and diffusion, it is important to articulate the synergies between the business case for CDxs and public health. . The review presented in this SSP aims to illuminate the dynamic environment of CDxs and is intended to educate/inform public health decision makers so that there is a climate of evidence based policy making with respect to financing and investment decisions.

CHAPTER TWO: METHODS

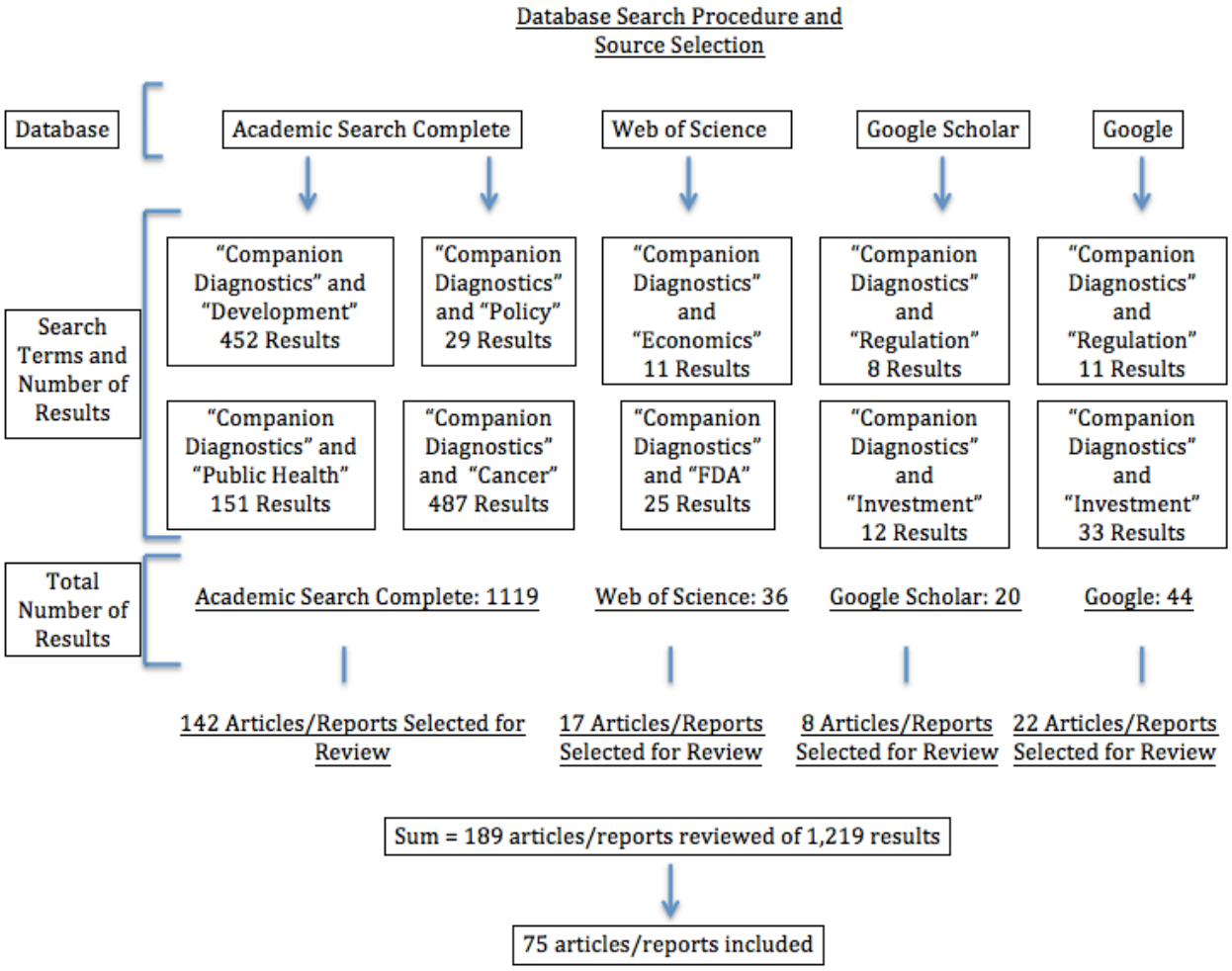
2.1 SEARCH PROCEDURE

This paper conducted a systemic review of the literature using four databases: Academic Search Complete, Web of Science, Google Scholar and Google. In order to provide a comprehensive literature review and reduce bias, four databases were used to broaden search coverage and identify as much relevant literature as possible (Figure 1). In Academic Search Complete and Web of Science the advanced function “find all my search terms” was turned on in order to refine the results. All search criteria were restricted to publications written in English and made available between 2003 and 2017. The year 2003

was chosen as the earliest search date because that is when the Human Genome Project made their data publicly available, data which has been the catalyst for CDx development[6].

Google and Google Scholar were used to search for both primary and grey literature. The inclusion of grey literature was necessary due to the financial disclosure protections that allow the pharmaceutical industry to restrict financial data from the public. Google was searched using advanced search features for must “include all words” and only “terms appearing in title page”. These filters were applied in order to increase the relevance of the Google results considered for review. All source material selected for review was uploaded in Zotero citation software.

Figure 1)



2.2 INCLUSION / EXCLUSION CRITERIA

Search results that came from using the search terms "cancer" and "public health" were refined and considered for inclusion only if they utilized a cohort, case control, or randomized control trial design. In addition, results yielded using these search terms were only considered for inclusion if they were primary literature. These steps were taken in an effort to ensure the validity of health data presented in this review.

Search results using the terms "policy", "economics", "development", "regulation" and "investment" were considered for inclusion if they were from a peer-reviewed journal, government report, life science consulting firm white paper, or pharmaceutical industry white paper. White papers were only considered for inclusion if they used the problem/solution methodology. This methodology is designed to educate and must include an abstract, problem statement, problem solution and a conclusion section. In total 1,219 results were returned using the search criteria, of results returned 189 were considered for further review. Of results considered for review, 75 met the inclusion criteria and were included in this review (Figure 1).

CHAPTER THREE: RESULTS

3.1 ASSESSMENT OF KEY STAKEHOLDERS

To understand the steps in bringing a CDx to market, an analysis of key stakeholders is critical. The first stakeholder is the pharmaceutical developer. The developer invests in discovery and development of a CDX with the goal of enhancing the performance and profitability of a therapeutic. The term therapeutic is used throughout this review because most academic papers use the term rather than drug because of the somewhat negative connotation of the latter term. The pharmaceutical developer's primary concerns are cost control, clinical utility, achieving regulatory approval, clinical trial design, labeling and usability of CDx affecting uptake.

If pharmaceutical developers partner with an outside medical device developer, then the medical device developer shares in discovery and development responsibility. Medical device developers typically share responsibility in ensuring labeling, clinical trial design, CDx regulatory approval, test efficacy and cost of the CDx. Nevertheless, the pharmaceutical company is highly invested in the successful co-development of the therapeutic and CDx. The pharmaceutical developer must collaborate heavily with the device developer to ensure the device is properly detecting the biomarkers they are intended to detect. In some cases, the pharmaceutical company has the capacity to develop the CDx in-house and has no use for an outside medical device developer.

Regulatory authorities, like the FDA or EMA, review and approve a therapeutic and CDx combination. If the regulatory agents deny an application then payers will not provide reimbursement. Regulators are largely concerned with laboratory and clinical trial data to determine market approval status and labeling requirements. Whether it is the FDA or EMA, their decision to approve or reject ultimately returns to the question of whether the public health benefits outweigh the risks. The FDA's profound interest in public health, and unique position at the intersection of public health and business will be expanded upon later in this review.

An important bridge between the developers and patients is the payer, e.g. Medicare, Medicaid or private health insurers. Payers are most concerned with the clinical utility and value of the therapeutic CDx pair. Payers measure "value" by measuring the potential decrease in total costs incurred as a result of increased therapeutic performance in

patients. Payers hope that by paying for a CDx they will save on costs by increasing treatment efficacy and therefore reducing adverse drug reactions, treatment time and cost of failed therapies.

Once the payer determines reimbursement protocols a physician can then implement the CDx. Physicians are primarily interested in clinical utility, ease of test implementation and readability of results. Developer, payer, physician and regulatory authorities may all have their interests satisfied, but public health and economic gains will not accrue unless there is sufficient patient uptake. Patients, who are the ultimate consumers, care about two things above all else: efficacy of the CDx-therapeutic pair and what they must pay toward their treatment[7].

Physicians and patients are concerned with the effectiveness of a particular CDx on n=1, or individual patient basis; however, changes in treatment outcome at the individual level can produce trends at the population level. Once a CDx and treatment have an impact at the population level, CDxs become relevant to the mission of many public health entities. Public health organizations concerned with population level cancer morbidity and mortality rates include The American Cancer Society, the Surveillance, Epidemiology, and End Results Program (SEER), and The National Program of Cancer Registries (NPCR), which is part of the Centers for Disease Control and Prevention[8]. Upon conclusion of this review, the public health effect of CDxs on cancer treatment, adverse reaction rates and diseases of the CNS will become evident.

3.2 BIOMARKER STATUS / FDA MEDICAL DEVICE:

CDxs operate in two ways: by determining biomarker-positive or biomarker-negative status. A biomarker-positive response indicates that a patient is positive for a genetic marker, which increases the likelihood of an effective response to a particular therapeutic. A biomarker-negative response indicates that a patient is unlikely to respond to a particular therapeutic[9]. Both types of biomarker response can also measure risk of any adverse drug reactions based on the presence or absence of predictive biomarkers.

Although an evaluation of biomarker-negative patients is preferred and often required, many regulatory bodies, including the FDA, have recognized that by reducing trial size to include only patients expected to benefit from treatment the potentially toxic effects of therapeutics in specific focal populations can be reduced. In clinical trials involving cancer therapeutics an evaluation of biomarker-negative patients is not always required. In fact, it may be unethical for a clinical trial to proceed with the inclusion of biomarker negative patients if existing data suggests they are likely to have negative health outcomes as a result of the trial[10].

Companion Diagnostics come in two primary types: laboratory developed testing (LDT) and test kit and reagents based assays. LTDs are the dominant form of CDx, accounting for approximately 3 of every 4 CDxs. LDTs are colloquially termed “home brews” in the CDx industry; they are popular amongst developers because they do not require FDA regulatory approval. LDTs are considered a service, as opposed to a platform or content based test (see Figure 11), because they are performed in house, i.e, they can be performed in the

clinicians office. LDTs thus adhere to the less stringent 1988 Clinical Laboratory Improvement Amendments (CLIA), not those of the FDA[11]. The FDA categorizes medical devices as class I, II or III. Class I and II are devices that have low to moderate risk, examples include dental floss or blood pressure cuffs, respectively. Companion diagnostics fall into class II or III due to their moderate to high risk potential and are therefore subject to the more stringent medical device regulation[12].

3.3 REGULATORY AVENUES TO MARKET

Companion diagnostic developers have several avenues to gain market approval. The CDx route to market approval has thus far been widely up to the discretion of the developer, with most developers opting for the less regulated, less costly LDT CLIA route to market. With the evolution of CDx role in patient treatment, the FDA is formulating a regulatory guideline for future implementation that gives it authority over most LDTs[13]. The formulary tiers LDTs into three categories with varying levels of FDA oversight (see Figure 2)[11].

Figure 2)[11]

Risk-based regulatory levels LTDs (2017)

Regulatory Level: 1	**LDTs subject to full enforcement discretion**	• LDTs used solely for forensic (law enforcement) purposes; and • LDTs for transplantation when used in a CLIA-certified, high-complexity histocompatibility laboratory.
Regulatory Level:2	**LDTs subject to partial enforcement discretion**	• The second group encompasses a broader array of LDTs: • Low-risk LDTs (Class I devices). • LDTs for rare diseases and "Traditional LDTs." These types of LDTs reflect the types of LDTs that existed when the enforcement discretion policy was initially implemented. • "LDTs for Unmet Needs," when no FDA-approved or cleared equivalent device is available
Regulatory Level:3	**LDTs subject to full enforcement discretion**	• The third group of LDTs spans high- and moderate-risk tests that FDA intends to fully regulate. The draft guidance defines the highest-risk devices as including: • LDTs with the same intended use as a cleared or approved companion diagnostic • LDTs with the same intended use as an FDA-approved Class III device • Certain LDTs for determining safety and effectiveness of blood or blood products • All LDTs in this third group will be subject to full regulation, including premarket notification or approval and compliance with the quality system regulation.

Despite the direct CLIA to market option, 98% of oncology CDxs are regulated by both the CLIA and FDA. Oncology accounts for 87% of the total CDx market[14]. The chief reason developers choose to pursue FDA approval is because physician uptake, a core component to market success, is much higher with FDA approval/clearance than CLIA approval alone[4,11].

There are three routes through which CDxs can receive FDA approval: the 510k, the PMA, or the de novo processes The most common approach CDx developers take to entering the market is through the 510k processes. *"A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims."*[15]

The 510k method was used in the case of Roche's BRAF CDx and is often a preferred method because it reduces dependency on the assay platform[4]. The assay platform is the combination of tools (e.g. reagents, instruments, antibodies) necessary to perform the test. In essence, the assay platform allows more flexibility and can be performed in a larger number of medical environments. It reduces costs and need to assess.

The 510k method is accompanied by laboratory testing data, but rarely human subject clinical testing data. As a result of clinical data exclusion a CDx that gains clearance through the 510k method is generally a class II medical device[16]. It is important to note that the FDA "clears" 510k devices; it does not "approve" them. As a result of this distinction 510k cleared devices cannot be advertised as "FDA-approved" like a device that receives PMA[16]. The FDA has 30-90 days to accept, question or reject a device submitted for 510k clearance. At the time of clearance a substantially equivalent (SE) status will be given and a developer can then legally market their product[15].

"If the new diagnostic technology cannot be considered substantially equivalent to an existing technology, and will be used to make a critical medical decision concerning the diagnosis, treatment, or medical management, then the premarket approval (PMA) is the regulatory path of choice"[16].

Often novel cancer CDxs, like the one accompanying Merck's NSCLC therapeutic Keytruda, which will be discussed later, must receive PMA. Pre-market approval demands more rigorous standards and generally requires both laboratory and clinical trial test data be submitted in an application. The FDA must decide to approve, question or reject a PMA submission within 180 days of submission[16].

A third option is submitting a de novo request. This option exists if there is no predicate(i.e. a similar previously approved medical device) and if the device is either class I or II[17]. A de-novo request can be initiated within 30 days of a failed 510k approval. The de novo request allows a CDx to be marketed as a predicate for future 510k submissions. A de novo approval is a way for developers to move forward with bringing a CDx to market, usually while gathering further data to gain a 510k approval[17,18].

3.4 FDA RECCOMENDATION FOR PARALLEL DEVELOPMENT

"Ideally, a new diagnostic intended to inform the use of a new drug will be studied in parallel with early drug development (phase 1 or 2 trials) and diagnostic development will then have led to pre-speciation of all key analytical and clinical validation aspects for the subsequent (late phase 2 and phase 3) clinical studies. These include the intended

population and selection of diagnostic cut-off points for the biomarker intended to delineate test positives, test negatives, and, when appropriate, equivocal zones of decision making. "[19]

This recommendation is needed because if the therapeutic and CDx are co-developed, the CDx can then be included on the therapeutics clinical trial protocol. If the CDx is included in the protocol, the FDA allows the clinical utility measures of the CDx established during the therapeutics clinical trial to be submitted as evidence of efficacy. In effect, co-development prevents the CDx developer from having to invest in gathering additional evidence, such as animal trials or more extensive laboratory work, which is time consuming and costly, in order to receive 510k or PMA approval. If the CDx is developed separately from the therapeutic, or not written into the trial design correctly any data about the efficacy of the CDx will be considered "exploratory", i.e. supplemental to validated evidence [19].

In co-developed trials, the FDA recommends that the trial consist of patients treated for disease with known biomarkers that the CDx tests for and those known not to have these same biomarkers. "If all patients had a reasonable, albeit different, response to treatment," then review of the diagnostic "can be subsumed in the general review of the therapeutic and may not require independent credentialing of the assay as a diagnostic test for expected clinical use of the drug"[20].

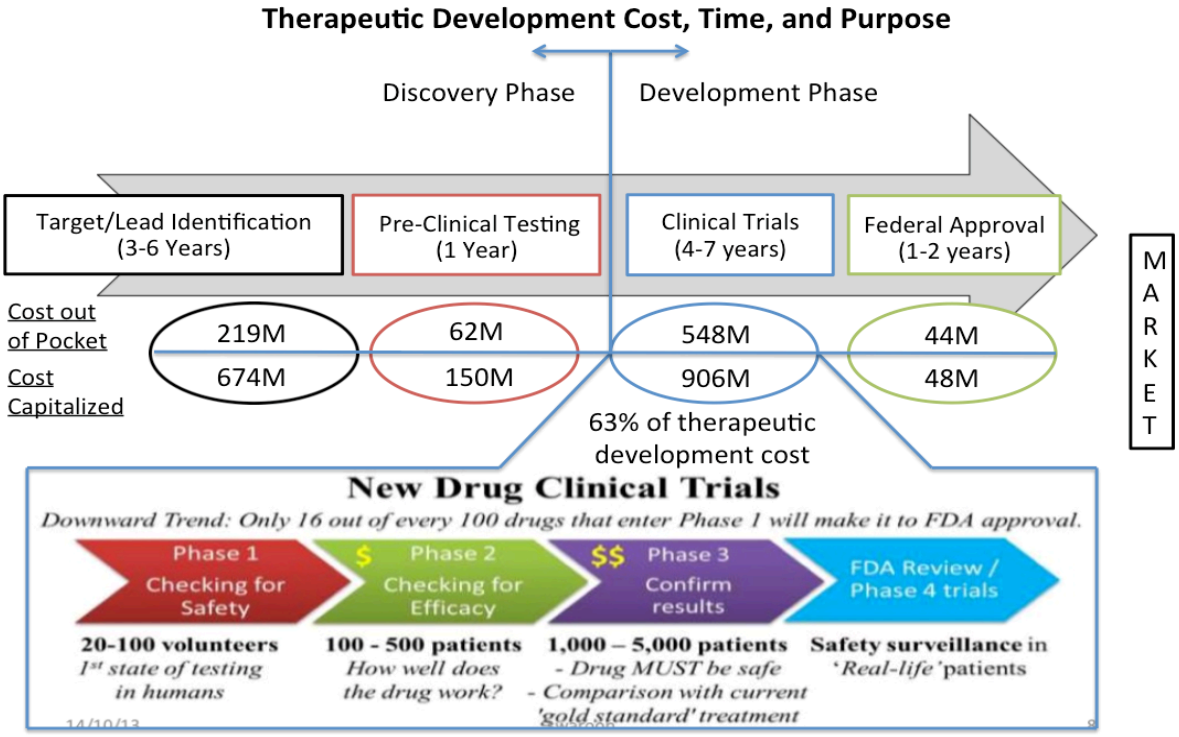
Should the diagnostic "prove to be so integral [to] the use of the new drug that testing will be considered a prerequisite to use. " then the FDA may require the CDx be used in order to administer the therapeutic[20,21]. If multi-site testing is expected, FDA will require premarket review of the diagnostic and the drug may be labeled as requiring prior use of the

diagnostic before initiating the therapy. Additionally, the FDA may require "simultaneous approval" of the therapeutic and CDx[20].

3.5 PHARMACEUTICAL DEVELOPMENT PROCESS

All information discussed in this section is depicted in Figure 3[22–24]. A pharmaceutical trial begins with the development stage, which starts with the determination that a target molecule has an effect on an in vitro laboratory assay. Upon this discovery, a developer can then move to the second stage 'hit to lead', which is where a small molecule hits from a high throughput screen and can undergo an optimization for cell treatment. The third stage of development is lead optimization; here the small molecule is optimized for treatment in pre-clinical trials. The final stage of discovery is pre-clinical testing, where key determinants for validity in clinical testing are measured. A primary component of this is testing in animal subjects. The discovery phase usually takes between 4-6 years and costs drug developers approximately $281 million,[24]. The biggest share of cost and time investment is in the development phase, i.e. clinical trials. Out of pocket, nearly $700M is invested in the clinical trial phase and the time to market can be expected to be between 5 and 9 years[23].

Figure 3)[22–24]



3.6 CO-APPROVAL PROCESS

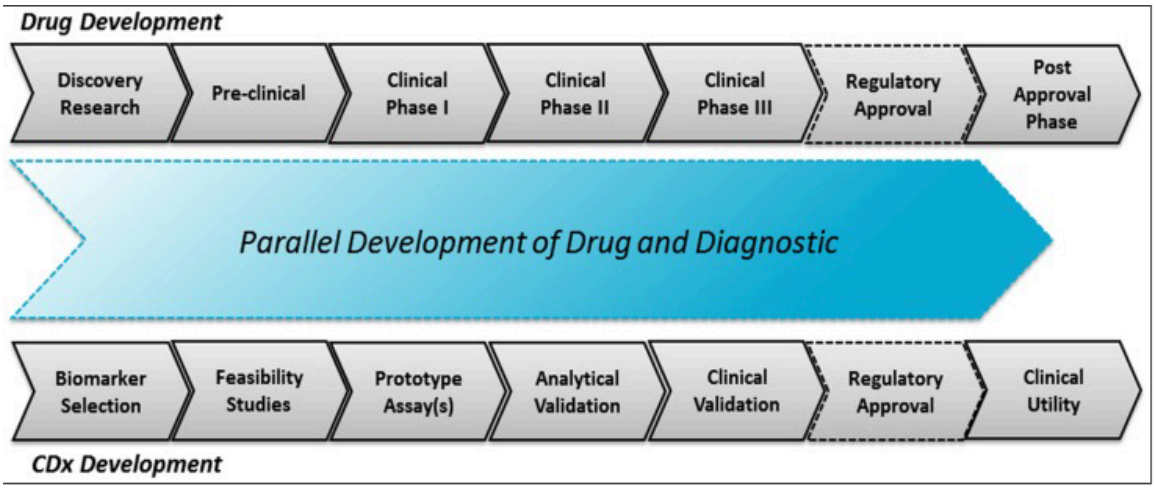
A co-development model first proposed by the US Food and Drug Administration in 2014 involves setting up an integrated team from an early stage of drug and diagnostic research. The first step of the FDA recommended co-development process is target and compound selection of the therapeutic and simultaneous identification and stratification of biomarkers for the CDx[10]. Co-development requires that both the medical device and therapeutic meet the same standards as if they were being submitted separately. The typical process from discovery to end of development is shown in Figure 3[9].

Co-development offers therapeutic developers several attractive benefits. The first is that therapeutic submission approval rates are increased; in the case of NSCLC, the FDA

approval success rate increases from 31-62%[9]. Second, co-approval simplifies labeling requirements by introducing both CDx and therapeutic to market simultaneously. When a therapeutic and CDx enter the market separately the manufacturer must adjust labeling on the product first to market, submit a new labeling request for FDA approval and change physician educational material. A third motivation for co-development is that the CDx generates efficacy data during the development phase, which will be discussed in the business and public health analyses sections.

Figure 4)[9]

Therapeutic and CDx development process



Co-development also increases the amount of testing time that a CDx developer has to make improvements to the diagnostic before submission for review. Once a CDx is developed it can then be used to select patients for clinical trials, which can reduce clinical trial costs by up to 60%[9,9,12,13,25].

The FDA issued a 2015 draft recommending "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product", which offers many FDA recommendations for a fluid co-submission[13]. In addition, the FDA notes that consistency in labeling between co-developed therapeutic and CDx is essential to receiving market approval[13].

3.7 LABELING

Labeling is an important component of marketing. If a developer fails to receive labeling approval for a specific biomarker then a therapeutic or CDx cannot be marketed as capable of detecting that biomarker[4]. In terms of both public health benefit and developer ROI, failure to obtain FDA labeling approval reduces the synergistic value generated by CDx and therapeutic.

3.8 INTERNATIONAL REGUALTION

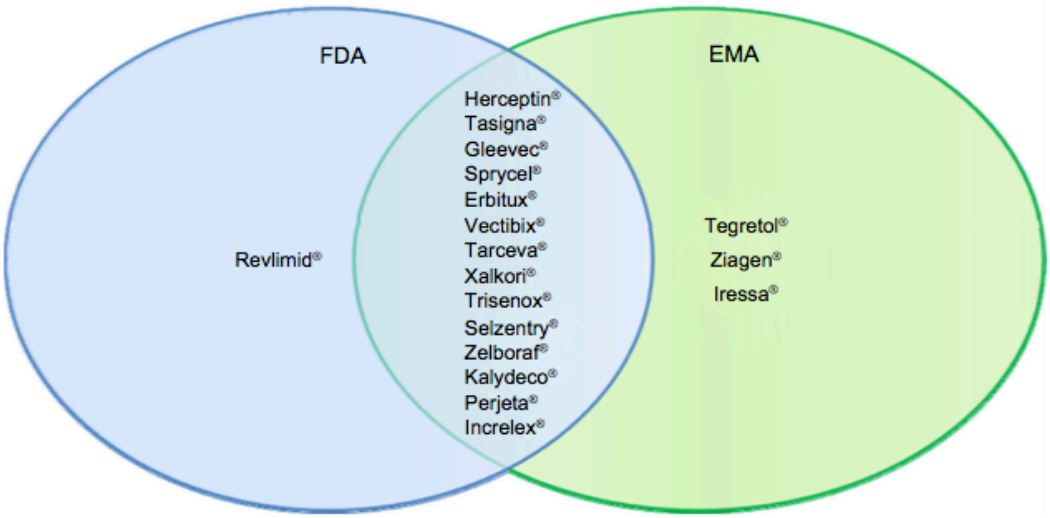
There are significant differences in the regulatory processes of the European Medicines Agency (EMA) and FDA. For instance, "any CDx assay entering the EU market is classified as low risk device based on a conformity assessment and CE-marking by the manufacturer, the so-called self-certification procedure"[3]. The result is that CDx market approval is much easier to obtain in the EU. However, within the next few years fully promulgated CDx legislation in the EU seems an inevitable reality. Newly introduced legislation proposes that CDxs should fall under the IVD Directive, which would impose comparable EMA regulatory standards on CDxs as those of the FDA[3].

In instances where a company plans to export their device to foreign markets after FDA approval, the FDA will provide a 'Certificate for Foreign Government' assuring that the safety and efficacy standards of the FDA have been met and verified[26].

Despite disparity between FDA and EMA approval process of therapeutic and CDx, market approval standards there is little difference in therapeutics actually making it to market (see Figure 5). Additionally, the labeling between EMA and FDA has been assessed to be the same in 78% of cases[27].

Figure 5)[27]

Total Therapeutics With a Required Pharmacogenetic CDx in 2015 by Regulatory Agency



3.9 REIMBURSMENT

While regulatory differences make a negligible difference in CDx adoption, reimbursement policies have major impacts. The impact of reimbursement on CDx adoption becomes clear

when comparing nations with divergent policies. There are significant differences between the U.S. and EU; however, there is also variation within the E.U. For instance, the UK has a comparatively restrictive reimbursement policy when compared to France or Germany[4].

Let us first examine France Germany, Spain and Italy, which have similar reimbursement systems for diagnostics. In these nations, "pharmaceutical drugs and the associated companion diagnostics are evaluated separately"[28]. The result of separate reimbursement evaluation for therapeutic and CDx is reduced CDx uptake rates across nations.

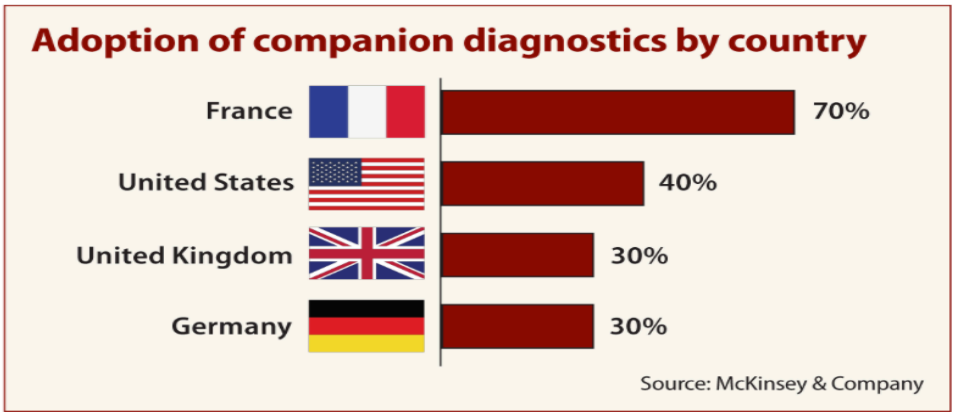
In fee-schedule systems like Germany, France and Italy, the procedure codes and associated tariffs are used to reimburse testing services on a per patient basis. In fee-schedule systems, stakeholders agree upon a fee paid per service provided. A patient that is prescribed and uses a CDx would be charged a fixed price based on the service codes for that test. In this system, the practice of "code stacking" often occurs, which involves adding generic codes to one another in an attempt to code for a generic CDx. Code stacking may be good from a public health perspective in that code stacking allows nations to code for a CDx as soon as it is approved for market. The downside is that generic code stacking is achieved by combining pieces of old medical device codes which may fail to incorporate essential, and expensive cutting edge medical advances in the CDx reimbursement price[28].

In terms of CDx regulatory approval rate France is at the forefront of CDx adoption (see

Figure 6). “In France, the National Institute of Cancer (INCA) facilitates access to pharmaceutical drugs associated with companion diagnostics in oncology by providing molecular testing free of charge at the time of drug launch”[28]. No other government in the EU has this type of partnership with the pharmaceutical and medical technology developers. Interestingly, pharmaceutical partners sometimes offer to pay the cost of the CDx because CDx cost is usually negligible compared to the potential therapeutic profits[28].

The U.K. uses the NHS “to provide a comprehensive service available to all with access based on clinical need, not an individual’s ability to pay”[28]. In the U.K. CDxs are evaluated together. This method avoids delays and inconsistent decisions.

Figure 6)[29]



In the U.S. CDxs are reimbursed by Medicare Part B. Medicare Part B contractors grant reimbursement approval based on their assessment of medical necessity and cost[30]. Private payers approve CDxs for reimbursement on an individual basis. However, in the U.S. private and public payers determine approval status based on a number of variables

including proven biomarker status, clinical utility, and ultimately cost benefit analysis. There are only a small handful of biomarkers approved by CMS for reimbursement; they include K-RAS, BRAF, ALK and HER-2[30]. CMS approval of these biomarkers is highly significant to reimbursement across the nation not only because CMS is the largest payer in the U.S., but also because private payers traditionally defer to and replicate CMS reimbursement policies when they are uncertain about clinical utility.

In California and ten other western states, CMS CDx reimbursement rose from $37M to $108M, over 200%, from 2013 to 2015[31]. This increase takes into account approximately 21% of the U.S. market; however, it shows a clear trend of increasing payer acceptance to reimburse CDxs.

These same states also saw an 84% increase in the number of tests approved for metabolism biomarkers, and an inverse decline in the number of cancer biomarker reimbursements. Figure 7 depicts the 2013 to 2014 shift in CMS test reimbursement type. CYP2D6, CYP2C19 and G6PD are metabolic biomarkers, and the rest are traditional cancer biomarkers[31].

Figure 7)[31]

CMS reimbursement volumes and amounts in 2013 and 2014 for tests that use six companion diagnostic biomarkers

	Units Billed (n)		Total Allowed (,000)		Avg. Allowed Amount		$0 (n)		$0 (%)	
Biomarker	2013	2014	2013	2014	2013	2014	2013	2014	2013	2014
BRAF	6,315	6,887	$457	$977	$113	$180	2,277	1,471	36%	21%
KRAS	10,299	8,549	$1,193	$852	$225	$198	5,008	4,238	49%	50%
EGFR	11,951	11,155	$1,803	$2,779	$239	$332	4,388	2,788	37%	25%
CYP2D6	99,370	183,770	$19,114	$63,156	$344	$451	43,733	43,697	44%	24%
CYP2C19	97,483	180,590	$14,077	$40,254	$250	$292	41,064	42,630	42%	24%
G6PD	1,690	1,517	$16	$13	$12	$11	307	294	18%	19%
Total/Avg	**227,108**	**392,468**	**$36,662**	**$108,034**	**$232**	**$291**	**96,777**	**95,118**	**42%**	**29%**

It is important that a CDx developer not underestimate the difficulty in gaining reimbursement approval across a spectrum of payers. In fact, a CDx developer has a greater chance of gaining FDA approval than gaining Medicare reimbursement approval. Additionally, it takes 3-4x longer to receive CMS coverage than it does to receive FDA approval[32]. New medical technologies that fall under the DRG's bundled payment system have a clearer and shorter path to reimbursement than those that do not. Unfortunately, for CDx developers CDxs are usually not considered under the bundled payment system and must provide additional clinical evidence for nearly any increase in reimbursement rate[32]. "Medicare's bundled payment systems, i.e., diagnosis-related groups (DRGs) for inpatient care and ambulatory payment categories (APCs) for outpatient services, allow payment for incremental improvements without additional clinical evidence"[32].

The system in the U.S. has historically used cost-based reimbursement, as opposed to value based, for CDxs. For diagnostic developers, this type of reimbursement system has major implications, "with private payers keying their payments to the CMS schedule, plus or minus a percentage", i.e, using Current Procedural Terminology (CPT) service codes to determine reimbursement rates. "This system has the perverse effect of correlating reimbursement amounts with the complexity of a test rather than its value"[33]. Similar to the code stacking seen in fee-schedule systems, CPT coding often results in payers overpaying for old tests and underpaying for cutting edge CDxs. This is a clear example of the U.S. reimbursement system failure to keep pace with the evolution of medicine and diagnostics. Nonetheless, there are signs of adaptation. As of January 2017, CMS will begin reimbursing for diagnostics based on the average price paid by private payers [33].

Relying on private payers to determine reasonable reimbursement is unlikely to be the panacea for CDx reimbursement. Although, payer uptake is increasing as evidence for clinical utility mounts there is still resistance in the private sector to reimburse for CDxs. For example, the CDx for Warfarin reduces adverse events by 30%, annually preventing 12,900 adverse reactions in the U.S. Nevertheless, the CDx was found to have a "comprehensive lack of reimbursement"[34]. The lack of reimbursement comes even after FDA required labeling for a CDx, and an official FDA recommendation that a CDx be used with warfarin therapy[34]. When private payers were surveyed to identify the most important requirements for reimbursement they identified clinical utility as the single most significant factor[33,34].

Clinical utility is established by the CDC's Academy of Managed Care Pharmacy (AMCP)[35]. The AMCP uses a set of standards that includes analytical validity, clinical validity and clinical utility. Most private reimbursement agencies utilize the AMCP metrics to help them determine reimbursement status. Generally, private insurers replace the ethical section that is included in the full AMCP report with a section on economic value[35]. The revised section seems to touch on all the important variables, but it is a post hoc rubric for diagnostics of the 20th century. The problem is that clinical utility is very difficult to establish for a CDx developed after a therapeutic (e.g. Warfarin and its CDx). Unlike a co-developed pair where clinical utility data is collected during the clinical trial period, a separately developed CDx must prove clinical utility by gaining market acceptance, which is very challenging to gain without the clinical utility data needed to show evidence of effect.

3.10 COMPANION DIAGNOSTIC MARKET EVALUATION

Companion Diagnostics are defined as an in vitro diagnostic device that increases the safety and efficacy of a corresponding therapeutic. The FDA defines three areas where CDxs are essential "1) to identify patients who are most likely to benefit from a particular therapeutic product; (2) to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with a particular therapeutic product; and (3) to monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness. So according to the FDA, a CDx assay can be used both to predict outcome (efficacy and safety) and to monitor the response." [3]

Health impact and return on investment (ROI) are how public health practitioners and pharmaceutical producers, respectively, assess the impact of a given therapeutic. If there is no or a very limited population of patients in need of treatment then there is no margin for public health value gain. Similarly, if a market of consumers that can pay does not exist, there is no profit margin within that pool of consumers. The market is one locus where public health and private industry often have parallel interests. If a health problem affects a large population then there may be often synergistic public health and profit gains to be made. For example, a comparison of 1990 -1994 and 2005-2009 U.S. cancer mortality rates showed an average 43% decline in the risk of death. The comparison utilized data from the SEER program and attributed the decline to "cancer treatments, along with advances in cancer screening and diagnosis"[36]. During this period cancer expenditure in the U.S. increased from $27.5B to $124.6B[36,37]. Improvements, specifically in treatment and diagnostic advancement are estimated to have reduced cancer mortality by 16.5% between 2007 and 2010[38].

In many competitive business environments, competitor price setting influences the adoption of a particular product. However, CDxs currently occupy a unique niche in that they are not subject to direct market competition; rather CDx developers compete to establish a relationship with a therapeutic developer[4]. McKinsey research on the factors that drive growth concluded that 80 percent of growth was due to "where" companies decide to compete (i.e., capturing underlying growth in existing markets and moving to new markets via M&A) and only 20 percent was due to "how" they compete (i.e., share

gain)[4]. For this reason, it is important that developers understand the growing health specialty areas where CDxs may have the most relevant application.

If a pharmaceutical company decides to contract with an outside CDx developer the CDx developer is protected from competition by limited-time exclusivity agreements, decreasing the CDx developers financial risk[4]. Once both the therapeutic and CDx receive FDA approval they essentially compete on the market as a health package against competitors meaning that the effectiveness of the pair matters far more than the effectiveness of the therapeutic alone – a clear example of this can be seen in the case of Keytruda and Opdivo, discussed later in this review[39].

3.11 MARKET GROWTH

"The majority of the experts believe that although the number of new drugs with associated diagnostics will follow linear growth patterns, the use of advanced diagnostics for therapy selection will have exponential growth. On the drug side, despite several drugs with associated biomarkers being in the pipeline, if we apply the typical attrition factors in drug development we are likely to see a 2 to 3x increase in the number of drugs with CDx over the next five years"[4].

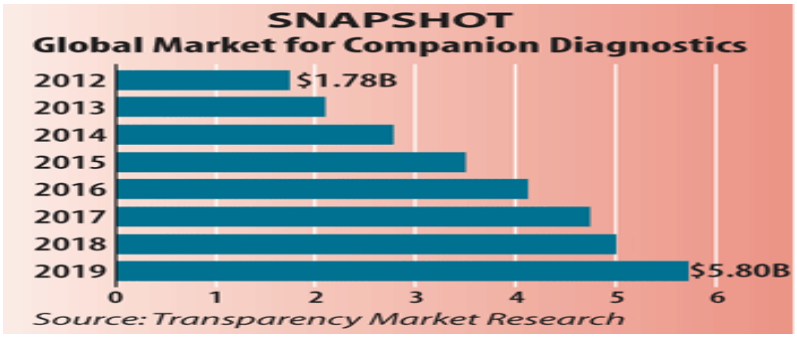
By 2018, the CDx market growth rate is projected to accelerate in key market segments including oncology, immunology and CNS. By 2018, nearly half of the pre-clinical phase 1 pipeline in these sectors is projected to have an associated companion CDx. Key drivers of this increase include increased identification of biomarkers, which makes CDxs more

accurate and therefore more valuable. According to McKinsey, "The identification of markers for safety, sensitivity and resistance for on-market drugs will drive growth to a larger extent in the near term"[4].

In 2013, the global CDx market had an estimated worth between $1.1B and $2.2B. The CDx market is projected to grow at 18.1% CAGR and by 2019 have a market value between $5.6B and $5.8B[5,40]. In Figure 8, the the CDx market value is illustrated on a year to year basis[41]. The value of the precision medicine market, including the therapeutic and CDx market, is projected to reach $149B by the year 2020 with total CAGR of 8.74%. The annual growth rate of the market is reflective of the growing percentage of therapeutics in the pipeline with a CDx.

Figure 8)[41]

Annual companion diagnostic market value prediction (2013)



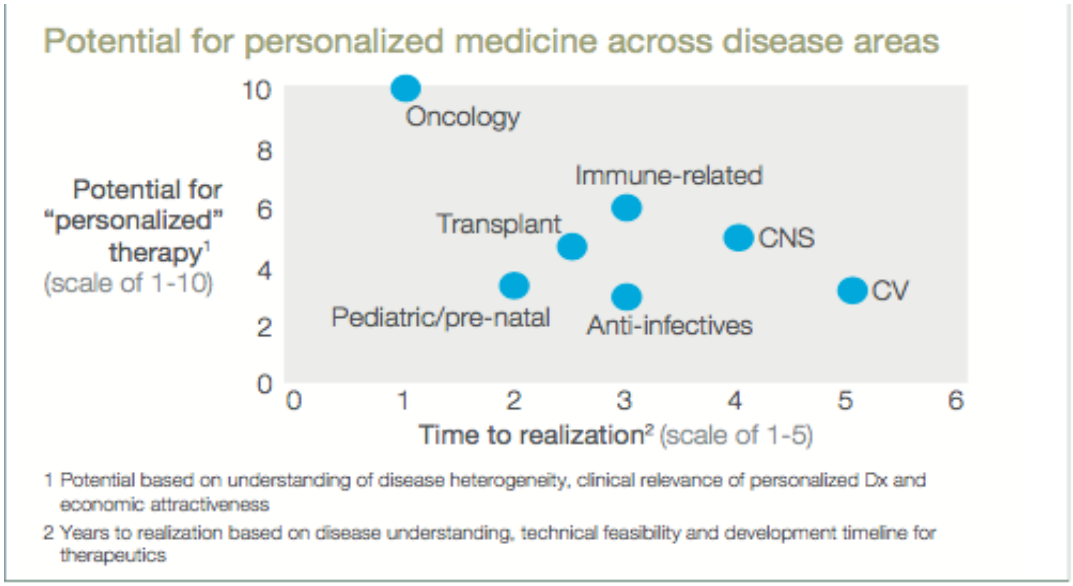
3.12 SPECIALTY GROWTH AREAS

Based on the current range of predictive biomarker science, particular medical specialty areas are projected to benefit most from companion CDxs. Figure 9 illustrates the anticipated profit potential and time needed to reach maximum potential. Currently, 87%

of companion CDxs on the market are paired with an oncology therapeutic, this is largely a result of the financial incentive payers have for reducing costly trial and error style cancer treatment[14]. By authorizing the reimbursement cost associated with companion CDxs payers save cost by increasing the odds the beneficiary receives the right treatment the first time, an outcome appealing to all stakeholders interests[4].

Companion diagnostics have applications in several disease areas (see Figure 9), however, most experts agree that "that within 10 years immunology/transplant, CNS, pediatrics, pre-natal, infectious diseases and cardiovascular will hold the greatest potential"[4]. Currently development of companion CDxs in the oncology sector account for 90% of all CDx development. A 2013 Mckinsey & Company study found that 50% of all newly detected cancers would benefit from the genetic sequencing data provided by companion CDxs[4]. More current research suggests that up to 73% of all cancer treatments in the pipeline have potential to benefit from CDxs[1].

Figure 9)[4]



Current estimates suggest that "42% of all drugs in the pipeline have a companion diagnostic" and that a 69% increase will be seen within the next 5 years[1]. This market trend exposes the competitive advantage that will be lost by drug developers that do not utilize CDxs. Although CDxs are primarily used by the oncology sector, other medical specialties including immunology, neurology, cardiovascular, psychiatry, and anti-invectives (e.g. antiretroviral treatment) will see increased CDx usage and benefit within the next 5 years[4,1,27,42]. The most promising specialty areas for future application are immunology, ant-infectives, transplant medicine, and diseases affecting the central nervous system (CNS) (see Figure 10).

Firms researching future companion diagnostic application by medical specialty area have varying predictions. Firms base their assessment on three primary factors; genomics application, need for precision medicine and potential for cost savings[4,14].

Figure 10)

	Companion Diagnostic Market Potential by Disease Area		
Specailty Area	Genomics Application	Need for precision medicine	Potential for Cost Savings
Oncology	High	High	High
CNS	High	High	Moderate
Immunology	Moderate	Moderate	High

Diseases of the CNS include psychiatric disorders including depression, demyelinating diseases such as multiple sclerosis and conditions such as Alzheimer's disease. These conditions are often associated with some degree of genetic predisposition. In the case of major depressive disorder, which affects 10% of Americans, approximately 50% is due to heritability[43]. Comparatively, 33% of cancer is due to heritability[44]. Of course, a barrier to CDx development is the amount and understanding of genomic data needed to create an effective CDx. Genetic pre-cursers to major depressive disorders are not as well understood as those in oncology and therefore the cost gradient to creating a CDx for depression is higher.

In terms of market profit psychiatric therapeutics make up 8% of the pharmaceutical market share while oncology therapeutics comprise 15.1%, therapeutics used for psychiatric treatment garner $27B annually[45]. However, the need for more effective psychiatric therapeutics is high. The current failure rate of SSRI type antidepressants is 38%[14]. This analysis does not discuss other diseases of the CNS, however, the potential for precision medicine in the treatment of major depressive disorder is high.

Before assessing why CDxs have seen their greatest impact in the oncology sector a brief analysis of other immunological diseases with CDx application is worth discussion. Other applications include anti-infective diseases (e.g. HIV), allergies, multiple sclerosis, and transplant treatments.

Interestingly, CDx applications in anti-infective and CNS diseases have not only intra-specialty application but also inter-specialty application. A prominent example of this is the mutating effect of HIV treatment regimens on CYP2D6 and CYP2C19 gene expression, a gene which is essential for the normal metabolism of SSRI antidepressants[46]. The incidence of depression in the HIV positive community is estimated as high as 47%, a high level of comorbidity that would likely justify the cost of CDx in this population[47,48]. CDxs paired with anti-depressant drugs, specifically individuals taking tricyclic class antidepressants or venlafaxine, typical antipsychotics, risperidone, sertraline, escitalopram or citalopram could benefit from determining if they are 'rapid' or 'slow' metabolizers. In effect, pharmacokinetic (how therapeutic absorption is influenced by body chemistry) and pharmacogenomics (how genetic factors influence therapeutic absorption) analysis provides the physician with information that may help him/her decide to adjust dosage or pursue a different course of therapy[46].

A second emerging application from immunological CDx testing is screening to predict hypersensitive drug reactions. A recent example of this can be seen in the case of abacavir, where a CDx detecting human leukocyte antigen realized a >50% decrease in hyper

sensitive reactions[49]. The market for CDxs predicting adverse treatment effects could prove large and valuable for pharmaceutical developers.

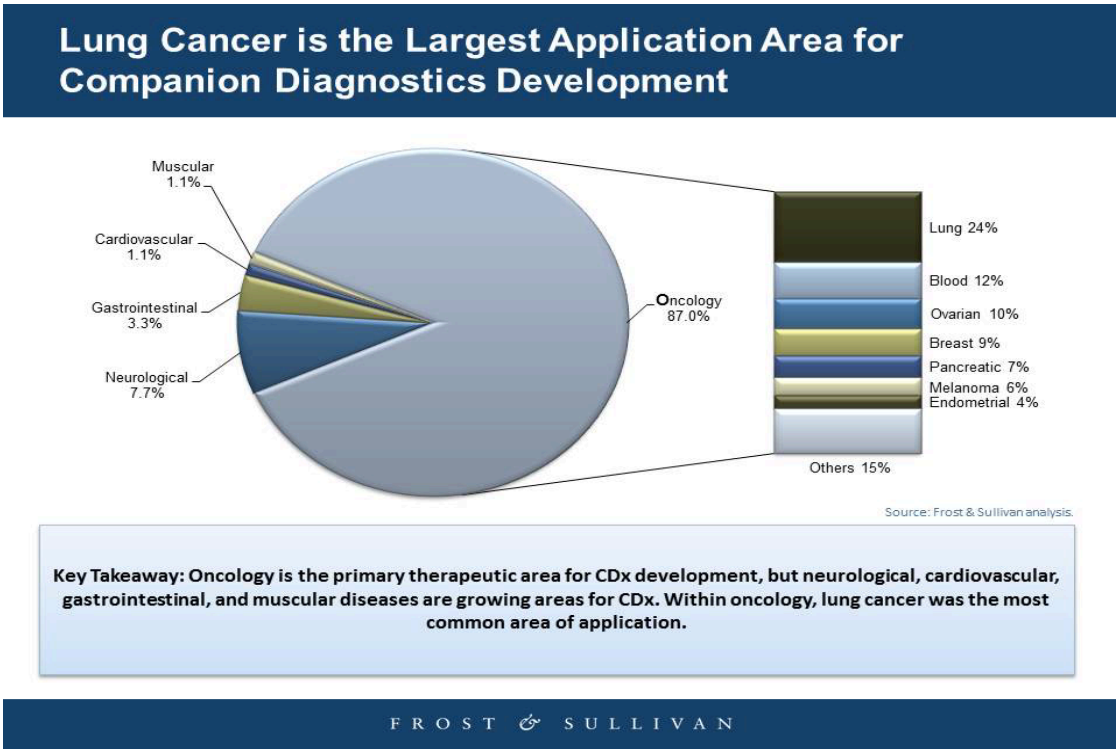
3.13 ONCOLOGY MARKET

Cancer treatment accounts for 87% of CDx applications today and for good reason[14]. Cancer treatments have a large number of genetic determinants, creating high genetic relevance. The need for cost savings is great due to the expense of cancer therapies and low 25% treatment success rate. Payers are less resistant to reimbursement for cancer therapy CDxs, which might ultimately save them money on failed treatment regimens. Finally, the need for targeted therapy is high. Patients undergoing cancer treatment are often in a race with time to find the right treatment option before their cancer metastasizes, or further metastasizes. They want the best treatment in the least amount of time[4,10,14,27,50,51].

Within cancer treatment, non-small cell lung cancer (NSCLC) accounts for approximately 55% of the total CDx market value and 85% of all lung cancer[50,52]. NSCLC is an ideal target for personalized medicine and CDxs because there are 185,000 new cases in the U.S. each year and approximately 40% of cases are driven by genetic factors. “Genetic testing for these mutations can provide important insight into a patient’s disease, and help determine an individual’s diagnosis, prognosis, and whether they are likely to respond to certain treatments.”[52].

In summation, CDxs implementation is possible across several specialty areas but CDx value per-segment varies. Figure 11 illustrates what specialty areas, in 2015, CDxs experienced the greatest application[14].

Figure 11)[14]



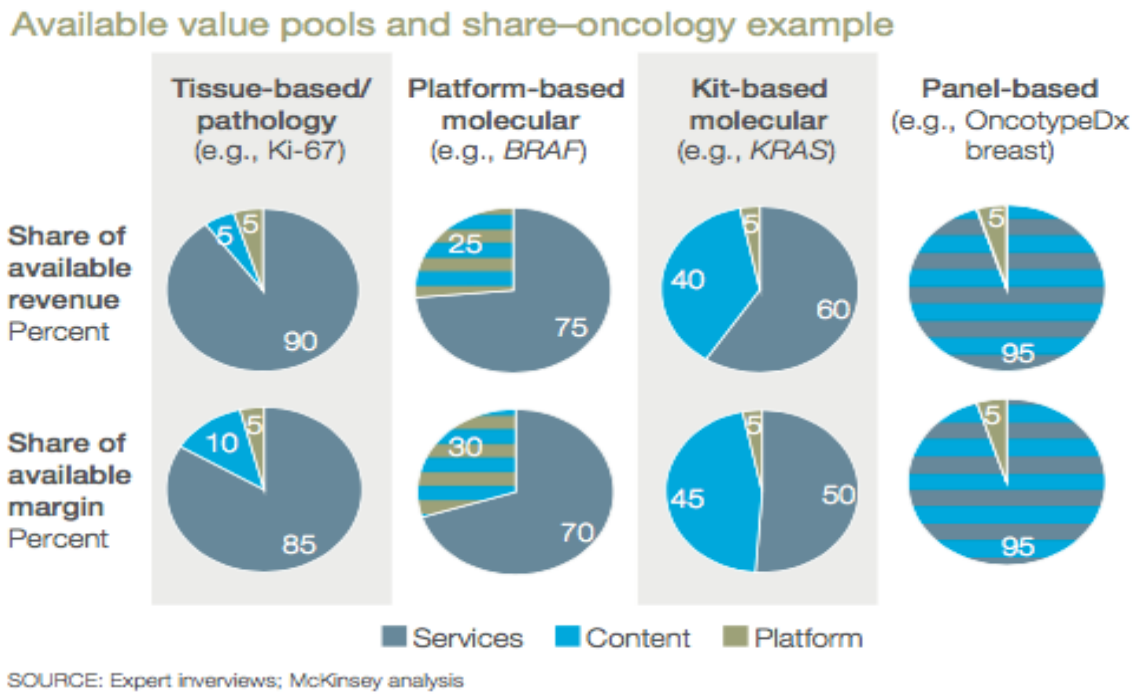
3.14 TYPES OF CDX TESTING

Companion diagnostic test design can affect implementation and uptake. Test design influences ease of use, degree of physician input, cost, and infrastructure necessary to perform the test. Figure 12 illustrates where value and service is allocated by CDx type. A platform test is one that is designed to allow for some calibration, allowing the physician greater level of control over which markers are tested. A panel- based assay has an unchangeable set of markers that it measures, giving the provider less flexibility and

restricting the diagnostic applicable to the treatment of a single or few diseases. A Kit-based molecular assay is usually the easiest to use because the kit is designed to collect genetic data that can then be easily read by a western blot, PCR, or other readily available test[53]. The tissue-based/pathology is not used for genotypic, but phenotypic analysis which allows for complimentary tissue phenomic data related to cancer progression[54,55].

Figure 12 indicates that most revenue is generated in the 'services' area regardless of the type of test. In Figure 12 'services' refers to the service provided by personnel trained to perform an assay, which is needed to generate results from the CDx. The content refers to the cost of a CDx device, and the platform means the lab test performed on the kit, e.g. PCR, western blot[4].

Figure 12)[4]



3.15 INTERNATIONAL MARKETS

Market growth across nations varies and reflects a number of factors especially regulatory practices and national health system policies. By analyzing CDx approval and uptake in nations with varying health policy the impact of the previously discussed regulatory practices and policy become clearer.

The French market has the highest levels of CDx penetration due to broad and generous reimbursement coverage. International variation in regulation requiring one diagnostic form over another can greatly affect uptake and therefore profit and public health impact. Nationalized healthcare systems, such as that in Europe, are generally not conducive for

outsourced lab service offerings. “Emerging markets such as Brazil or Turkey can be more attractive for esoteric testing within the private-pay market. Finally, the type of product offering to pursue can be critical. For example, our analysis indicates that multi-gene approaches (panels or NGS) in oncology are likely to capture more value than traditional “one drug–one Dx””[4].

CHAPTER FOUR: CONCLUSION/ DISCUSSION

4.1 PUBLIC HEALTH IMPACT

If the best methods of improving public health are through prevention than public health policy makers should take notice of CDxs. The Organization for Economic Co-operation and Development (OECD) notes in “Policy Issues for the Development and Use of Biomarkers in Health” that:

“biomarkers are allowing early identification of disease, improved diagnoses, and safer and more efficacious treatments leading to better patient outcomes and efficient and effective public expenditure on health”[56].

The OECD gives specific examples of CDxs that have had great impact in terms of reducing the economic impact of disease and increasing public health. In HIV clinical trials the number of patients with a measured viral load of zero after 24 weeks of treatment doubled while using the CDx Trofile™ and Pfizer’s’ therapeutic Maraviroc, compared to those treated with Maraviroc alone [56,57]. In the case of Gleevec, a breakthrough oncology

therapeutic for the treatment of chronic myelogenous leukemia, the CDx was able to predict clinical response to treatment with 94% accuracy[56]. Gleevec was the first CDx approved though the FDA's recommended co-approval process. Gleevec has high-risk side effects and received FDA approval only if the CDx is used alongside the therapeutic. The public health impact of Gleevec and its CDx is clearly summarized by the Harvard Business Review:

"When a diagnostic test determines that a patient has the abnormal BCR-ABL gene, the Novartis drug Gleevec can be prescribed to bind to and deactivate it. More than 95% of patients with this type of leukemia respond positively to initial Gleevec treatment. The five-year survival rate of CML patients receiving Gleevec is 89%; before the drug was approved in 2001, five-year survival for CML patients was only 69%. Such breakthroughs explain why cancer deaths fell in both 2003 and 2004, the most recent years for which data are available, and why survival rates for several cancers have been improving for more than a decade."[58]

Another way that CDxs have public health impact is by reducing adverse drug reactions and subsequent health expenses. Warfarin provides a particularly salient example. Warfarin (Coumadin) is a lifesaving blood thinner prescribed for the prevention of strokes, blood clots and heart attacks. Annually, two million people in the U.S. begin warfarin treatment and 43,000 cases of adverse reactions are treated in the emergency room. Warfarin is a very potent therapeutic that leaves physicians guessing patient sensitivity on a case-by-case basis. In 2004 a CDx assessing patient drug metabolism based on the presence of two genes CYP2C9 and VKORC1 was introduced to market resulting in a 30% decrease in

adverse events[27,59]. . The average healthcare cost per adverse reaction to warfarin is $10,819. A reduction of 30% in the total number of adverse reactions would result in $129,828,000 annual savings[60]. If the cost of adverse events is stratified across all patients (including those with no adverse event), the average cost of adverse event per patient is $835. Considering that Warfarin CDx costs $400-550 per test, the net healthcare savings gain alone should have public health, physician, patient and payer support[61].

In 2013 Mckinsey & Company estimated that 30-40% of novel drugs in the pipeline currently have an associated CDx[4]. The oncology therapeutic market with a CDx will increase from 20% in 2015 to 30% in 2017[62]. The health impact of CDxs is most salient in the case of chemo-therapeutics; chemo-therapeutics alone have a 6.8-45% efficacy for patients at risk of NSCLC. Figure 13 shows the 2015 investment of three major oncology therapeutic developers[63].

Figure 13)[64]

Personalized Medicine Pipelines: Oncology

Company	New Drugs in Pipeline	Personalized Medicines in Pipeline	% Personalized Medicines	Phase I Personalized Trials	Phase II Personalized Trials	Phase III Personalized Trials
AstraZeneca	29	14	48%	7	6	1
Genentech	17	6	35%	3	3	0
Novartis	17	13	76%	3	8	2

At AstraZeneca the investment in precision medicine has increased, in the words of AstraZeneca Vice President of Precision Medicine, Cecilia Schott:

"Now at AstraZeneca, about 85% of our pipeline has personalized care embedded in our development programs. We follow the science to identify if a patient population will respond better. The reason is very simple…having good biomarkers decreases the chances of a drug's failure. It means that the pivotal trials have a greater chance of succeeding, which is good for everyone"[64].

4.2 STRATEGIC BUSINESS MODEL

Thus far we have discussed the landscape developers must navigate to gain therapeutic and CDx market access. In the following section the competitive advantage developer's gain through CDx development will be discussed.

The most significant gains from having a CDx accompany a therapeutic are:

1. The decrease in clinical trial costs;
2. The increase in to market success rate;
3. The decrease in time needed to complete clinical trials;
4. The increase in physician uptake.

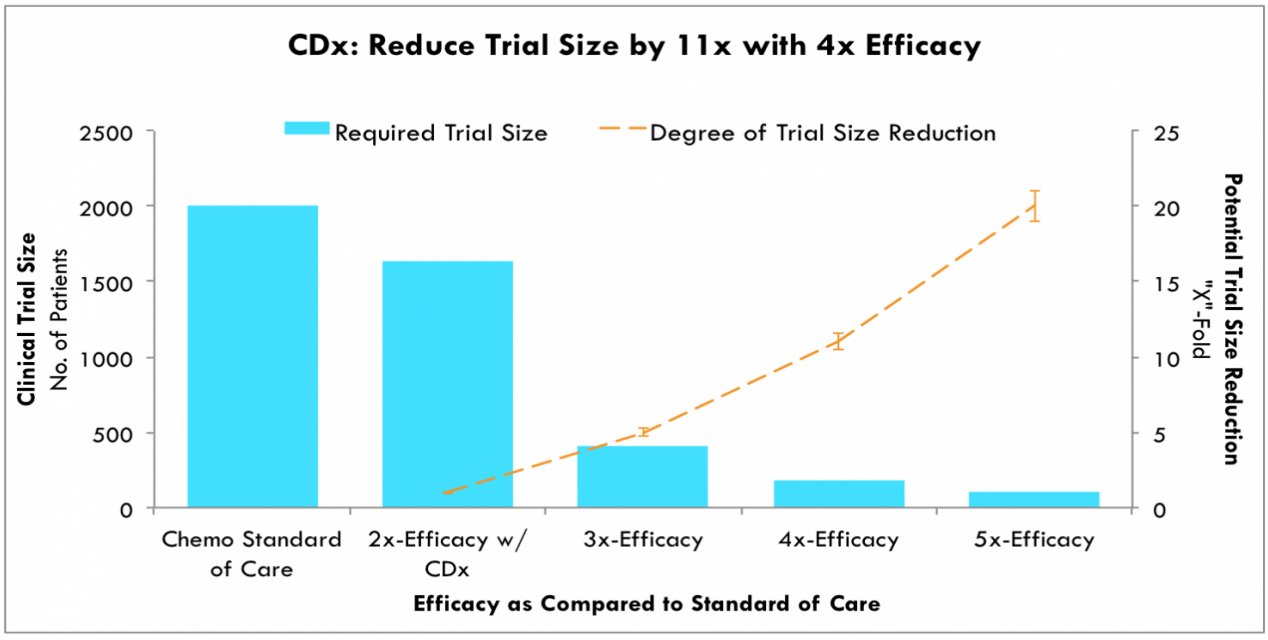
4.3 DECREASED CLINICAL TRIAL COSTS

A reduction in pharmaceutical research and development costs is anticipated to result from CDxs being developed in parallel with a therapeutic[42]. Reductions in R&D costs accrue in

several ways, the first being the ability to produce a precise clinical trial population. A precise clinical trial population is a study population that is pre-determined to be the most likely responders to treatment. The current standard necessitates that clinical trials utilize a large, expensive patient pool to determine therapeutic efficacy[27].

The implementation of a CDx enables therapeutic developers to pre-screen study candidates, determine those expected to be most responsive to treatment and those expected to have adverse or negligible reaction. Depending on the efficacy of the CDx developers may be able to reduce clinical trial size. For instance, if a CDx is able to increase treatment efficacy 4x then the reduction in trial size can be expected to be 11x (see Figure 14),[27].

Figure 14[42])

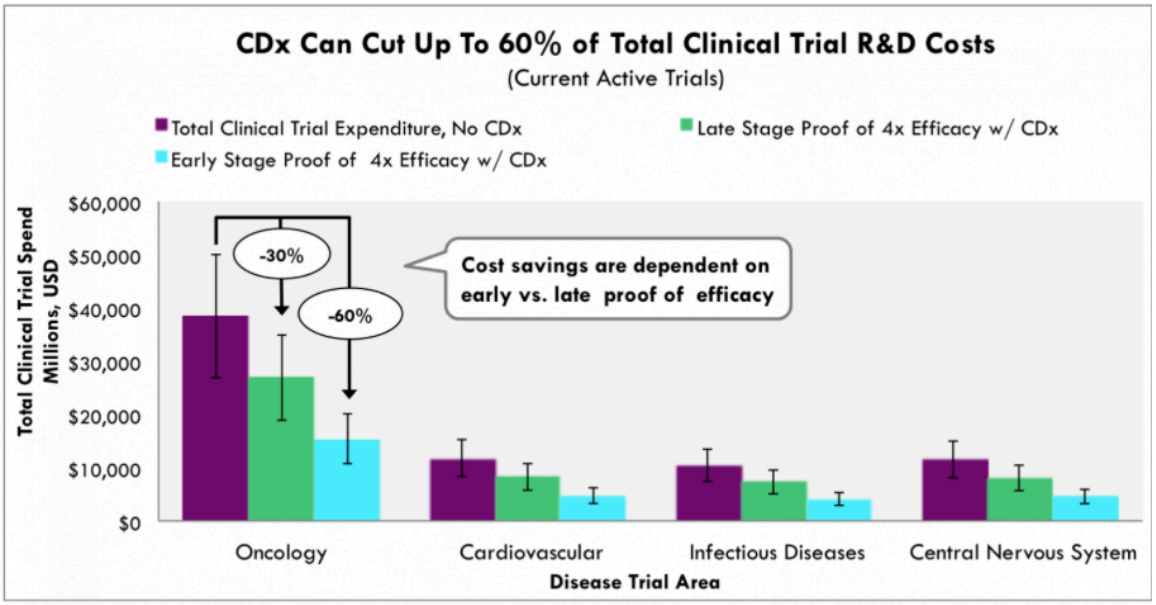


Source: ARK Investment Management LLC

Logarithmic relationship between increased efficacy with CDx and trial size reduction. Estimates based on two-tailed T-Tests, 90% study power, 5% alpha, and 16% chemo efficacy rate.

The use of CDxs to inform therapeutic development during the clinical trial phase has the capacity to reduce expense by as much as 60% (see Figure 15)[42]. The total disease area savings from CDxs are considerable for both business and public health savings standpoint (see Figure 16)[42]. Considering the average clinical trial phase for a new molecular therapeutic is estimated to cost developers approximately $548M ,the savings can be as high as $328.8M by utilizing a CDx[22–24].

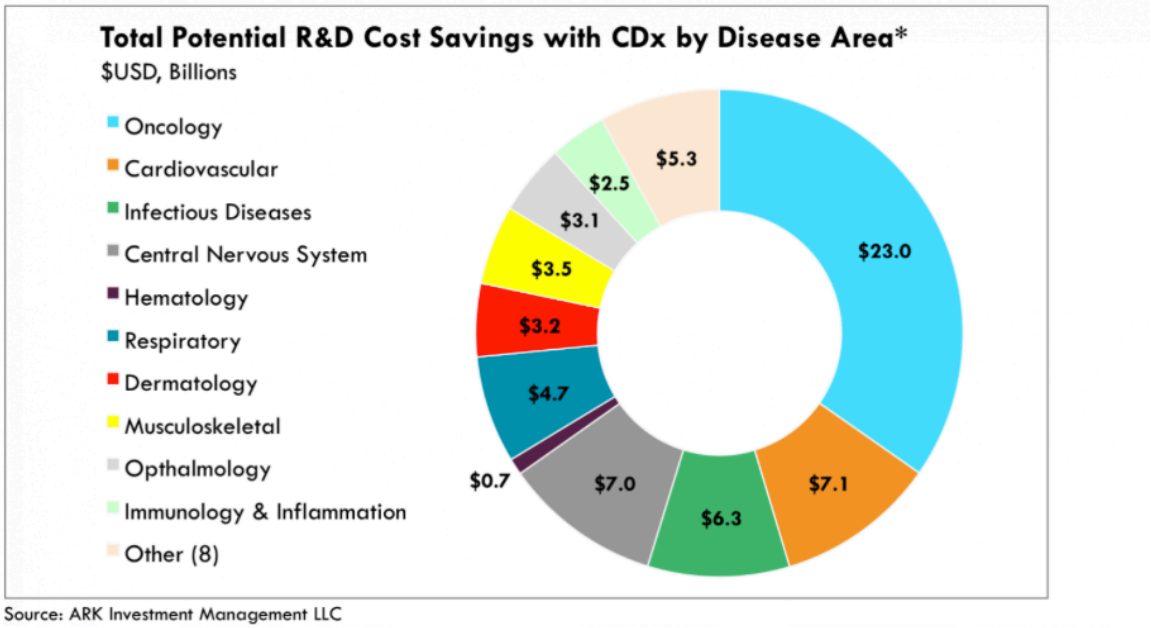
Figure 15)[42]



Source: ARK Investment Management LLC

Fig. 2 CDx guided drug development exhibits 30-60% cost reductions. Based on 10x reduction in required trial size based on proven 4x efficacy rates against standard of care and average cost per patient per disease area. Total estimated number of patient in clinical trials as of YE 2015. Validated against historically approved co-developed therapeutics [4, 5]

Figure 16)[42]



Source: ARK Investment Management LLC

Fig 3. CDx guided drugs could generate $50 billion in R&D cost-savings across all disease areas. Based on 10x reductions from historical trial sizes, a proven 4x efficacy rate against standard of care [4 ,5] and average cost per patient per disease area. Total estimated number of patients in clinical trials as of YE 2015. Cost-savings are contingent on advanced biomarker discovery and diagnostic toolsets.

4.4 INCREASE IN TO MARKET SUCCESS RATE

In addition to price reduction, the ability to bring a therapeutic to market is drastically increased through the use of CDxs in clinical trials. A NSCLC therapeutic has an 11% chance of progressing from clinical trial stage one to FDA approval or clearance for market. A NSCLC therapeutic with an accompanying CDx has a 62% chance of progressing from clinical trial stage one to FDA approval or clearance, representing a 6x greater chance of FDA approval for market[65]. The increased likelihood of delivering a therapeutic to market, coupled with reduced research and development costs represents a compelling strategy for pharmaceutical companies to invest in the development of CDxs.

CDxs have also been effective in reducing the time for therapeutic approval. For example, in the case of Xalkori®, a NSCLC therapeutic, the time from phase I to new drug application filing was reduced by two years due to the implementation of a parallel CDx[66]. Figure 17 compares three similar NSCLC therapeutics and shows Xalkori® required 960 patients for the clinical trial compared with 3,110 patients, and a 3x reduction in time compared to competitors from Phase I to market approval. Additionally, Xalkori® had a lower development cost per patient[27]. Not only does this reduction in time save money but it also provides a competitive advantage by allowing earlier entry, which allows a developer to capture market share before competitors.

(Figure 17)[27]

Clinical Trials With and Without a CDx

Drug name and developer	Date of US approval	Relative development cost (% based on standard cost/patient)	Number of patients in clinical trials	Time from Phase I to New Drug Application filing (years)
Xalkori®a (crizotinib) – Pfizer	August 2011	100	960	1.8
Iressa® (gefitinib) – Astra Zeneca	May 2003	146	2,850	7.0
Tarceva® (erlinotib) – OSI and Genentech	November 2004	154	3,110	5.3

4.5 PHYSICIAN UPTAKE

Physician uptake is a major barrier or driver of potential net present value (NPV). A special report by Roth, Keeling and Smart highlights ten key financial drivers affecting NPV realized from a CDx[39]. The report notes that drug sales take on average 4.5 years to reach peak sales. This is due to lags in physician uptake and hesitancy to proscribe a new therapeutic[39].

A CDx provides the physician assistance in prognosis and monitoring, helping to reduce adverse events, a primary concern of physicians. The Institute for Health Metrics and Evaluation estimates physicians are 70-90% more likely to prescribe a therapeutic if it has an accompanying diagnostic test. [39]. Also CDxs help generate greater awareness among physicians compared to competitors that lack a CDx. "For example, Merck (NJ, USA) effectively used a companion diagnostic strategy to increase awareness of bone-density measurement prior to, and during, the launch years of Fosamax®. This directly helped Fosamax achieve and retain market leadership"[39].

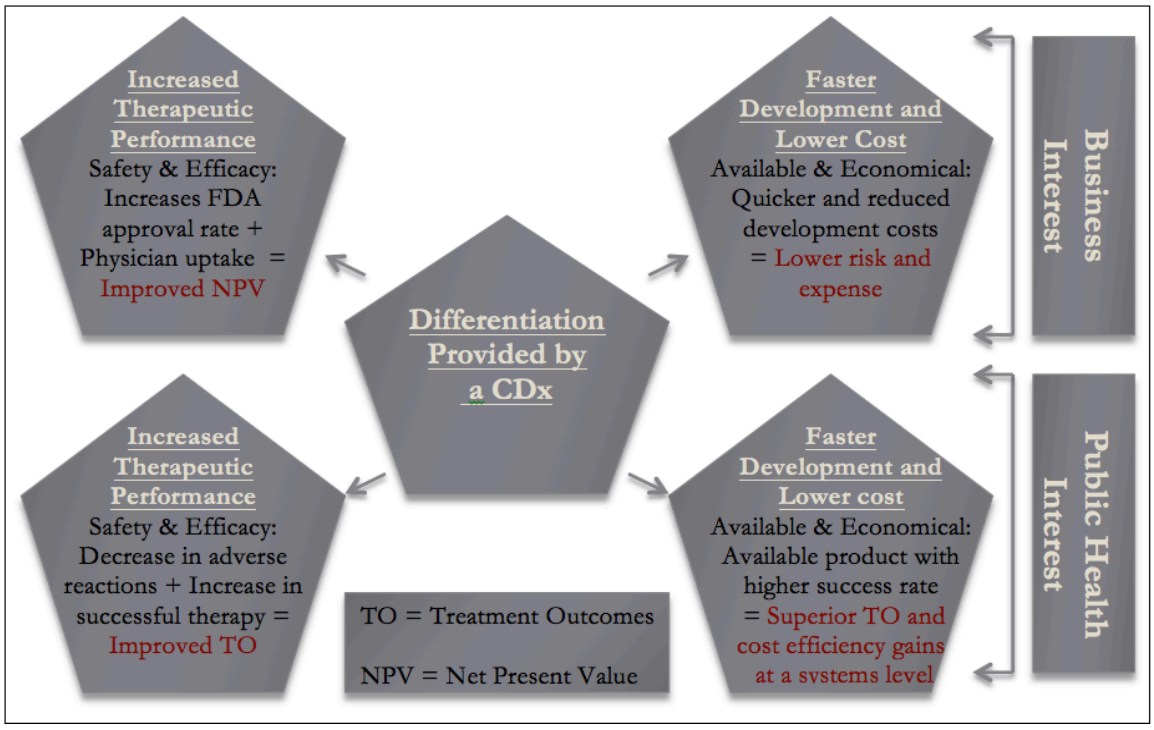
Physicians are most likely to be early adopters of a therapeutic if they are provided clear, concise scientific evidence supporting the medical benefits from utilizing a CDx[39]. Adoption by physicians is essential for gaining access to market. However, CDxs add an additional barrier to initial physician uptake; physicians do not utilize CDxs when they don't understand how to implement or read them[39]. Developers who want to maximize product uptake must assess and engage in educational promotions targeted at physicians.

4.6 DIFFERENTIATION

Diaceutics, a consulting group, estimates that even late stage CDx development can result in a $34 Million increase in ROI[39]. If a market is already saturated with a competitor's product, differentiation is necessary to acquire some of the occupied space. An improvement in safety and efficacy provided by a CDx can provide differentiation for a therapeutic, underscoring why CDxs "can result in the ability to capture a greater market share, charge higher prices, detect competitive initiatives, command greater buyer loyalty"[39].

Interestingly, some of the key modes of differentiation provided by CDxs for business purposes also have public health benefits. Figure 18 portrays two differentiators, increased therapeutic performance and faster development at lower cost. In brief, the systems level efficiency gains referenced in Figure 18 accrue from the $129,828,000 saved annually on Warfarin related ER visits, doubling the NSCLC treatment success rate, or Gleevec's impact on cancer mortality between 2003 and 2004[42,60,58].

Figure 18)



4.7 CDX VALUE PROPOSAL FOR DEVELOPERS

The following factors constitute a compelling value proposition, encouraging developers to invest in a CDx:

- Double digit percent reductions in clinical trial cost;

- Improved chances of FDA approval;
- Reduced adverse reactions in study population;
- Faster development to market times;
- CDx as potential market differentiator;
- Publicity tool targeting physicians.

4.8 CASE STUDY KEYTRUDA & OPTIVO

The following example illustrates how the competitive advantages gained through CDx development can drive, or stunt profit. In 2016 Merck and Bristol Myers Squibb planned to launch their small molecule NSCLC treatment on the market. Both companies intended that their therapeutic would become the new first line NSCLC treatment although they employed distinctively different development strategies. Both therapeutics are checkpoint inhibitors, they work by disrupting the communication between PD-L1 and PD-1, a cancer protein and an immuno-receptor, respectively[67]. Both drugs were approved for specific treatments in 2014. However, the majority of the profit margin was anticipated to come from NSCLC treatment, a $10-15 Billion market. Upon the announcement that the small molecule NSCLC drug Opdivo would not receive FDA approval, BMS share value dipped 20%, approximately $32 Billion in market value[68]. The Bernstien investment group immediately reduced Opdivo's earnings potential by $3 Billion [67,69]. BMS's strategy for Opdivo was to test a wide study population of NSCLC patients[67,70]. BMS randomized patients into those treated with chemotherapy and those treated with Opdivo.

Ultimately, Opdivo's impact on tumor growth was statistically the same compared to standard treatment with a chemotherapeutic. Given the unimpressive metrics BMS elected not to bring Opdivo before the FDA for approval[67,70]. BMS's development of Nivolumab (the molecular nomenclature for Opdivo) began in 2000 and took a total of 14 years to make it to market[71].

Merck announced Keytruda's FDA market approval and promising clinical results days apart from Opdivo's announcement of failure to receive approval. The same day Merck's stock value increased by 14% and their market lead resulted in a $1 Billion increase in potential annual sales projections[67,70]. Merck's development strategy for Keytruda focused only on those patients likely to respond, those whose cancer cells have at least 50% PD-L1 expression. Merck invested in a CDx to determine the PD-L1 protein expression. This allowed them to narrow their clinical trial pool and present data to the FDA showing a 50% reduction in tumor progression compared to those treated with chemotherapeutics, delayed tumor growth 4 months greater than chemotherapeutics, a 17% increase in tumor response, a 25% compared to 53% adverse reaction rate, and ultimately a 40% reduction in morbidity[6772]. In addition to increased efficacy, Pembrolizumab's (the molecular nomenclature for Keytruda) development began in 2006 making it to market 6 years earlier than Opdivo[71–73].

The development cost of both drugs is insider knowledge, which prevents accurate analysis of cost savings. Nonetheless, given what we know about reduced development costs stemming from reduced clinical trial size and time to market, it is reasonable to infer

Keytruda cost millions less than Opdivo to develop. BMS continues to develop Opdivo for NSCLC treatment, as a part of a therapeutic cocktail. However, the market lead gained by Keytruda has won Merck billions of dollars in the NSCLC market segment, mostly at BMS's expense.

Despite the promising results generated by Keytruda, many experts believe that Keytruda and Opdivo have more similar efficacy than the results suggest. The differentiator was the trial design. Merck was able to restrict the trial population to likely responders and therefore show a higher efficacy rate. This was made possible through their investment and implementation of a CDx, which allowed Merck to determine PD-L1 levels. BMS used a larger clinical trial population with a greater percent of anticipated non-responders, a move that likely resulted in their poor results. Gene expression is not intuitive. An analogous hypothetical would be if Merck and BMS were competing to reduce pregnancy in teenage girls, but BMS had to blindly include men in their study population while Merck only included women. Naturally, Merck's results would seem more significant.

4.9 CONCLUSION

Precision medicine is an emerging field, which allows patient specific treatment based on biomarkers. A core tool enabling the shift towards precision medicine is CDxs. Currently "42% of all drugs in the pipeline have a companion diagnostic" and a 69% increase will be seen within the next 5 years[1]. CDxs have the potential to have an impact on public health in several ways. For instance, they reduce adverse reactions, improve treatment outcomes, and reduce the need for trial and error style treatment in oncology [27,39,52,60,71].

Companion diagnostics exist because of the investment made by pharmaceutical and medical technology developers. Developers are motivated to invest in the creation of CDxs because of the potential for a return on their investment. The body of evidence indicating that CDxs are improving public health continues to grow and if policy makers wish to encourage their development they need to know how to influence business motivations through policy.

In 2014 and 2016 the FDA drafted new policy for CDx approval although both drafts were rejected. In new policy guidance, policy makers should consider the factors presented in this review. In particular, understanding the various testing platforms, key stakeholders, emerging CDx markets, the pharmaceutical development process, and how FDA approval affects CDx uptake.

Based on the literature review, both peer-reviewed and publically available industry and consulting documents, there is no information educating health policy makers about CDx development and implementation from the developer's perspective. This is perhaps because until very recently CDxs were considered science fiction. Existing literature from a developer perspective is highly siloed and public health literature is limited. As the market for combined therapeutics and CDxs grows, public health implications should become more apparent. Now is the time for well designed, objective, research studies that focus on the potential and real effects on the burden of disease and potential health system cost savings

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