Overview of Companion Diagnostics in the pharmaceutical industry

Current escalating costs of drug discovery, development and drug launch continue to concern the pharmaceutical sector. This has been compounded by the advent of personalised medicine and its associated demands for individualised products as well as the demise of the 'blockbuster' model. In order to satisfy the demands afforded by this new paradigm, the next generation of drugs has to be safer and more efficacious and pharmaceutical companies must produce more genotype and/or phenotype-focused therapeutic agents. The development of Companion Diagnostics appears to offer a set of tools as well as the portent of relevant biological and clinical information that addresses many of the problems that the pharmaceutical companies must overcome. Here, we describe the current state of Companion Diagnostics and its impact on the pharmaceutical sector. We discuss the need for Companion Diagnostics in the drug discovery and development process. This perspective is augmented by a consideration of the development of Companion Diagnostics as well as a listing of the major companies providing tools, technologies, markers and services in this rapidly growing area.

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Pharmaceutical companies have been subject to a plethora of external forces that have forced internal changes over the past 20 years. The 1990s saw the development of numerous high-throughput analytical platforms in conjunction with powerful IT and bioinformatics tools that produced the 'Decade of Measurements' and 'Omic wave' technologies[1]. The subsequent integration of all these tools and technologies led to the advent of second generation systems biology in the late 1990s[2]. In parallel there was a surge in the growth of biomarker use[1,3] and a rush by pharmaceutical companies to adopt and adapt such technologies for application in their drug discovery and development (DDD) processes[4]. Much of this change was driven and facilitated by the scientific and pharmaceutical communities without significant outside, independent analyses and critique.

In the late 1990s and into the 'Noughties' (2000 and beyond) a series of additional changes was buffeting medical communities and healthcare systems across Europe, North and South America and parts of Asia. The initial impetus was driven by recognition that our understanding

Table 1
Analysis of percent GDP spent on healthcare compared to life expectancy and individuals afflicted with Diabetes, Obesity and Asthma. All data from OECD 2009 Report[8]
[a] Percentage of annual GDP spent on healthcare
[b] Based on adult population aged 20-79
[c] Asthma hospital admission rates for individuals aged 15 and older. These data standardised to a rate of per 100,000 population

COUNTRY	%GDP[a]	LIFE EXPECTANCY		DIABETES[b] %	OBESITY[b] %	ASTHMA[c] PER 100K
		FEMALE	MALE			
USA	16.8	80.7	75.4	10.3	34	120
Switzerland	10.8	84.4	79.5	5.6	8	32
UK	8.4	81.7	77.3	3.6	24	75
Japan	8.1	86.0	79.2	5.0	3	58

of disease etiology, onset, progression, treatment and outcome was limited. Current medical practice, at the time, focused on being reactionary and the physician attempted to treat symptoms and hence not the individual patient. This limitation of medical practice led to a grass-roots level recognition and demand for better service and treatment of the individual patient, and thus was born personalised medicine[5]. The continued development of personalised medicine and its ready adoption by the general public has forced most healthcare systems to consider how they provide more efficient, cheaper and relevant services to their patients.

The advent of personalised medicine and recognition of human complexity and variability has forced pharmaceutical companies to reconsider their current business model. There is now a general consensus that the blockbuster model has significant limitations[6] and that the future must include therapeutic agents that are more closely tailored to specific patient populations. By necessity this must mean that such drugs are safer, more efficacious, more specific and less costly to develop[5]. The demands and constraints imposed by such a demanding new model have had the pharmaceutical companies rushing to inspect their technology toolkits for answers. One 'solution' that has been somewhat embraced and cautiously adopted is Companion Diagnostics. In this paper we will provide a broad overview of Companion Diagnostic efforts in the pharmaceutical sector. We will discuss the development and current status of this area as well as who are the key suppliers of Companion Diagnostics markers and services to the pharmaceutical sector. In a subsequent article we will discuss the business complexities of developing and/or acquiring Companion Diagnostics as well as the defining role of regulatory bodies such as the FDA (USA) SFDA (China) or EMEA (Europe) in this nascent and complex space.

Factors in Companion Diagnostic adoption

Historically, our understanding of disease aetiology and pathobiology was predicated on simple observations of physiological changes and homeostatic imbalance. More recently this concept has been replaced with an understanding that disease causality and onset is a complex multi-component process. For example, breast cancer is now categorised into at least five distinct subtypes and there may indeed be many other unique molecular types[5]. Our inability to unravel the complexity of disease onset, progression and ensuing treatment has led to escalating healthcare costs. In turn this has had a concomitant impact on all strata of society, but particularly it has negatively affected the poor and elderly. For example, the USA Congress just recently passed the Patient Protection and Affordable Care Act[7], after a year of contentious debate. The Act contains provisions to cover approximately 32 million of the now 48.3 million uninsured Americans (~16.%[3] of the nation's population).

Efforts to offer universal healthcare are a paramount driving force in most developed and developing countries. However, such efforts come at a substantial cost. The OECD estimates that healthcare costs have increased more than 4% annually in member countries in the past decade (1997-2007)[8]. In addition the resultant effects of increased spending have had mixed results depending on country and focus of the specific healthcare system and this is summarised in **Table 1**. It is noteworthy that the USA spends by far the largest percentage GDP on healthcare at 16.8%, compared to Switzerland (10.8%), United Kingdom (8.4%) and Japan (8.1%). This is in stark contrast to outcome as measured by life expectancy and percentage of the population afflicted with diabetes, obesity and asthma hospital admission rates (**Table 1**). The US population has the shortest lifespan expectancy for

both females (80.7 years) and males (75.4 years), and the highest incidence rate of diabetes (10.3% of the population), obesity (34% of the population) and asthma hospital admission rates (120/100,000)[8] compared to the UK, Switzerland and Japan.

Rising healthcare costs are also influenced by ever-increasing drug discovery and development costs as well as the limited efficacy and safety of the resultant commercially available drugs. For example, the Parexel Report states that the general consensus for the developmental cost of a new molecular entity is $1.4 billion[9]. The cost is driven in part by a long and tedious timeline to develop the new compound which can still take as long as 15 years[9]. Unfortunately, this long time period does not necessarily guarantee that a drug is either efficacious or completely safe. The efficacy of a specific drug can vary from approximately 30-75%, depending on the drug class and therapeutic use[5]. In addition, most consumers are aware of the potential side-effects from therapeutic drugs as well as the widely publicised safety concerns of drugs such as Vioxx and Avandia.

The demands of a relatively well-informed patient consumer aware of personalised medicine, and the necessity of treating the individual or specific patient populations rather than an ill-defined population have significantly changed the business landscape for pharmaceutical companies. Companies are aware of the need to produce cheaper, safer, more-efficacious products that meet the growing demand of 'tailor-made' products. In order to achieve this goal the DDD process pipeline has to be made more biologically and clinically transparent so that issues such as toxicity, adverse events and patient stratification can be much more readily detected and explained. This should facilitate decision-making events along the DDD process allowing cost cutting and ultimately better products for defined patient populations. Pharmaceutical companies believe that Companion Diagnostic products afford biological information tools that will promote such activities.

Definition of Companion Diagnostics

The evolutionary process of a nascent and emerging discipline is embodied by chaos, confusion and circumlocution. In that regard the adoption and growth of Companion Diagnostics by and of the various stakeholders is no different. Indeed, much of the current process is similar to that observed during the initial flurry of activity and excitement surrounding the biomarker sector[1,3]. As expected, the lexicon of this field is still evolving and there are competing synonyms for Companion Diagnostics that include pharmacodiagnostic and theranostic descriptors. For example, Dako, which developed the Hercep Test™ used in conjunction with Herceptin to treat metastatic breast cancer defines a pharmacodiagnostic as a "Diagnostic test(s) employed to identify cancer patients eligible for treatment with targeted therapies"[12]. Lesko at the FDA has defined a pharmacodiagnostic output as "A characteristic that is objectively measured and evaluated as an indication of normal processes, pathogenic processes or pharmacological responses to a therapeutic intervention"[13]. In the case of theranostics, an early definition provided was "...a term used to describe the proposed process of diagnostic therapy for individual patients – to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results"[14]. More recently, the term has found expanded use and Schloss described theranostics in a variety of ways that included "a system combining diagnosis, therapy and monitoring"[15].

A Google search of the individual terms 'Companion Diagnostic', 'Pharmacodiagnostic' and 'Theranostic' revealed 132,000, 22,400 and 44,200 hits respectively, and suggests that Companion Diagnostic is the most widely used term at the present time. The Index Pharmab.com defines a Companion Diagnostic as "a bioanalytical method designed to assess whether a patient will respond favourably to a specific medical treatment or not"[16]. A more recent definition describes a Companion Diagnostic as "...the particular diagnostic test under evaluation [that] is specifically linked to a known therapeutic drug. This linkage could be important in the therapeutic application and clinical outcome of a drug (personalised medicine), or an important component of the drug development process"[17]. There appears to be widespread agreement that a Companion Diagnostic is a biomarker(s) used in a specific context that provides biological and/or clinical information that enables better decision making about the development and use of a potential drug therapy[10,11]. This can be applied anywhere along the preclinical, clinical and post-product launch of the drug. Indeed, Frueh has argued that any type of "biomarker involved in making a therapy decision" can be classified as a Companion Diagnostic[11]. Clearly this debate will continue and the terminology plus definitions will continue to evolve and be refined, as happened in the development of biomarkers[1].

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Stakeholders and their needs

Historically, pharmaceutical companies have enjoyed a dominant role in the discovery, development, marketing and post-marketing surveillance of their therapeutic drug products. However, with the advent of an informed patient-base, personalised medicine and the need for Companion Diagnostics along with associated domain expertise, the landscape has changed. Hence pharmaceutical companies must recognise that other stakeholders exist and their needs and goals may be different. This recognition will go some way to ensure that Companion Diagnostics are employed correctly in order to meet the expectations of the other stakeholders and have real impact on the quality and therapeutic effect of the therapeutic drugs produced. The stakeholders and their expectations of the Companion Diagnostic(s) have been discussed in detail elsewhere by Finley Austin (US External Science Policy, Hoffmann La Roche Inc)[10], and have been modified and summarised here. Note that the relative importance level of each factor listed here is shown in ascending order:

1 **Pharmaceutical company**
- Control costs in DDD (most important)
- Clinical utility; improve safety, outcome and clinical trial design
- Labelling; intended use in association with the drug
- Potential medical guideline changes
- Reliability, availability and accessibility of Companion Diagnostic test
- Regulatory approval of the Companion Diagnostic test
- Cost of the Companion Diagnostic test (least important)

2 **Companion Diagnostic Manufacturer**
- Reimbursement mechanisms and pricing
- Clinical utility; improve drug effects, trial design and test feasibility
- Labelling; intended use in association with the drug
- Potential medical guideline changes
- Regulatory approval of the Companion Diagnostic test
- Reliability, availability and accessibility of Companion Diagnostic test
- Cost of the Companion Diagnostic test

3 **Patient/consumer**
- Clinical utility; help disease management, and decision making
- Physician recommendation; why this test?
- Reliability
- Reimbursement; who pays? Insurance, out-of-pocket, value

4 **Physician**
- Clinical utility; help manage patient disease and decision making
- Labelling; intended use in association with the drug
- Potential medical guideline changes
- Regulatory approval of the Companion Diagnostic test
- Reliability, availability and accessibility of Companion Diagnostic test
- Cost and reimbursement

5 **Payer**
- Clinical utility; value in disease outcome both short and long term
- Clinical utility; decision making and management for disease
- Potential medical guideline changes
- Reliability, availability and accessibility of Companion Diagnostic test
- Labelling; intended use in association with the drug
- Regulatory approval of the Companion Diagnostic test
- Cost

6 **Testing laboratory**
- Clinical utility; evidence to support use of the test
- Clinical utility; how important to patient management
- Reliability of Companion diagnostic test
- Cost of the Companion Diagnostic test
- Logistics of undertaking measurement
- Regulatory approval

7 **Regulatory authorities**
- Regulatory approval; determined by clinical data
- Define regulations for Companion Diagnostic use

All the different stakeholders have obvious vested interests in the development and use of companion diagnostic tests. In some cases those interests may be radically divergent, as in the case of the cost and price of the companion diagnostic test. The Companion Diagnostic manufacturer as well as the laboratory testing facility would prefer to realise a high margin on the price charged to the end user/payer, whereas the patient would obviously

Table 2
Companion Diagnostic markers required by the FDA. Testing is required prior to deciding on therapeutic drug use

COMPANION DIAGNOSTIC	DRUG	INDICATION	PHARMACEUTICAL COMPANY
Philadelphia Chromosomepositive Responders	Sprycel (dasatrib)	Cancer (Leukaemia)	Bristol Myers Squibb
Epidermal Growth Factor Receptor (EGFR)	Erbitux (cetuximab)	Colorectal Cancer	Bristol Myers Squibb
CCR5-Chemokine C-C Motif Receptor	Selzentry (maraviroc)	Infectious Disease (HIV)	Pfizer
Her2/neu Overexpression	Herceptin (trastuzuumab)	Breast Cancer	Genentech

prefer to pay a minimal price accompanied by maximum information content for their disease management. However, there is considerable agreement as to the importance of a number of issues across all stakeholders. Finley Austin refers to this as the "All Roads lead to Rome" syndrome[10]. There is widespread agreement that clinical utility is of paramount importance. The Companion Diagnostic test clearly must provide meaningful clinical insight as well as change current medical practice and patient outcome. Similarly, albeit for different reasons, all stakeholders concur that the Companion Diagnostic test must be accurate and provide clinical information content that can be reliably used in disease management. The test must be based on a foundation of data that shows good specificity and sensitivity through appropriate clinical trials.

These encompassing stakeholder goals appear to afford some optimism for the future development of Companion Diagnostics. However, this simplistic analysis ignores the many considerable barriers that exist between all the stakeholders. The demands and expectations of the patient who needs a cheap or free marker that provides valuable clinical information to help him/her better manage disease is in stark contrast to the Companion Diagnostic company which has expended considerable financial assets to produce a clinically relevant biomarker and is looking to recoup those sunken costs and build a successful business. The pharmaceutical companies, who have no experience in marker/diagnostic discovery and development, are unsure as to the monetary value of Companion Diagnostics and business models involving pharmaceutical companies and Companion Diagnostic companies are still evolving. However, in all cases it is imperative that lines of communication are developed in order to ensure the successful development and acceptance of high-quality companion diagnostics continues into the future.

Current status

Regulatory agencies including the FDA and the EMEA are now actively encouraging the use of Companion Diagnostics in the development and use of prescription drugs. This guidance initially started back in 2004 in the form of an FDA Critical Path Initiative and the white paper entitled *Innovation-Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*[18]. This was followed by the Drug-Diagnostic Co-Development Concept Paper in 2005[19]. Today, both the FDA and EMEA require Companion Diagnostic marker testing prior to the prescribing of certain drugs. At present four companion Diagnostic markers are required by the FDA to be tested before deciding the therapeutic drug use. The list includes CCR5 Chemokine C-C Motif Receptor, Epidermal Growth Factor Receptor (EGFR), Her2/neu Overexpression and Philadelphia Chromosome Sensitive Responders[20]. The details are summarised in **Table 2**.

The EMEA has been less transparent in its leadership role regarding Companion Diagnostics. However, at least 11 therapeutic drugs now require Companion Diagnostic testing and they include: Ziagen (GSK-Infectious Disease), Epitol/Tegretol (Novartis-Neuropsychiatric Disease), Herceptin (Genentech/Roche-Cancer), Tasigna (Novartis-Cancer), Sprycel (Bristol Myers Squibb-Cancer), Trisenox (Cephalon-Cancer), Erbitux (Bristol Myers Squibb-Cancer), Tarceva (Genentech/Roche-Cancer), Vectibex (Amgen-Cancer), Tyverb (GSK-Cancer) and Iressa (Astra-Zeneca/Teva-Cancer). It should be noted that the EMEA

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Table 3: Companies that offer tools, technologies, services and biomarkers in the Companion Diagnostic sector. In terms of Focus: 1 = Companies which have approved Companion Diagnostic markers in use by pharmaceutical partner; 2 = Companies which have completed deals with pharmaceutical companies for Companion Diagnostic markers; 3 = Companies which offer Companion Diagnostic tools, technologies and services

COMPANY NAME	WEBSITE	LOCATION	FOUNDED	FOCUS
Abbott Diagnostics	www.abbottdiagnostics.com	Abbott Park, IL USA	1972	1
Almac Group	www.almacgroup.com	Craigavon, Northern Ireland	2001	1
Aureon Laboratories	www.aureon.com	Yonkers, NY USA	2002	1
bioMerieux	www.biomerieux.com	Marcy L'Etoile, France	1897	1
Celera Diagnostics	www.celera.com	Alameda, CA USA	1998	1
Clinical Data Inc	www.clda.com	Newton, MA USA	1969	1
Dako	www.dako.com	Glostrup, Denmark	1966	1
DxS	www.dxsdiagnostics.com	Manchester, UK	2001	1
Dyax	www.dyax.com	Cambridge, MA USA	1995	1
Epigenomics	www.epigenomics.com	Berlin, Germany	1998	1
Monogram Biosciences	www.labcorp.com	S. San Francisco, CA USA	1995	1
Novartis AG	www.novartis.com	Basel, Switzerland	1895	1
Power3 Medical Products	www.power3medical.com	The Woodlands, TX USA	1992	1
Prometheus	www.prometheuslabs.com	San Diego, CA USA	1995	1
Qiagen	www.qiagen.com	Venlo, Netherlands	1986	1
Rosetta Genomics	www.rosettagenomics.com	Rehovot, Israel	2000	1
Source MDx	www.sourcemdx.com	Boulder, CO USA	1998	1
Tercica	www.tercica.com	Brisbane, CA USA	2002	1
20/20 GeneSystems	www.2020gene.com	Rockville, MD USA	2000	2
Agendia BV	www.agendia.com	Amsterdam, Netherlands	2003	2
Allegro Diagnostics	www.allegrodx.com	Boston, MA USA	2006	2
Artemis Health, Inc	www.artemishealthinc.com	San Carlos, CA USA	2001	2
AssuerRx Health	www.assuerxhealth.com	Cincinnati, OH USA	2006	2
Axial Biotech	www.axialbiotech.com	Salt Lake City, UT USA	2002	2
BioCurex	www.biocurex.com	Richmond, BC Canada	2002	2
Biodesix	www.biodesix.com	Broomfield, CO USA	2005	2
Biomarker Strategies	www.biomarkerstrategies	Baltimore, MD USA	2007	2
Brain Resource Company Ltd	www.brainresource.com	Ultimo, Sydney Australia	2004	2
Cangen Biotechnologies	www.cangenbio.com	Bethesda, MD USA	2000	2
Caprion Proteomics	www.caprion.com	Montreal, Quebec Canada	2000	2
CardioDx	www.cardiodx.com	Palo Alto, CA USA	2004	2
Caris Life Sciences	www.carislifesciences.com	Dallas, TX USA	1996	2
Crescendo Bioscience	www.crescendobio.com	S. San Francisco, CA USA	2002	2
Curidium	www.curidium.com	London, UK	2001	2
DiagnoCure	www.diagnocure.com	Quebec City, Quebec Canada	1994	2
EXACT Sciences Corp	www.exactsciences.com	Madison, WI USA	1995	2
Exagen Diagnostics	www.exagen.com	Albuquerque, NM USA	2002	2
Genomic Health	www.genomichealth.com	Redwood City, CA USA	2000	2
Health Discovery Corp	www.healthdiscoverycorp.com	Savannah, GA USA	2001	2
Incyte	www.incyte.com	Wilmington, DE USA	1991	2
InterGenetics	www.intergenetics.com	Oklahoma City, OK USA	1999	2
Miraculins	www.miraculins.com	Winnipeg, Manitoba Canada	2002	2
Myriad Genetics	www.myriad.com	Salt Lake City, UT USA	1991	2
Nodality	www.nodalityinc.com	S. San Francisco, CA USA	2003	2
Northwest Biotherapeutics	www.nwbio.com	Bethesda, MD USA	1996	2
OncoMethylome Sciences	www.oncomethylome.com	Liege, Belgium	2003	2
Oncothyreon	www.oncothyreon.com	Seattle, WA USA	1985	2
Optherion	www.optherion.com	New Haven, CT USA	2005	2
Orion Genomics	www.oriongenomics.com	St Louis, MO USA	1998	2
Oxford Genome Sciences	www.oxbt.co.uk	Milton, Abingdon UK	2004	2
Panacea Pharmaceuticals	www.panaceapharma.com	Gaithersburg, MD USA	1999	2
Quintiles	www.quintiles.com	Durham, NC USA	1982	2
SensiGen	www.sensigen.com	Ann Arbor, MI USA	2002	2
TcLand Expression	www.tcland-expression.com	Nantes, France	2002	2
Tyrian Diagnostics	www.tyriandx.com	N. Ryde, Sydney Australia	2008	2
Upstream Biosciences	www.upstreambio.com	Vancouver, BC Canada	2004	2
Abano Healthcare	www.abanohealthcare.co.nz	New Zealand	1999	3
Affymetrix	www.affymetrix.com	Santa Clara, CA USA	1992	3
Agilent Technologies	www.agilent.com	Santa Clara, CA USA	1999	3
Althea Technologies	www.altheatech.com	San Diego, CA USA	1998	3
Becton, Dickinson & Co	www.bd.com	Franklin Lakes, NJ USA	1897	3

COMPANY NAME	WEBSITE	LOCATION	FOUNDED	FOCUS
Beckman Coulter	www.beckmancoulter.com	Brea, CA USA	1997	3
Biomarker Technologies	www.advancedbiomarker.com	Knoxville, TN	2006	3
Biomedical Diagnostics	www.bmd-net.com	Marne La Vallee, France	1986	3
Biomerica	www.biomerica.com	Irvine, CA USA	1971	3
BioModa	www.biomoda.com	Albuquerque, NM USA	1990	3
BioStat Solutions	www.biostatsolutions.com	Mt. Airy, MD USA	2001	3
Bruker Daltonics	www.bdal.com	Billerica, MA USA	1980	3
Cepheid	www.cepheid.com	Sunnyvale, CA USA	1996	3
Claros Diagnostics	www.clarosdx.com	Woburn, MA USA	2004	3
Clarient	www.clarientinc.com	Aliso Viejo, CA USA	1993	3
Correlogic Systems	www.correlogic.com	Germantown, MD USA	2000	3
Cylex	www.cylex.net	Columbia, MD USA	1992	3
CytoCore	www.cytocoreinc.com	Chicago, IL	2006	3
deCode Genetics	www.decode.com	Reykjavik, Iceland	2001	3
DiaDexus	www.diadexus.com	S. San Francisco, CA USA	1997	3
DNA Vision	www.dnavision.be	Charleroi, Belgium	2004	3
DRG International	www.drg-international.com	Mountainside, NJ USA	1970	3
EDP Biotech	www.edpbiotech.com	Knoxville, TN	2005	3
Exiqon	www.exiqon.com	Vedbaek, Denmark	1985	3
Expression Analysis	www.expressionanalysis.com	Durham, NC USA	2001	3
Expression Pathology	www.expressionpathology.com	Rockville, MD USA	2001	3
GeneDx	www.genedx.com	Gaithersburg, MD USA	2000	3
Genesis Genomics	www.genesisgenomics.com	Thunder Bay, ON Canada	2001	3
Genomas	www.genomas.net	Hartford, CT USA	2004	3
Genomic Health	www.genomichealth.com	Redwood City, CA USA	2000	3
Genoptix Medical Lab	www.genoptix.com	Carlsbad, CA USA	1999	3
Gen-Probe	www.gen-probe.com	San Diego, CA USA	1983	3
Ikonisys	www.ikonisys.com	New Haven, CT USA	1999	3
Immunomedics	www.immunomedics.com	Morris Plains, NJ USA	1982	3
Interleukin	www.ilgenetics.com	Waltham, MA USA	1986	3
Ipsogen	www.ipsogen.com	Marseille, France	1999	3
LabCorp	www.labcorp.com	Burlington, NC	1971	3
LineaGen	www.lineagen.com	Salt Lake City, UT USA	2002	3
Lipomics Technologies	www.lipomics.com	West Sacramento, CA USA	2003	3
Luminex	www.luminexcorp.com	Austin, TX USA	1995	3
Matritech	www.matritech.com	North America	1987	3
Mitsubishi Kagaku Latron	www.m-kagaku.co.jp	Tokyo, Japan	2003	3
Molecular Image	www.molecularimage.com	Redwood Shores, CA USA	2005	3
MolecularMD	www.molecularmd.com	Portland, OR USA	2005	3
Nanosphere	www.nanosphere.us	Northbrook, IL USA	2000	3
NimbleGen Systems	www.nimblegen.com	Madison, WI USA	1999	3
On-Q-ity	www.on-q-ity.com	Waltham, MA USA	2009	3
Osmetech	www.osmetech.com	London UK	1993	3
ParagonDx	www.paragondx.com	Morrisville, NC USA	2007	3
Parexel	www.parexel.com	Waltham, MA USA	1983	3
Patterson Companies	www.pattersoncompanies	St Paul, MN USA	1877	3
Polymedco	www.polymedco.com	Cortlandt Manor, NY USA	1980	3
Prognomix	www.prognomix.com	Montreal, Quebec Canada	2005	3
Proventys	www.proventys.com	Durham, NC USA	2004	3
Provista Life Sciences	www.provistals.com	Phoenix, AZ USA	2006	3
Quest Diagnositcs	www.questdagnostics.com	Madison, NJ USA	1967	3
Radient Pharma	www.radient-pharma.com	Tustin, CA	1988	3
RedPath Integrated Pathology	www.redpathip.com	Pittsburgh, PA USA	2004	3
Saladax Biomedical	www.saladax.com	Bethlehem, PA USA	2004	3
Sanko Junyaku	www.sank-junyaku.co.jp	Tokyo, Japan	1954	3
Sequenom	www.sequenom.com	San Diego, CA USA	1994	3
Singulex Inc	www.singulex.com	Alameda, CA USA	2003	3
SomaLogic	www.somalogic.com	Boulder, CO USA	2003	3
Source BioScience	www.sourcebioscience.com	Nottingham UK	2007	3
Theranostics Health	www.theranosticshealth.com	Rockville, MD USA	2006	3
Tosoh Biosciences	www.tosohbioscience.com	Tokyo, Japan	1989	3
Transgenomic	www.transgenomic.com	Omaha, NE USA	1997	3
TrimGen	www.trimgen.com	Sparks, MD USA	1999	3
Ventana Medical Systems	www.ventanamed.com	Tuscon, AZ USA	1990	3
Veridex	www.veridex.com	Raritan, NJ USA	2004	3
VitaPath Genetics	www.vpgenetics.com	Foster City, CA USA	2008	3
XDx	www.xdx.com	Brisbane, CA USA	2000	3

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requirements are somewhat different from the FDA in that the former requires that you start with the drug that requires a Companion Diagnostic test rather than with the biomarker which needs to be tested for initially[20].

It is interesting to note that there are now also cross-communication efforts between the FDA, EMEA and Japanese regulatory authorities. This international co-operation has been facilitated through the Critical Path Institute (C-Path). The latter acted as a neutral third party with whom pharmaceutical companies have been willing to share proprietary data. C-Path is a non-profit organisation founded in 2005 out of the University of Arizona and is based in Tucson[21]. The Institute has broad general interest in personalised medicine, but also has specific interests in Companion Diagnostics.

It is imperative that pan-national efforts are made to ensure that regulations are similar for pharmaceutical companies to develop and sell their therapeutic products. In that regard the Companion Diagnostics arena is in a state of flux. The pharmaceutical sector is taking a cautious but embracing approach to Companion Diagnostic adoption. However, new Companion Diagnostic companies are emerging and old, established companies are switching focus to provide the tools, technologies and services needed by pharmaceutical companies to ensure efficient therapeutic drug development and global distribution.

Companion Diagnostic companies

In **Table 3**, we present a list of companies that offer tools, technologies, services and biomarkers in the Companion Diagnostic sector. The list includes the company name, location, year founded, website and primary focus in the Companion Diagnostic arena. The list is broken down into three distinct sections. Those companies listed with a Focus = 1 have Companion Diagnostic markers that have already received regulatory approval and/or are in practical use by their pharmaceutical company partners. Companies listed with a Focus = 2 have announced Companion Diagnostic deals and/or partnerships with a pharmaceutical company. Finally, those companies listed with a Focus = 3 provide some sort of service, tools or technologies to the pharmaceutical sector. As you will note this section is by far the largest with 72 companies listed, and the array of offerings is diverse. For example, Bruker Daltonics provides mass spectrometry equipment and reagents in the form of its ClinProt products that can be used in the discovery stage of Companion Diagnostics, whereas LabCorp and Quest Diagnostics provide lab services for analytical measurements.

In total there are 128 companies listed as providing some sort of Companion Diagnostic products or services. We have attempted to make the list as comprehensive as possible. However, this is such a rapidly expanding space, and companies are moving into this exciting new sector on a daily basis, and this list will continue to expand.

Companion Diagnostic deals

Several themes emerge out of an analysis of recent Companion Diagnostic deals:

1 Oncology is the most active area to attract Companion Diagnostic tests.

2 Pharmaceutical companies are the key drivers in signing Companion Diagnostic deals. Most active pharmaceutical companies have been Roche, Pfizer, Merck, Astra Zeneca, Bristol Myers Squibb, Amgen, Biogen and Eli Lilly.

3 Several niche specialists in the Companion Diagnostic arena have emerged and they include Celera, Dako, DxS and Epigenomics. The major diagnostic companies have for the present not entered this market sector.

This is all summarised in **Table 4** which contains a listing of representative deals in Companion Diagnostics over the past 10 years. The table contains the name of the company providing the Companion Diagnostic marker(s), the pharmaceutical partner, the therapeutic drug or field of use and the year the deal was completed.

Oncology Companion Diagnostics

As noted above much of the activity in Companion Diagnostics has been focused in the area of oncology. A number of Companion Diagnostic markers have been developed for targeted therapeutics such as Herceptin (Genetech), Tarceva (OSI Pharmaceuticals/Genetech), Iressa (Astra Zeneca) and Erbitux (Imclone/Bristol Myers Squibb). More recently the wild type K-ras gene has been identified as a predictor of treatment response to Erbitux as well as Vectibex (Amgen)[20]. In addition there has been considerable activity in the use of Companion Diagnostic markers to predict toxicity, efficacy and drug dosage in order to ensure hitting critical endpoints. As discussed above new therapies need to demonstrate a significant improvement over existing treatments by 'selectively targeting responsive patient populations to enhance efficacy and lower toxicity'[22] in order to overcome those hurdles. One such example in the oncology field is the attempt by Bristol Myers Squibb to gain regulatory approval for its breast cancer drug,

Table 4: Representative Companion Diagnostic deals reported in the past 10 years
[a] Deal done sometime after 2000. [b] Companion Diagnostic apparently developed by in-house efforts

CD COMPANY	PHARMA CLIENT	DRUG OR FIELD OF USE	DATE
Dako	AstraZeneca	Oncology Projects	2010
Monogram Biosciences/LabCorp	GlaxoSmithKline	Tykerb/Tyverb	2010
Qiagen/DxS	Pfizer	PF-04948568	2010
Abbott Labs	GlaxoSmithKline	MAGE-A3	2009
Abbott Labs	Pfizer	PF-02341066	2009
Almac	Lilly	Alimta & Cisplatin	2009
Dako	Genetech/Roche	Herceptin	2009
Monogram Biosciences/LabCorp	GlaxoSmithKline	Ziagen	2009
Qiagen/DxS	BMS/Imclone	Erbitux	2009
Qiagen/DxS	AstraZeneca/Teva	Iressa	2009
Dyax	Biogen	BIIB-O22 & LINGO-1	2004/2009
Abbott Labs	Genentech/Roche	Tarceva	2008
Abbott	OSI/Genetech/Roche	Cancer	2008
Aureon Labs	Pfizer	Prostate Cancer	2008
Celera	Abbott	Undisclosed	2008
Celera	Merck	Cancer	2008
Dako	Genetech	Cancer	2008
bioMerieux	Ipsen SA	Cancer	2007
Celera	Ipsen SA	Short Stature	2007
Celera	Merck	Cancer	2007
Rosetta Genomics	Regulus Therapeutics	Liver Cancer	2006
Tercica	Ipsen SA	Increlex	2006
DxS	Amgen	Vectibix	2005
Clinical Data Inc	Merck	Vilazodone	2004
Epigenomics	Biogen	Cancer	2004
Monogram Biosciences	Pfizer	Selzentry	2002
Source MDx	Pfizer	Cancer & Inflammatory disease	2002
Novartis Molecular Diagnostics	Novartis	Epitol/Tegretol	2000[a]
Novartis Molecular Diagnostics	Novartis	Tasigna	2000[a]
In-house[b]	Cephalon	Trisenox	2000[a]
In-house[b]	BMS	Sprycel	2000[a]

Table 5
Selected examples of Companion Diagnostics used in Cancer therapies. These data are adapted from reference 22

CD FUNCTION	THERAPEUTIC	CANCER TYPE	DIAGNOSTIC TARGET
Efficacy	Herceptin, Tykerb	Breast Cancer	Her2/neu
Efficacy	Tamoxifen, Arimidex, Aromasin, Femara	Breast Cancer	Estrogen/Progesterone Receptors
Efficacy	Tarceva, Iressa	Non-Small Cell Lung Cancer	EGFR
Efficacy	Erbitux	Colorectal Cancer	EGFR
Efficacy	Erbitux, Vectibix	Colorectal Cancer	K-ras
Efficacy	Gleevec	Chronic Myelogenous Leukaemia	Brc-Abl mutations
Efficacy	Gleevec	Gastrointestinal Stromal Tumour	c-Kit
Efficacy	Rituxan	Non-Hodgkin Lymphoma	CD20
Efficacy	Tamoxifen	Breast Cancer	Cytochrome P450
Efficacy	Gemzar	NSCLC, Breast, Ovarian Pancreatic	RRM1
Efficacy	Cisplatin	NSCLC, Colorectal Cancer	ERCC1
Efficacy	Cisplatin	NSCLC, Colorectal Cancer	Thymidylate synthase
Safety	Camptosar	Colorectal Cancer	UGT1A1
Safety	Purinethol	Leukaemia	TPMT
Safety	5-Fluorouracil, Xeloda	Colorectal Cancer	DHPD
Safety	Elitek	Leukaemia, Lymphoma	G6PD

Sprycel (dasatinib). Researchers studied a panel of biomarkers, characterised the ideal responders to the therapy, and are using these data to screen for clinical trial candidates. A list of Companion Diagnostic markers used in conjunction with cancer therapies to determine either efficacy or safety is shown in **Table 5**. These data are adapted from reference 22.

Conclusions

The growth of the Companion Diagnostic sector has been significant in the past several years. This is evidenced by the number of major pharmaceutical companies undertaking deals (**Table 4**) as well as the number of Companion Diagnostic companies (**Table 3**). There appears to be widespread acceptance of the potential value of Companion Diagnostics. The regulatory authorities including the FDA and EMEA are moving down a pathway of accepting and in some cases demanding the use of Companion Diagnostics in conjunction with a specific therapeutic drug. Based on the current optimism is it possible that Companion Diagnostics affords part of the panacea needed to produce cheaper, safer more efficacious drugs?

The field is too nascent for any realistic determination of the impact of Companion Diagnostics on the DDD process and product launch success. The many stakeholders appear to have common goals but all speak very different languages. They all have different expectations and are driven by very different goals and needs. This raises some cause

for concern, but as discussed above, provided there are lines of communication established and willingness for stakeholder groups to educate each other this may not create insurmountable hurdles. Time will tell.

In this article we have attempted to provide an overview of the Companion Diagnostic sector. We have provided detail on the pharmaceutical and Companion Diagnostic companies as well as introduced the key stakeholders. In the subsequent article we will discuss in more detail the difficulties of constructing Companion Diagnostic-pharma business deals as well as the regulatory issues that are looming on the near horizon.

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