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Healthcare & Life Sciences

Vital Signs

Strategic Insights for Healthcare Executives

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This Week's Industry Focus:

Drug Discovery Technologies & Clinical Diagnostics

Stratified Medicine: Elements and Implementation

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The transformation of medicine from an art to becoming a science is certainly driven by technology innovation and our ever increasing information processing capabilities. One of the most dramatic shifts in medical outlook that has begun to impact therapeutic strategies has been the movement of medicine to a stratified targeted practice model. The recent buzz around "Stratified Medicine" is timely as it coincides with the predicted erosion of the blockbuster model in the pharmaceutical industry. Biomarkers form the basis for pursuing stratified medicine. While biomarkers have been used for many years in multiple contexts for diagnosing disease, they have only recently been employed to classify patient populations for clinical trials or therapeutic intervention.

Biomarker Discovery and Development

Biomarker discovery and development has become an active area of growth in past three to four years. In its infancy, biomarker discovery and development was the preserve of academia and a few select cutting edge biotechnology and pharmaceutical companies that had a very strong R&D focus. However, during the period from 2003 to present, and more so beginning in 2005, there has been a burst of companies and boutique R&D shops pursuing the discovery and development of biomarkers. This demand came from the major shift in attitude of the large drug developers (Big Pharma). The time tested methods of one target-one drug has given way to a pathway focused approach for many diseases. This approach of targeting pathways in disease states as opposed to a single molecular target is extremely relevant and necessary when battling diseases such as cancer.

In the field of oncology, a tumor can result from errors in regulation of cell proliferation at multiple check points in a cell's cycle with origins in mutations or overexpression/underexpression of multiple genes and proteins in myriad pathways. The complex interplay of the intracellular and intercellular communication networks and gene regulation circuits is very tightly monitored and orchestrated. However, due to genetic abnormalities or external and environmental factors, errors can creep into the system resulting in the loss of control over cell proliferation leading to cancer. The errors can occur at multiple levels in the control mechanisms as well as at various nodes in the pathways, thus making cancer a very complex disease and its

therapy an even more challenging pursuit. Accordingly, it is no surprise that most current advances in stratified medicine have been in the field of oncology therapeutics with Genentech's drug Herceptin (trastuzumab) being the first approved stratified therapeutic and Dako's HER2 test being the pioneering test in stratifying patients for such selective targeted therapy. There have been several other such tests in development and many biomarkers have since been identified that can characterize populations for therapeutic strategies based on individual differences.

Below is a listing of valid genomic biomarkers in the context of approved drugs obtained from the FDA's Center for Drug Evaluation and Research (CDER) website on genomics:

(http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm)

	Biomarker	Drug
1	(CCR5 -Chemokine C-C motif receptor)	Maraviroc
2	(EGFR expression with alternate Context)	Cetuximab
3	(Her2/neu Over-expression)	Trastuzumab
4	Philadelphia Chromosome	Dasatinib
5	CYP2C9 Variants	Warfarin
6	LDL Receptor Mutations/ expression	Atorvastatin
7	G6PD Deficiency	Rasburicase
8	HLA-B*1502 allele presence	Carbamazepine
9	HLA-B*5701 allele presence	Abacavir
10	Protein C deficiencies	Warfarin
11	TPMT Variants	Azathioprine
12	UGT1A1 Variants	Irinotecan
13	UCD	Valproic acid
14	VKORC1) Variants	Warfarin
15	CYP2D6 Variants	Atomoxetine
16	CYP2D6 with alternate Context	Fluoxetine HCL
17	Deletion of Chromosome 5q(del(5q))	Lenalidomide
18	DPD Deficiency	Capecitabine
19	EGFR expression	Erlotinib
20	(NAT) Variants	Rifampin
21	Philadelphia Chromosome-positive responders	Busulfan
22	PML/RAR alpha gene expression	Tretinoin
23	CYP2C9 Variants	Celecoxib
24	CYP2C19 Variants	Voriconazole
25	C-KIT expression	Imatinib mesylate
24	UGT1A1 variants with alternate context	Nilotinib

Development of Companion Diagnostics

The mere discovery of a biomarker is not sufficient for the development of a companion diagnostic test. Multiple factors must be considered for an assay to be developed. Primarily, characterization and qualification of the biomarker is extremely important. Biomarkers can be transient and can be expressed or silent depending on the stage of disease as well as the unique mechanism or pathway of disease development. The crux is to link a particular disease state to a reliable biomarker and follow the course of disease employing one or multiple biomarkers. For a candidate biomarker to evolve into a marketable companion diagnostic, it has to go through multiple steps through an average three-to-four year development timeline.

Generating a working hypothesis around a new biomarker identified in a particular disease pathway or phenotype requires a strong clinical rationale. Initially multiple biomarkers might be identified, many of which might be coincidental with the pathology and not as much as a hallmark indication or a candidate biomarker. Once the false positives have been weeded out, the biomarker of choice is selected for further prototype assay development. This is followed by a clinical validation of the assay employing an easily adaptable technology platform on which the assay is developed. The aim here is not for commercial viability but to demonstrate very high clinical relevance for the biomarker. Once the prototype has been successfully tested, a change of technology platform may be essential to best meet the market standards and needs for the commercialization of the companion diagnostic assay.

Clinical Validation and Assay Development

The assay can then be offered as a CLIA approved assay from a commercial lab or can be further refined to go through the FDA process for PMA/510K clearance to get classified as an in-vitro diagnostic assay (IVD). Although the FDA route is a more time and cost intensive proposition, for the implementation of a global companion diagnostic strategy, it is advisable to initiate FDA review while the initial assay is rolled out from a CLIA approved facility. Regulatory approval of a companion diagnostic test alone does not guarantee market success. The companion diagnostic has to be distributed through an appropriate channel and revenue sharing agreements have to be in place if the drug and diagnostic are developed by different entities.

Risks in the Development of Companion Diagnostics

There are multiple risks involved in the co-development of a drug and diagnostic. Some of these risks are of a scientific and clinical nature while others stem from the business models and means of collaboration. The most significant scientific and clinical risks stem from the possibility of a drug's harmful side effects and, as a result, the suspension of drug development during early stage clinical trials. Business risks, on the other hand, can be associated with the external cooperation model. This model involves arm's length market transactions for managing the close cooperation and synchronization required during the co-development of a drug and diagnostic. On the other hand, the internal development model circumvents risks associated with

arm's length market transactions. However, the internal model can suffer from lack of efficiency along the development path. Moreover, when acquisition strategies are developed, it is critical to maintain a constant focus on the ROI and integration mechanisms.

Economic Value in Stratified Medicine

The further growth of "stratified medicine" will depend on the value generation potential of this model for multiple stakeholders in this paradigm shift. Most importantly, we can identify the pharma/biotech companies, the insurance providers or payers, healthcare providers, and the diagnostic companies as the four quadrants at the base of this pyramid with the patient groups at the apex of the pyramid. The advent of stratified medicine is a result of delivering patient satisfaction and has a scientific basis for its development. The development of this field will depend on how strongly the scientific basis can be supported by an economic rationale. Rapidly expiring patents and a steady decline of the blockbuster drug model has resulted in some very significant M&A bids. Prime amongst such bids include the recent successful bid made by Pfizer for Wyeth as well as the ongoing discussions of Roche taking full control of Genentech. While the context for both these deals may be different, there is no denying that pipeline strengths and FDA approvals for new drugs has considerably decreased over the last ten years. Stratified medicine can help remedy some of these trends by spurring the growth of more targeted drugs as well as more potent and effective candidate molecules. The biomarkers can help make the clinical trials process more efficient and cost effective, thereby reducing the cost of developing a drug from the present $1.2 Billion to about $850 million. Such a cost structure can then be seen to justify sub-blockbuster levels of revenues from drugs, while their increased patent lives compensating partially for the loss of revenue. This together with the "value addition" of having a companion diagnostic test on the market for large number of drugs significantly increases the market size and growth potential for the pharma/biotech industry.

Company Spotlight: PGx HEALTH, Inc.

Clinical Data Inc (NASDAQ: CLDA) is a publicly traded multinational biotechnology company. It is structured into two divisions, namely the PGxHealth™ and Cogenics™ divisions. While Cogenics™ is focused on the genomics services segment, PGxHealth™ specializes in biomarker discovery and development leading to the development of pharmacogenomics tests. Thus PGxHealth™ aims to further stratified medicine therapeutics and companion diagnostics.

PGx HEALTH™ A DIVISION OF CLINICAL DATA

PGx Health is a division of Clinical Data Inc. committed to leveraging its extensive knowledgebase and IP portfolio in the pharmacogenomics (PGx™) space via identification and validation of genetic biomarkers, to develop and market effective companion diagnostic tests for therapeutic selection and adverse effects determination. PGxHealth builds its biomarker portfolio via both in-house R&D as well as a long term in-licensing strategy. Taking advantage of the recent strides made in the fields of biomarker discovery and development, pharmacogenomics, laboratory practices, and the stratified medicine revolution, have established a strong foundation for PGxHealth™'s brand of Therapeutic Diagnostics™. The ultimate goal of PGxHealth is to serve patients through its diverse array of genetic tests that would aid in treatment selection based on the molecular basis of disease while taking into consideration the individual genetic makeup of the patient population.

Stratified Medicine Solutions

The core focus areas for PGx™ are CNS, cardiovascular, and oncology. PGxHealth™'s products on market include the PGxPredict™: RITUXIMAB Test, the PGxPredict™: WARFARIN test, the PGxPredict™: CLOZAPINE test, and the FAMILION test for inherited cardiac disease.

Noteworthy milestones

2009: Clinical Data, Inc. signs contract with Blue Cross and Blue Shield Association for National Access to FAMILION(R) genetic tests for inherited cardiac syndromes

2008: Clinical Data launches genetic test for arrhythmogenic right ventricular cardiomyopathy (ARVC)

2008: Clinical Data, Inc. announces acquisition of Avalon Pharmaceuticals

2008: PGxHealth launches genetic test for HCM

2008: Clinical Data nets $19.5 million cash from the sale of Vital Scientific

2007: Clinical Data Launches PGxPredict™: RITUXIMAB on Schedule

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Reimbursement & Regulatory News

Date	Company	Product Name	Function	Designation
23-Feb	**Neuisys (Greensboro, NC)**	NeuViz 16 Multi-Slice CT System	The NeuViz 16 provides clinical applications including CT angiography of peripheral and neuro vasculature, virtual colonoscopy, lung nodule protocols, pulmonary embolism protocols, CT urography, and tissue perfusion studies. Product developed was carried out jointly by Philips Neusoft Medical Systems, a joint venture between Royal Philips Electronics of the Netherlands and Neusoft Corporation of China.	FDA approval
23-Feb	**Oridion Systems Ltd. (Jerusalem, Israel)**	Capnostream™20 Monitor with Integrated Pulmonary Index™	Technology for ventilatory status monitoring of patients. The Integrated Pulmonary Index™ utilizes sophisticated algorithms to integrate the real time measures and interactions of four parameters - end tidal CO2 (EtCO2), respiration rate, pulse rate and SpO2 (oxygen saturation) into a single index value. The result is displayed on a scale from 1-10, where 10 indicates optimal pulmonary status.	510(k) clearance
25-Feb	**Serica Technologies, Inc. (Medfor, MA)**	SeriScaffold™ Technology for Soft Tissue Repair	The SeriScaffold technology is developed on silk-based biomaterial platforms for tissue regeneration. The long term bioresorbable scaffold technology has applications in tissue repair and wound healing.	510(k) clearance
26-Feb	**Biomerix Corporation , (Fremont, CA)**	REVIVE™ for Use in Soft Tissue Repair Procedures	REVIVE acts as a tissue scaffold facilitating rapid tissue ingrowth and can be utilized in a variety of soft tissue repair procedures, including the repair of inguinal hernias.	510(k) clearance
26-Feb	**Sanofi-Aventis (Paris, France)**	Apidra®SoloSTAR®	Apidra®SoloSTAR® is a pre-filled disposable pen containing rapid-acting insulin analog Apidra(R), for adults and children with type 1/2 diabetes.	FDA approval
27-Feb	**Cantel Medical Corp. (Little Falls, NJ)**	Advantage(TM) Plus Endoscope Reprocessing System	Endoscopinc investigation at GI centers.	510(k) clearance
27-Feb	**Derma Sciences, Inc. (Princeton, NJ)**	BIOGUARD™ Barrier Dressing with NIMBUS® Technology	Treatment of wound care and prevention of MRSA and other bacterial infections.	FDA approval

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The Healthcare Group

The Frost & Sullivan Healthcare Group specializes in closely monitoring the healthcare marketplace to provide critical information, opportunities, and strategic recommendations for market participants. Our global team of highly skilled industry analysts and consultants are educated and experienced in a variety of healthcare market sectors, and maintain well-developed, long-standing relationships with key industry participants. Leveraging these assets, the team provides clients with comprehensive industry knowledge, including detailed coverage of market, technology, economic, and customer-focused trends and forecasts.

The Frost & Sullivan Healthcare team offers extensive coverage of the following markets and sectors:

Drug Discovery
- Proteomics
- Protein Markets
- DNA & Protein Microarrays
- Research Consumables
- High Throughput Screening
- Bioinformatics
- SNP
- Pharmacogenomics
- Mass Spectrometry
- Gel Electrophoresis
- Laboratory Information Systems

Medical Devices
- Cardiovascular Devices
- Orthopedic Devices
- Home Care
- Surgical and Infection Control Products
- General Medical Devices
- Hospital Supplies and Products
- Wound Care/ Management Products

Clinical Diagnostics
- Molecular Diagnostics
- Immuno-chemistry
- Point-of-Care
- Cell Culture
- In Vitro Diagnostics
- Genetic Testing
- Infectious Disease Diagnostics
- Cancer Diagnostics

Medical Imaging
- Core Imaging Modalities
- Imaging Agents
- Imaging Software
- PACS & Imaging IT
- Digital Imaging

Pharmaceuticals & Biotechnology
- Biopharmaceuticals
- Contract Research & Manufacturing
- Specialty Pharmaceuticals
- Drug Delivery
- Vaccines

Patient Monitoring
- Cardiac Monitoring
- External Defibrillators
- Multi-Parameter Monitoring
- Glucose Monitoring
- Blood Pressure Monitoring
- Temperature Monitoring
- Pulse Oximetry
- Remote Patient Monitoring
- Patient Monitoring IT
- Sleep Apnea Monitoring

Healthcare & Life Sciences IT
- Electronic medical records
- Data and storage management
- Emerging wireless technologies
- Acute Care Information Systems
- CPOE
- Enterprise clinical information systems
- Claims management through IT
- RFID in Healthcare
- RHIOs

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