

COMPANION DIAGNOSTICS IN PERSONALIZED MEDICINE AND CANCER THERAPY *(SAMPLE COPY, NOT FOR RESALE)*

Trends, Industry Participants, Product Overviews and Market Drivers

TABLE OF CONTENTS

1	Overview	7
1.1	Statement of Report	7
1.2	About This Report	7
1.3	Scope of the Report	7
1.4	Objectives	8
1.5	Methodology	9
1.6	Executive Summary	10
2	Companion Diagnostics and Personalized Medicine	14
2.1	Scope of this Section	14
2.2	Introduction to Companion Diagnostics and Personalized Medicine	14
2.3	Drug Metabolism and Companion Diagnostics and Personalized Medicine	18
2.4	Examples of Personalized Medicine and Companion Diagnostic Tests	22
2.5	Personalized Medicine and Companion Diagnostic Testing Product Pipeline	25
2.6	The Personalized Medicine Coalition (PMC)	27
2.7	Regulatory Trends and Guidelines in the Personalized Medicine Space	29
2.7.1	The Changing Regulatory Landscape for Personalized Medicine	30
2.8	Companion Diagnostics Play an Increasing Role in Cancer Care	32
2.9	Specific Examples of Clinical Situations Where Companion Diagnostics Are Being Deployed	32
2.9.1	Epidermal Growth Factor Receptor (EGFR) Assay	33
2.9.2	Individualized Warfarin Therapy	35
2.9.3	UGT1A1 Molecular Assay for Camptosar	36
2.9.4	Response to Gleevec in GIST	36
2.9.5	LabCorp, ARCA Personalized Medicine Deal for Cardiovascular Diseases	36
2.9.6	Osmetech Licenses Epidauros Biotechnologie AG CYP2D6 Biomarker to Enter Companion Diagnostics	36
2.10	Diagnostic Tests for Personalized Analysis of Cancer Therapy Effectiveness	37
3	Companion Diagnostics: Qualitative and Quantitative Market Analysis	38
3.1	Market Analysis of Molecular Diagnostics and Companion Diagnostics	38
3.2	Costs of Companion Diagnostics in Healthcare Expenditures	39
3.3	Molecular Diagnostic Market	40
3.4	Molecular Diagnostics Technology Platforms and Their Impact on Clinical Medicine	42
3.5	Snapshot of Companion Diagnostics Industry Structure	44
3.6	The Case for Theranostics	45
3.7	Companion Diagnostics Market Analysis—Market Survey Data Characterizing the Qualitative and Quantitative Industry Parameters	46
4	Trends and Overview	49
4.1	Companion Diagnostics: Industry SWOT Analysis	49
4.2	Macro Trends in Companion Diagnostics	49
4.3	Challenges for Companion Diagnostics Development	52
4.4	Timeline for Impact of Various Segments in Companion Diagnostics	53
4.5	Use of Proteomics to Develop Individualized Tests	55
4.6	The Market Problem: Finding Value with Diagnostics for Personalized Medicine	56
5	Biomarker Tests Co-developed with Cancer Therapeutics as Companion Diagnostics	58
5.1	Sector Overview	58
5.1.1	Impact of New Technology Platforms	58
5.1.2	Impact on Drug Discovery	59
5.1.3	Biomarkers as Endpoints in Drug Discovery	59
5.1.4	Targeted Therapy	61
5.2	Companion Diagnostics on the Market	62
5.3	Epidermal Growth Factor Receptor Companions	62
5.3.1	Bevacizumab (Avastin)	63

5.3.2	EGFR for Colorectal Cancer and Camptosar (Irinotecan)	64
5.3.3	EGFR Express and Erbitux (Cetuximab)	64
5.3.4	HER2 and Heceptin (Trastuzumab)	65
5.3.5	Irressa and Tarceva Companion Test	67
5.3.6	Tykerb (GSK), and Vectibix™ (Amgen) Companion Tests	67
5.3.7	EGFRx Assay	68
5.3.8	Monogram eTag	69
5.3.9	Veripath OncoDiagnostics EGFR PharmDX	69
5.4	Myriad's TheraGuide 5-FU	69
5.5	Companions for Tyrosine Kinase Inhibitors: Erlotinib and Gefitinib	70
5.5.1	TheraScreen: EGFR29	70
5.5.2	The K-RAS Mutation Detection Kit	70
5.6	Irinotecan and UGT1A1	70
5.7	Gleevec (Imatinib) Companions	70
5.7.1	DakoCytomation's c-Kit (9.7) pharmDx	71
5.8	Companion Diagnostics Involving Metabolizing Enzymes	71
5.8.1	Companions for TMPT, CYP2C9, and UGT1A1 Enzymes	71
5.8.2	Companions for Aromatase Inhibitors	72
5.8.3	Companions for Actos and Avandia	72
5.9	Drivers and Barriers to Companion Diagnostics	73
5.10	Partnerships with Pharma Companies to Identify Therapeutic Targets	73
5.11	Circulating Tumor Cell Assay: Prognostic and Predictive Factors for Breast Cancer	74
5.12	Companion Diagnostics Used by Clinical Service Laboratories	74
5.13	New Technologies and Products under Development	75
5.13.1	OncoMethylome	75
5.14	Blood-Based Technologies	77
5.14.1	Oncotech	77
5.15	Monogram Biosciences HIV Personalized Platform	78
5.16	Wako LBA/AFP Test for Liver Cancer	78
5.17	Future Developments for Companion Diagnostics	78
6	Business and Regulatory Trends in the Companion Biomarker Testing Sector	80
6.1	Industry Consolidation	80
6.2	Breath of Product Offering and Pricing	81
6.3	Government Regulation of Medical Devices	81
6.3.1	FDA Guidance on Drug Test Co-development	83
6.3.2	Device Classes	83
6.3.3	Investigational Use of IVDM Assays	83
6.3.4	Post-market Requirements	84
6.4	Strategic Business and Marketing Considerations	85
6.5	Commercial Opportunities in Companion Markers	86
6.6	Moderators of Growth	87
6.6.1	Roadblocks to Integrating Companion Biomarkers into Clinical Practice	87
6.6.2	Management of Targeted Therapeutics by Third-Party Payers	88
6.7	Biotechnology Industry Trends	88
6.8	Pharmaceutical Industry Trends	88
6.9	Acquisition, License Agreement, Partnerships	89
6.10	Legal Developments	92
6.11	Sales and Marketing Strategies for Tumor Marker Tests	93
6.11.1	International Markets	95
6.12	Product Commercialization	97
6.13	Reimbursement	97
6.14	Self-Referral Rules	98
6.15	Health Insurance Portability and Accountability Act	99
6.16	Clinical Laboratory Improvement Amendments (CLIA)	100
6.17	In Vitro Diagnostic Directive (IVDD) and Medical Device Regulations	100

6.18	FDA's Quality System Regulation (QSR)	101
6.19	FDA'S OIVD on IVDMIAs	102
6.20	FDA's Qualification of Cancer Biomarkers	103
6.20.1	Regulatory Perspectives of Biomarker Validation	103
6.21	Genetic Tests and Medical Records	103
6.21.1	Laws against Genetic Discrimination	104
6.22	Medicare Reimbursement	104
6.22.1	Medicare Part B Spending Trends	104
6.23	Global Drivers of Clinical Laboratory Testing	106
6.24	Global Outlook	107
6.25	Oncology Biomarker Qualification Initiative	108
6.26	FDA Critical Path	109
6.27	Biomarkers and FDA's Voluntary Genomic Data Submission	109
6.28	From Personalized to Predictive Medicine	109
6.29	Analysis of Cost-Effectiveness at the Individual Level	109
6.30	The Patient and Advocate Perspective: An Evolution of Influence	109
6.31	Real-World Experiences Translating the Vision of Personalized Medicine into Practice	109
7	Companies Entering the Companion Diagnostics Market	111
7.1	Industry Overview	111
7.2	Representative Companion Diagnostic Development Companies	111
7.2.1	20/20 GeneSystems	113
7.2.2	Abbott Diagnostics	113
7.2.3	Affymetrix	115
7.2.4	Agendia BV	117
7.2.5	Agensys	118
7.2.6	Almac Group	118
7.2.7	AMDL	118
7.2.8	Arcturus Bioscience	120
7.2.9	Aureon Biosciences	120
7.2.10	Beckman Coulter	121
7.2.11	Biocode S.A.	122
7.2.12	BioCurex	122
7.2.13	Biomarker Technologies	123
7.2.14	Biomedical Diagnostics	123
7.2.15	Biomerica	123
7.2.16	bioMérieux	124
7.2.17	Biomira	124
7.2.18	BioModa	125
7.2.19	Bruker Daltonics	125
7.2.20	Byk Gulden	126
7.2.21	Cangen Biotechnologies	126
7.2.22	Caprion Proteomics	127
7.2.23	Celera Diagnostics	127
7.2.24	Cepheid	128
7.2.25	Claros Diagnostics	129
7.2.26	Clinical Data: PGxHealth and Cogenics	129
7.2.27	Ciphergen Biosystems	131
7.2.28	Clariant	132
7.2.29	Correlogic Systems	133
7.2.30	Cytogen	133
7.2.31	Cytc Corporation	136
7.2.32	Dako	136
7.2.33	DiaDexus LLC	137
7.2.34	Digene Corporation	138
7.2.35	DiagnoCure	138

7.2.36	Diagnostic Systems Laboratories	139
7.2.37	DRG International	139
7.2.38	DxS	140
7.2.39	EDP Biotech	141
7.2.40	Epigenomics	142
7.2.41	Exact Sciences Corporation	142
7.2.42	Exagen Diagnostics	143
7.2.43	Gene Logic	144
7.2.44	Genesis Genomics	144
7.2.45	Genomic Health	145
7.2.46	Gen-Probe	145
7.2.47	Health Discovery Corporation	146
7.2.48	Ikonisys	146
7.2.49	Immunicon	147
7.2.50	Immunomedics	150
7.2.51	Incyte Pharmaceuticals	151
7.2.52	InterGenetics	152
7.2.53	Ipsogen	152
7.2.54	LabCorp	152
7.2.55	Matritech	153
7.2.56	Miraculins	156
7.2.57	Mitsubishi Kagaku Medical	156
7.2.58	Molecular Diagnostics (CytoCore)	156
7.2.59	Monogram Biosciences	157
7.2.60	Myriad Genetics	157
7.2.61	NimbleGen Systems	161
7.2.62	Northwest Biotherapeutics	161
7.2.63	Oncotech	162
7.2.64	Orion Genomics	163
7.2.65	Oxford Genome Sciences	163
7.2.66	Panacea Pharmaceuticals	164
7.2.67	Perlegen Sciences	164
7.2.68	Polymedco	164
7.2.69	Power3 Medical Products	165
7.2.70	Prometheus	165
7.2.71	Proteome Systems	165
7.2.72	Qiagen	166
7.2.73	Sanko Junyaku	167
7.2.74	SensiGen	167
7.2.75	SuperArray Bioscience	167
7.2.76	Third Wave Technologies	167
7.2.77	Tosoh Medics	168
7.2.78	TrimGen	168
7.2.79	TriPath Imaging	168
7.2.80	Upstream Biosciences	170
7.2.81	Ventana Medical Systems	170
7.2.82	Veridex	171

Appendix 1: FDA Guidance for Industry: Pharmacogenomic Data Submission (March 2005)	173
Appendix 2: Histochemical Markers for Cancer	185

LIST OF TABLES

Table 2.1: Timeline for Development of Companion Diagnostics	15
Table 2.2: Personalized Medicine at the Nexus Point	16

Table 2.3: Percentage of Non-Responders in Various Drug Classes	17
Table 2.4: High-Profile Drug Withdrawals from the Marketplace	17
Table 2.5: Metabolism of Drugs by Hepatic Enzymes	19
Table 2.6: Drug Metabolism Drives Drug Efficacy/Toxicity	22
Table 2.7: Population Frequency of the Various Cytochromes	22
Table 2.8: Selected List of Personalized Medicine Tests	24
Table 2.9: Personalized Medicine Product Pipeline	26
Table 2.10: Marketed Personalized Therapies in 2006	27
Table 2.11: Typical Response Rates in Therapeutic Areas	33
Table 2.12: Prevalence of People Taking Medications Metabolized by Liver Enzymes	34
Table 2.13: UGT1A1 Helps to Determine Risks Associated with Irinotecan	34
Table 2.14: Current Product Labels: Enzyme Metabolism	35
Table 3.1: Timeline for Impact of Various Molecular Diagnostics Technologies on Personalized Medicine	43
Table 3.2: Impact of Molecular Diagnostics Technologies on Therapeutic Areas in Personalized Medicine	43
Table 3.3: Challenges of Various Molecular Diagnostics Technology Platforms in Personalized Medicine	44
Table 3.4: FDA Classification of Diagnostics by Risk	46
Table 4.1: Personalized Medicine Industry SWOT Analysis	49
Table 4.2: Market Opportunities in Personalized Medicine	51
Table 4.3: Challenges for Market Adoption of Various Personalized Medicine Tests	52
Table 4.4: Hurdles to Personalized Medicine and Companion Diagnostics Development	53
Table 4.5: Timeline of Impact in Areas of Personalized Medicine	54
Table 4.6: Impact of Personalized Medicine on Various Therapeutic Areas	55
Table 5.1: Potential Benefits of Biomarkers as Companion Diagnostics	60
Table 5.2: Utility of Biomarker as Companion Diagnostics to Drug Development	61
Table 5.3: ASCO-CAP Guidelines for HER2 Testing in Breast Cancer: How to Interpret Test Results	65
Table 5.4: Device Submission Elements for the FDA	73
Table 6.1: List and Discounted Prices for Abbott Tumor Marker Tests	81
Table 6.2: Medicare Spending on Clinical Lab Services, 1996 to 2005	105
Table 6.3: Hospital Laboratory Share of Part B Medicare Spending, 1996 to 2005	106
Table 6.4: Medicare Part B Lab Spending Per Medicare Enrollee, 1998 to 2005	106
Table 6.5: Summary of Biomarker Use in the Commercialization of Novel Oncology Pharmacotherapeutics	110
Table 6.6: Pharmacoeconomic Challenges to the Implementation of Biomarkers as Companion Diagnostic Tests	110
Table 7.1: Major Players in Companion Diagnostic Sector	111
Table 7.2: Tumor Diagnosis Immunoassay	140
Table 7.3: Tumor Diagnosis Radioimmunoassay	140
Table 7.4: Summary of Matritech's Product Development Programs	155

LIST OF FIGURES

Figure 2.1: Personalizing Drug Treatment	14
Figure 2.2: Approaches to Personalized Medicine	15
Figure 2.3: The Phase I and II Processes of Drug Metabolism	18
Figure 2.4: Hepatic Distribution of Human CYP450	19
Figure 2.5: Relative Contribution of CYP450 Enzymes to Drug Metabolism	20
Figure 2.6: Genetic Components Determine Drug Metabolism	20
Figure 2.7: Personalized Medicine Drugs in Development	25
Figure 3.1: From Genetic Content to Personalized Medicine	39
Figure 3.2: Impact of Diagnostic Testing on Healthcare Decision Making	39
Figure 3.3: Impact of Diagnostic Testing on Healthcare Spending	40
Figure 3.4: Breakout of the Molecular Diagnostics Marketplace by Country	40
Figure 3.5: Breakout of the Molecular Diagnostics Marketplace by Vendor	41
Figure 3.6: Molecular Diagnostics Market Segmentation	42
Figure 3.7: Molecular Diagnostics Market Segmentation by Technology	42
Figure 3.8: Market Survey Respondent Demographics	46
Figure 3.9: Breakout of the Respondent Pool by Affiliation	47

Figure 3.10: Segmentation of the Personalized Medicine Market	47
Figure 4.1: Personalized Medicine Market Drivers	50
Figure 4.2: Challenges in the Personalized Medicine Space	50
Figure 5.1: Carcinogenesis Is a Multi-Step Process	59
Figure 5.2: ASCO-CAP Guidelines for HER2 Testing in Breast Cancer: Equivocal Results with IHC	66
Figure 5.3: ASCO-CAP Guidelines for HER2 Testing in Breast Cancer: Results by FISH	66
Figure 5.4: MGMT Methylation Status Correlates to Survival Rate	76
Figure 6.1: Part B Spending on Clinical Lab Services, 1991 to 2005	105

SAMPLE

1 Overview

1.1 Statement of Report

The purpose of this report is to describe the specific segment of the diagnostics market that develops new technology platforms for evaluating the metabolism of therapeutic agents, or for evaluating which therapeutic regimes are most effective for a particular type of disease. The term *companion diagnostic* means that the particular diagnostic test under evaluation is specifically linked to a known therapeutic drug. This linkage could be important in the therapeutic application and clinical outcome of a drug (personalized medicine), or an important component of the drug development process. This report focuses on the former linkage, *i.e.*, the use of companion diagnostic tests in personalized medicine.

This review will provide an in-depth discussion and analysis of the application of biomarkers in targeted therapeutics, their predication response and efficacy, as well as their use in treating patients and selecting more efficacious medications. This summary emphasizes new and developing technology platforms meant to aid drug treatment of patients.

1.2 About This Report

The report describes new technology platforms developed for the analyses of constituents of blood, plasma, serum or tissue that are connected to the effectiveness of therapeutic agents in a clinical setting. This study tends to emphasize smaller biotech companies who have new products and procedures in this sector. Research companies in the process of developing new ideas are not reviewed in any detail here. The main objectives of this analysis are to:

- Identify viable technology drivers for companion diagnostic tests through a comprehensive look at platform technologies for *in vitro* diagnostics that are used to monitor the absorption, metabolism and efficacy of therapeutic drugs in individual patients.
- Provide a complete understanding of the new companion biomarker diagnostics tests—*i.e.*, predictive, screening, prognostic, monitoring, pharmacogenomic and theranostic—from their basic principles to their applications.
- Discover growing market opportunities in companion diagnostics by identifying high-growth applications in different diagnostic areas, focusing on the biggest and expanding markets in oncology (*e.g.*, biomarkers for cancer and predictive biomarkers).
- Focus on global industry development of companion diagnostic tests through an in-depth analysis of the major world markets for companion diagnostics, including growth forecasts.

1.3 Scope of the Report

This report differs from TriMark Publications' *Personalized Medicine* report in that it emphasizes diagnostic tests that are directly linked in their usage to specific therapeutic agents. Other tests like the IVDMA tests are inestimably characterized as personalized medicine tests because they determine a patient's sensitivity or susceptibility to various disease states. However, they are not strictly classified as companion diagnostic tests because they are not directly linked to a therapeutic agent, neither as a selection algorithm, nor as a guide to dosing regimes.

This analysis emphasizes companies that are actively developing and marketing new reagents and supplies for performing companion biomarker diagnostics tests in the clinical setting on patients undergoing administration of FDA-approved drugs. It discusses the various market trends and opportunities using new biomarkers, while providing an in-depth analysis of market share, revenue forecasts, market drivers and market restraints. The comprehensive focus of the study, backed by strategic recommendations, enables companies to position their growth strategies to benefit from the changing market conditions and obtain maximum return on investment.

The reader should consult other TriMark Publications reports at www.trimarkpublications.com for detailed discussions of important individual market segments related to the companion diagnostics market, such as clinical chemistry testing, high-growth diagnostic test markets, blood gas and electrolytes, over-the-counter diagnostic testing markets, and point of care testing. TriMark provides a separate market report titled *DNA Sequencing and PCR Markets*, which emphasizes the analytical methods and PCR technology platforms used in companion diagnostics. TriMark also publishes a separate report on routine clinical tumor markers in current use and their markets: *Cancer Diagnostic Testing World Markets*.

The biotech sector developing new companion biomarkers is the focus of this examination. But attention is paid to the hospital market segment, and separately, to the instruments, reagents and supplies marketed by major companies in this segment. Market size, growth rates and market components for instruments, reagents, controls and consumables used in this area are also analyzed.

Specialty companion diagnostics testing such as pathology screening methods and special tissue stains to examine companion cells *in situ* are mentioned, since they are often part of the overall analytical focus of companies that market companion technology platforms. However, no effort is made to quantify this older and broader market. These subjects are discussed in other TriMark Publications reports.

An analysis of business trends, technology trends and developing areas of companion diagnostics testing using new biomarkers is provided, along with a brief review of the routine market for clinical companion diagnostics testing equipment and supplies in the clinical hospital market, using screening reagents and instruments for analysis of individual components in blood, serum or plasma. This study defines U.S. and global market dollar sales volume and analyzes factors that influence the size and growth of market segments. Activity and trends in hospital markets, including the numbers of institutions that use companion diagnostics testing and the factors that influence purchasing, are addressed in this report.

This review surveys biotech companies known for marketing, manufacturing or developing instruments and reagents for the clinical companion diagnostics market, both in the U.S. and the world. Leading companies are discussed in-depth, with sections on the companies' histories, product lines, business and marketing analyses, and subjective commentary on the companies' market positions.

Several subjects related to the major elements of companion diagnostics testing, such as clinical chemical testing instruments, are discussed only briefly in this report because they are considered separate fields or markets. Fuller explorations of these areas of interest can be found in other TriMark Publications reports, such as *Clinical Chemistry Analyzers* and *Point of Care Diagnostic Testing World Markets*.

1.4 Objectives

The goal of this examination is to review the market for new companion biomarker testing equipment and supplies using reagents and instruments for analysis of individual components in blood, serum or plasma from patients, which depend on the breaking developments in the genomic and proteomic spaces.

The analysis defines the dollar volume of sales, both worldwide and in the U.S., and analyzes the factors that influence the size and the growth of the market segments. Also examined are the subsections of each market segment where diagnostic tests are performed, including the physician office labs, hospital labs and commercial laboratories. Additionally, the numbers of institutions using this type of testing and the factors that influence purchases are discussed. The report examines:

- Opportunities and hurdles in the quest for new companion biomarkers using proteomics.
- Secreted proteins as biomarkers.
- Adaptive design using biomarkers.
- Pharmacodynamic biomarkers identified with broad-based phenotyping as companion diagnostics.
- Tools for improving measurement, safety and validation of biomarkers.
- The gap between discovery and clinically validated biomarkers.
- Technologies for oncology biomarker discovery.

This report answers the questions:

- Which companies are utilizing cutting-edge technologies to develop, validate and implement companion biomarkers for clinical use in a personalized medicine setting?
- What impediments still exist to incorporating promising research into clinical practice?
- Which companion biomarkers show the most promise for approval?
- What are the economic challenges to approval?
- How can regulatory oversight drive approval and adoption of new technologies?
- Which alliances show the greatest synergy in bringing valid biomarkers to market?
- Which shared technologies are driving the most encouraging development?

Also:

- What can and what can't be done by personalized medicine?
- What are biomarkers and how are they used in disease prediction and prognosis?
- How can biomarkers help in assessing how far a disease has already progressed (disease staging) *e.g.*, in diseases like cancer?
- What is the promise genomic and proteomic approaches hold for personalized medicine?

1.5 Methodology

This report is based on interviews with sales and marketing professionals of companies in the companion diagnostics market. They were queried, some several times, about their companies' products and marketing strategies as well as their overall thoughts about their industry segment. Information was also obtained from interviews with founders, CEOs and vice presidents of some of the companies discussed in the report. Descriptions of the hospital laboratories and nearby patient facilities were derived from interviews with laboratory directors and medical technologists in these areas.

Sources of information for the study were trade association publications and meetings, product brochures and catalogs, and company literature. Where the companies under discussion were publicly held, an examination of the annual reports, 10k filings and financial reports were used as the basis of the data reported. Important data sources include the Health for All Database of the World Health Organization, data published by the statistical office of the European Commission (Eurostat), as well as various health data from the United Nations and the Organisation for Economic Co-operation and Development. Where possible and practicable, the most recent data available have been used.

The author of this report is a Ph.D. in biochemistry with decades of experience in science writing and as a medical industry analyst. He has been a senior director of several large regional and national clinical testing laboratories. The senior editor is a doctoral level clinical scientist. He has over thirty years of experience in laboratory testing and instrument and reagent development technology, as well as extensive experience in senior level positions in biotech and medical service companies.

Some of the statistical information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information set forth in this study was obtained from sources that we believe to be reliable, but we do not guarantee the accuracy, adequacy or completeness of any information, omission or for the results obtained by the use of such information.

Key information from the business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals with regard to commercial potential and market sizes. Senior managers from major company players were interviewed for part of the information in this study.

Primary Sources

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects and Sector Snapshots that we publish annually. We extract relevant data and analytics from TriMark's research of the past three years as part of this data collection. We also extract qualified data feeds from e-questionnaire responses and primary research responses for this compilation.

Secondary Sources

TriMark uses research publications, journals, magazines, newspapers, newsletters, industry reports, investment research reports, trade and industry association reports, government-affiliated trade releases, and other published information as part of our secondary research materials. The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations. The report conclusions are verified through intensive interviewing of top-ranking companies in the industry.

TriMark Publications Report Research and Data Acquisition Structure

The general sequence of research and analysis activity prior to the publication of every report includes the following items:

- Completing an extensive secondary research effort on a an important market sector, including gathering all relevant information from corporate reporting, publicly-available databases, proprietary databases, direct meetings and personal interviews with key personnel.
- Formulating a study outline with the assigned writer, including important items:
 - Market and product segment grouping and evaluating their relative significance.
 - Key competitors' evaluations including their relative positions in the business and other relevant facts to prioritize diligence levels and assist in designing a primary research strategy.
 - End-user research to evaluate analytical significance in market estimation.
 - Supply chain research and analysis to identify any factors affecting the market.
 - New technology platforms and cutting-edge applications.
- Identifying the key technology and market trends that drive or affect these markets. Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.
- Launching a combination of primary research activities including two levels of questionnaires, executive-direct focused, company-specific, and region-specific communications to qualified and experienced senior executives worldwide.
- Completing a confirmatory primary research assessment of the report's findings with the assistance of Expert Panel Partners from the industry being analyzed.

1.6 Executive Summary

Market Size and Forecasts for Companion Diagnostic Tests for Cancer Therapeutics

A near-term market opportunity for cancer companion diagnostic tests exists in drug selection for cancer therapy. This is where cancer biomarkers can impact the drug selection for therapeutic treatment. The classic example here is screening for HER2/neu over expression before using Herceptin in breast cancer therapy. A specific example of a companion diagnostic test developed for a new drug and used in the setting of personalized medicine is the use of companion diagnostic tests for UGT1A1 gene activity designed to reduce possible patient toxicity for irinotecan.

The demand for new tests that are an aid to prognosis and recurrence risk in several prevalent cancers such as breast and colon cancer has led to the introduction of several new cancer biomarker products. TriMark sees these new cancer biomarkers adding several hundred million dollars to the market value of this testing sector within the next five years. The production of biomarker companion diagnostic tests will have an immediate impact on toxicology and metabolism studies.

Dozens of biotech companies are competing with one another and seeking collaborations with big pharmaceutical companies. Although the technology in these companies is still primarily in the research phase, some groups have demonstrated proof-of-concept for companion diagnostic technologies in animal and human models. Those companies that ultimately control the rights to cancer biomarkers and their uses will become dominant players. Companies that conduct biomarker-based drug discovery and product development will achieve the greatest value.

Companion Diagnostics

Co-development of molecular diagnostics and targeted therapeutics has already been proven to be a successful strategy in the development of novel anti-cancer drugs such as Gleevec[®]. Adoption of biomarker development in clinical research provides great opportunities to identify patient subpopulations with differential drug responses and to uncover the underlying mechanisms. These data could help to explain if clinical trials of new drugs are adequate, and offer the possibility of creating a clear prescription path based on predictive biomarkers.

Potential benefits of biomarkers as companion diagnostics include:

- Streamlining drug discovery programs.
- Providing a target for therapy.
- Identifying potential responders to a drug.
- Identifying individuals at risk for adverse events.
- Monitoring response to drug therapy.

Utility of biomarkers as companion diagnostics to drug development:

- For screening, diagnosis and prognosis:
 - Discover candidate biomarkers with enabling technologies.
 - Qualify biomarkers with acceptable sensitivity/specificity.
 - Monitor cancer chemotherapy with biomarkers.
- For therapy efficacy:
 - Verify the impact of drugs on novel targets/pathways.
 - Model PK/PD for optimal biological dose determination.
 - Evaluate molecular response as an early clinical efficacy read-out.
- For prediction of therapy response:
 - Increase drug development predictability.
 - Explore and confirm biomarkers/therapeutics in clinical trials.
 - Give the right drug to the right patients at the optimal dose.

Companion diagnostic tests for cancer therapy:

- EGFR for colorectal cancer and Camptosar (irinotecan).
- EGFR Express and Erbitux (cetuximab).
- HER2 and Herceptin.
- Myriad's TheraGuide 5-FU.

- TheraScreen: EGFR29.
- K-RAS mutation detection kit.

The most notable advance in the past five years has been the development of molecularly targeted anti-cancer therapies, with the first approved agent in this disease category being cetuximab. Others undoubtedly will follow.

Companion Diagnostics and Personalized Medicine

Genomics-based, molecular diagnostic profiling is one of the key tools for making personalized medicine a reality using well-established and reliable methods for the detection of genetic variations and single nucleotide polymorphisms (SNPs). SNPs are variations in a DNA sequence that occur when a single nucleotide (A, T, C or G) in the sequence is altered. Personalized medicine offers the benefits of being able to:

- Select the optimal therapy—based on the presence/absence of the molecular markers that the drug is targeting or that could cause a drug–drug interaction. For example, Herceptin and the presence of HER2 marker, or Gleevec and the presence of the Bcr-Abl protein.
- Reduce adverse drug reactions—based on the polymorphic status of the patient’s cytochrome P450 genes and/or other genes that cause drug toxicity. For example, polymorphisms in UGT1A1 and adverse response to irinotecan, or warfarin and variations in CYP2C9 and a vitamin K metabolizing enzyme (VKORC1).
- Increase patient compliance—reduced or non-existent side effects or adverse events make it easier for patients to complete the clinical trial or undergo extended drug therapy.
- Reduce time, cost and failure rate of clinical trials:
 - Use of pharmacogenomic data allows the clinical trial sponsor to “enrich” the clinical trial patient pool through better selection, enrollment and stratification of patients.
 - Pharmaceutical companies could potentially save up to \$██████████ per drug¹ by incorporating pharmacogenomic tools into clinical trials.
 - Pharmacogenomic testing-based clinical trials can save time by getting terminated early by the FDA due to success. For example, the Phase III clinical trial for GlaxoSmithKline’s Tykerb was terminated early due to remarkable efficacy in treating a defined subset of patients with breast cancer.²
- Rescue drugs that are failing in clinical trials or performing poorly in the market:³
 - Herceptin: Although clinical trials failed to show any efficacy in the general breast cancer population, Genentech re-analyzed the clinical data and correlated efficacy with the presence of the HER2 marker, thereby rescuing Herceptin, currently a blockbuster drug with \$██████████ in sales.
 - Iressa: Although Iressa is approved for non-small-cell lung cancer, it is effective in only a small subset of patients. AstraZeneca is developing a genetic test to select patients who would benefit from Iressa.
- Shift emphasis from reaction to prevention—Myriad Genetics’s BRACAnalysis identifies the hereditary propensity for breast and ovarian cancer development, allowing the patient to work with her doctor to incorporate preventative measures.

A key area of unmet market need is adverse drug reactions (ADRs)—the fifth leading cause of mortality in the U.S. Personalized medicine seeks to identify and mitigate these ADRs. The currently-practiced areas in personalized medicine include:

¹ Tollman *et al.* A revolution in R&D: how genomics and genetics are transforming the biopharmaceutical industry. The Boston Consulting Group, 2001.

² A. Pollack. New drug holds promise for type of breast cancer. *New York Times*, June 4, 2006.

³ The case for personalized medicine. The Personalized Medicine Coalition, 2007.