



PHARMACOGENOMICS
FOR CLINICAL USE AND IN
DRUG DEVELOPMENT
(SAMPLE COPY, NOT FOR RESALE)

Trends, Industry Participants, Product Overviews and Market Drivers

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1. Overview

1.1 Statement of Report

Pharmacogenomics, the science of individualizing drug therapy based on the genetic makeup of individual patients, offers an unusual opportunity for future market growth. Applying pharmacogenomics would allow doctors to treat a specific segment of the population based on its particular response to a drug. Knowledge of the likely effectiveness of a drug in a patient would make the drug more reliable. As a result, fewer drugs would have to be taken off the market due to adverse reactions which affect some, but not all, of the patients treated. Additionally, reducing the occurrence of adverse effects to a drug would effectually reduce the cost of patient care overall.

This study examines the market for diagnostic tests based on pharmacogenomics, the methods of clinical measurement, and the reagents and supplies being utilized in clinical medicine and the pharmaceutical industry. This report presents an overview of the latest information regarding emerging new products and industry trends and will not only quantify, but also qualify the pharmacogenomic market segments as an area of research, product development and investment opportunity. Forecasts of the pharmacogenomic market and an analysis of products in the worldwide diagnostics market will provide a basis for understanding the significance of past developments and the immense possibilities of the future.

1.2 Objectives of this Report

The principal objectives of this study are to:

- Identify viable technology drivers through a comprehensive look at various platform technologies for pharmacogenomic studies in the diagnostic testing market.
- Obtain a complete understanding of the important pharmacogenomic targets and their diagnostic test value, and to gain an understanding of these elements, from their basic principles to their applications.
- Discover feasible market opportunities by identifying high-growth applications in different pharmacogenomic diagnostic testing areas with a focus on the largest and expanding markets concerned with disease.
- Focus on global industry development through an in-depth analysis of the major world markets for pharmacogenomic diagnostic testing.
- Present market figures regarding the current value of the pharmacogenomic testing market, along with projections and growth rates.
- Examine the use of pharmacogenomic testing in pharmaceutical drug development and show specific examples of its use in development and repositioning of therapeutic agents.

By purchasing this report, the reader will have:

- An improved understanding of the current state and future of the most clinically well-accepted pharmacogenomic diagnostic testing market segments.
- The latest information on the leading companies engaged in R&D and products in the pharmacogenomic diagnostic pipeline.
- A penetrating perspective of recent developments and discoveries in the diagnostic test industry and insight into their influence on selected markets.
- Knowledge of the cardiac diagnostic testing market, the growing testing markets in cancer and infectious disease, and research and investment for pharmacogenomic testing.

This report will cover the following categories of diagnostic testing segments:

- Pharmacogenomic testing and clinical applications.
- Impact of pharmacogenomics in predicting drug response.
- Potential of pharmacogenomics in drug development.
- Barriers and drivers of pharmacogenomic testing.
- Pharmacogenomic disease markers.

- Business trends in the pharmacogenomic industry.
- Important technology trends in pharmacogenomics.
- Pharmacogenomic corporate profiles.

This examination answers the following questions pertinent to the pharmacogenomic diagnostics industry:

- What are the near-term business opportunities in the pharmacogenomic diagnostics market?
- What are the current and forecasted sizes of the pharmacogenomic diagnostics market?
- What are the business models currently used by companies in this market?
- How will manufacturers, researchers, physicians, patients and payors influence the growth and adoption of this market?
- What are the drivers and bottlenecks influencing the pharmacogenomic diagnostic testing market?
- What are the technologies used in pharmacogenomic diagnostics?
- Who holds the proprietary rights to the pharmacogenomic diagnostic testing market technology?
- What are current applications of this technology?
- What regulatory processes must pharmacogenomic diagnostic testing technologies undergo in the U.S., Japan and Europe?
- What are the updated recommendations concerning pharmacogenomics by the regulatory bodies?
- How will emerging pharmacogenomic diagnostic testing technologies change treatment and payment paradigms?
- How will these technologies reduce adverse clinical reactions and decrease the cost of total patient care?

This report contains:

- Full descriptions of the technologies involved and how these differ from existing and emerging technologies.
- An analysis of the technological approaches undertaken by the various competitors, and industry and end-user responses to these products.
- Regulatory issues and legislation affecting use and marketing of products.

1.3 Scope of the Study

The emphasis in this study is on companies that are actively developing and marketing pharmacogenomic testing technologies. The reader should consult other TriMark Publications' reports at <http://www.trimarkpublications.com> for a detailed discussion of the important individual market segments that are related to pharmacogenomic diagnostic testing technologies markets, such as molecular diagnostic testing, clinical chemistry, cancer testing, infectious disease markers, and other exciting new diagnostic methods.

This report reviews the market for pharmacogenomic diagnostic testing technologies in the clinical market. This study also introduces and explores the concepts of theranostics as an emerging segment of personalized medicine. It defines the dollar volume of sales in the pharmacogenomics markets, and analyzes the factors that influence the size and the growth of the market segments. It discusses the activity and trends in the clinical research markets, the trends that have developed and stimulated this market in detail, and comments in depth on the patterns of gene target development in pharmacogenomic diagnostic testing technologies.

The study also presents a survey of all the companies known to be marketing, manufacturing or developing pharmacogenomic testing technologies, as well as those known to be marketing, manufacturing or developing instruments and reagents for the clinical pharmacogenomic testing market in the U.S. and worldwide for the identified selected segments. Leading companies are discussed in depth with a section on the history of the company, its product line, business and marketing analysis, and a subjective commentary of the position of the company in its market.

Emphasis is placed upon pharmacogenomic testing market segments in important worldwide markets such as the U.S., Japan and Europe. The report focuses primarily on the clinical market and the pharmaceutical development segment, and, separately, on a description of the instruments, reagents and supplies marketed by major companies in

these segments. It also discusses the market size, growth rates and market components as well as the five-year projections for each of the important pharmacogenomic tests.

1.4 Methodology

The author of this report is a Ph.D. in biochemistry from the University of Minnesota, with many decades of experience in science writing and as a medical industry analyst. He has over thirty years' 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. The editor is a Ph.D. in life sciences from Jawaharlal Nehru University with an extensive background in molecular biology.

Company-specific information is obtained mainly from industry trade publications, academic journals, news and research articles, press releases and corporate websites, as well as annual reports for publicly-held firms. Additionally, sources of information include the non-governmental organizations (NGOs) such as the World Health Organization (WHO) and governmental entities like the U.S. Department of Health and Human Services (HHS) and U.S. federal agencies such as the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Where possible and practicable, the most recent data available have been used.

Part of the statistical information reported in this analysis was derived from Biotechnology Associates' databases and from TriMark's private data stores. The information 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 or omission or for the results obtained by the use of such information. Key information from business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals regarding commercial potential and market sizes. Senior managers from major company players were interviewed for part of the information in this report.

Primary Sources

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects, as well as Sector Snapshots that it publishes annually. TriMark extracts relevant data and analytics from its research as part of this data collection.

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 its 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.

TriMark Publications Report, Research and Data Acquisition Structure

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

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly-available data and proprietary databases.
- Formulating a study outline with the assigned writer, including important items, as follows:
 - 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.
- Completing a confirmatory primary research assessment of the report's findings with the assistance of expert panel partners from the industry being analyzed.

1.5 Executive Summary

The pharmacogenomics market today comprises three fast-growing core segments:

- Diagnostic testing associated with therapeutic drugs.
- Single nucleotide polymorphism (SNP) associated with genomic testing.
- Pharmaceutical drug development.

The field of pharmacogenomics becomes important in two ways by:

- Transforming the art of medical diagnosis and treatment into a predictive science.
- Playing a pivotal role in the development of new drugs—from the analysis of a lead structure and the clinical trials to the prescription of safer drugs with known metabolic characteristics.

The science of pharmacogenetics (the study of the genetic sequence for variable drug response) also holds the promise of delivering personalized medicine products that respond to a known genetic profile for specific individuals. Increasingly, pharmaceutical and biotechnology companies are developing therapeutics by targeting specific biological molecules. This approach contrasts traditional pharmaceutical development, in which therapeutics were developed against disease models rather than against specific genetic targets. Pharmacogenomics (PGx) and pharmacogenetics will have a major impact on the future of healthcare and are new and expanding sectors in diagnostic testing. Only a handful of such therapeutics has entered clinical use. There are a growing variety of clinical applications for diagnostic pharmacogenomic testing for drug efficacy and patient safety. Industry analysts project that there will be an explosive growth in these categories within the projected five-year period.

There are, at present, some clinical situations in which pre-therapeutic pharmacogenomic testing for drug selection is indicated or recommended; and currently on the market, there are a few drugs that do have an indication for prospective pharmacogenomic testing. On the diagnostic clinical side, the availability of pharmacogenomic tests will depend greatly on reimbursement rates, which to date have varied. Very few diagnostic tests are requested or performed in the absence of a clear reimbursement structure.

The key players that will shape the economic impact of pharmacogenomics include:

- Patients.
- Clinical providers.
- The pharmaceutical industry and its business model.
- Insurers and third party payors.
- Governmental institutions.
- Regulatory agencies.

The question remains whether *in vitro* diagnostic (IVD) manufacturers and companies in the pharmaceutical industry can work together to develop a sustainable model for personalized medicine. This question could be answered by emphasizing that pharmacogenomics has the potential to do the following:

- Resurrect failed drugs: Drug makers have libraries of compounds that they mothballed in development due to potential toxicities. But what if these toxicities only affected patients with a certain genetic makeup? Pharmacogenomics could help bring some of these drugs to the market; it is one of the main strategies employed by the drug-repositioning industry.
- Reduce development costs and risks: Pharmaceutical companies could design clinical trials that enroll only those patients who are most likely to benefit from treatment, presumably reducing the size and length of costly development programs. Pharmacogenomics can reduce drug development times by almost seven years.
- Increase profitability: Capturing a large portion of a small market, rather than a small percentage of a large market, may prove to be more profitable. Pricing is likely to be competitive when patients have a strong chance of benefiting, and clinical trial and marketing costs will probably be lower.
- Challenge the accepted paradigm for “blockbuster” drug sales. A case in point is Herceptin, which has achieved blockbuster status due to, not despite, pharmacogenomics.

These are a few of the ways in which the IVD and pharmaceutical industries can find common ground to simultaneously improve patient care and financial performance. Some progress is being made. For example, Response Genetics, Inc., a company focused on the development and sale of molecular diagnostic tests for cancer, and Roche Diagnostics are working together to validate biomarkers that may help to determine which patients are most likely to benefit from certain cancer drugs. Moreover, pharmacogenomic companies, like Gene Logic, are taking late-phase clinical trial drugs that have been discontinued in their clinical pipelines and are assessing these drugs for new clinical indications with the idea of putting them back into the pharmaceutical partners’ pipelines. Other similar collaborations will help the molecular diagnostics industry branch out beyond infectious disease testing into new fields such as oncology and predictive medicine. In turn, growth in these areas will provide excellent opportunities to communicate the value of molecular diagnostic technologies to key audiences. IVD manufacturers have a compelling story to tell since the potential of the IVD industry is practically limitless.

Some key developments attributed to the introduction of pharmacogenomics in the drug development industry are:

- Segmenting drug development industry. Larger pharmaceutical companies may be more inclined to produce those drugs for a common disease or for a large sub-group; biotech firms may tend to develop “orphan” drugs.
- Cooperation of large pharmaceutical companies with smaller biotech companies. The arrival of pharmacogenomics has led to several collaborations and strategic partnerships among big pharma and smaller biotechs.
- Immediate relevance in Mendelian one-gene-based diseases. Orphan diseases are expected to benefit greatly from the utility of pharmacogenomics in the search for better drugs.
- Genetic tests as diagnostics most pertinent in all-or-nothing benefit. There is mounting relevance of pharmacogenomic testing, which is giving the diagnostics industry a much needed boost.
- Genetic test to be first used in complement to a drug already on the market. With the FDA approval of several pharmacogenomic tests and greater compliance with the recommendations placed on drug labels, pharmacogenomics is advancing towards greater acceptance.
- New uses for current drugs. The drug repositioning industry, though still in its infancy, is on the rise, and it relies heavily on pharmacogenomic strategies to identify new indications for discarded drugs.

There are a number of factors which affect an individual’s response to a specific drug therapy. Perhaps more important than any other influence, is the specific genetic makeup of an individual. An understanding of this genetic blueprint is thought to be the key to developing drugs for personalized therapy, and ensuring safety and efficacy

during drug therapy. Using genes as a guidepost to developing new pharmacologic-based diagnostic tests means that there will be more than 1,500 possible gene and 6,000 protein-based diagnostic tests available for development.

CYP2D6 is important in the metabolism of tricyclic antidepressants. Patients who are poor metabolizers due to low activity of this hepatic enzyme are at risk for developing acute toxicity due to higher than acceptable blood levels of this drug class. This situation could routinely be avoided by pharmacogenomic screening of patients before administering these drugs. This might be particularly important for some selected ethnic groups where low CYP2D6 activities are more prevalent. Although this might be the ideal, it is very unlikely in routine clinical practice. Current medical practitioners do not often look to pharmacogenomic tests to manage their patients.

Findings from a new study have prompted Mayo Clinic researchers to recommend CYP2D6 gene testing for postmenopausal women about to begin tamoxifen therapy. These data confirm that women with an inherited deficiency in the CYP2D6 gene, which is important for the metabolism of tamoxifen, have a nearly fourfold higher risk of early breast cancer recurrence compared to women who have not inherited the deficiency. The research findings, announced jointly by investigators from Mayo Clinic and the Austrian Breast and Colorectal Cancer Study Group (ABCSCG) confirmed results from a previous study conducted by Mayo Clinic. The data, which serve to highlight the emerging science of pharmacogenomics, were presented at the Cancer Therapy & Research Center-American Association for Cancer Research (CTRC-AACR) 31st annual San Antonio Breast Cancer Symposium.

Additionally, in collaboration with bioTheranostics (a bioMerieux company), the researchers examined whether a tumor-based test, HOXB13:IL17BR gene expression ratio and a five gene molecular grade index were prognostic markers of distant breast cancer recurrence. The study confirmed that high expression of both HOXB13:IL17BR and molecular grade index, found in 25% of the tumors, led to a nearly threefold higher risk of recurrence elsewhere in the body compared to patients whose tumors were considered to be low risk according to these gene markers.

Pharmacogenomic testing is routinely available from commercial laboratories. For example, Genelex Corporation offers metabolic enzyme tests like CYP2D6, CYP2C9, CYP2C19, NAT2 and CYP1A2 that can be used by physicians as a guide to individual metabolic responses to many prescription, OTC (over-the-counter) and herbal medicines. These include such important medications as Coumadin (warfarin), Prozac, Zoloft, Paxil, Effexor, hydrocodone, amitriptyline, Claritin, cyclobenzaprine, Haldol, metoprolol, Rythmol, Tagamet, tamoxifen, Valium, carisoprodol, diazepam, Dilantin, Premarin and Prevacid (and the over-the-counter drugs Allegra, Dytuss and Tusstat).

Currently, physicians are still divided over the decision to test patients for a genotype to determine if they will respond to a particular drug treatment; though the much-publicized and FDA-approved HerceptTest has become the standard of care, lesser-known, newer tests still face hesitation on the part of physicians responsible for their implementation.

Individualized drug dosing based on metabolic profiling with the Roche AmpliChip[®] CYP450 Test represents a breakthrough in pharmacogenomic testing for clinical labs. Using the FDA-cleared tests for analysis of CYP2D6 and CYP2C19, two genes in the cytochrome P450 system that can greatly influence hepatic drug metabolism, the Roche AmpliChip[®] CYP450 Test identifies a patient's genotype. Physicians, based on this analysis, can estimate the predicted patient phenotype—poor, intermediate, extensive, or ultra-rapid metabolizers—in an easy-to-read printed report. These two genes code for enzymes that metabolize many antidepressants, antipsychotics, and ADHD drugs, as well as other medications.

Key factors driving global market demand for pharmacogenomics devices and applications:

- Unmet need for an intelligent, more structured approach to therapy design.
- Increasing demand for diagnostic tools worldwide.
- Use of microarrays and demand analysis for microarrays in pharmacogenomics research.
- Demand analysis for biochips arrays in MEMS sector.
- Increasing utility of PCR-assays in pharmacogenomics research.
- Use of pharmacogenomics in specific disease applications.
- Pharmacogenomics and breast cancer treatment, estimated number of cases and demand for Herceptin.

- Prior knowledge of genetic status is an absolute requirement for trastuzumab therapy in breast cancer in combination with the genetic test for HER-2/neu.
- Leukemia survival rates and the use of pharmacogenomics to select drug therapy.
- Pharmacogenomics in HIV/AIDS treatment and genetic resistance testing.
- Growth of total patents filed.
- Study of drug metabolism by types and enzymes (cytochromes P450 isozymes: CPY2D6, CPY2C9, CYP2C19).
- Global market for AmpliChip arrays in diagnostic use.

There are a growing variety of clinical applications for diagnostic pharmacogenomic testing. Industry analysts project that there will be an explosive growth in these categories within the forecast projected five-year period. The most promising diagnostic products to emerge in the pharmacogenomic markets are found among the following disease groups:

- Cancer (breast, colon and more).
- CNS diseases (schizophrenia, Alzheimer's disease).
- Diabetes (both Type 1 and 2).
- Asthma (leukotriene influence).
- Cystic fibrosis.
- Atherosclerosis (statin response).

In the future, the diagnostics industry will play a critical role in the implementation of drug therapy. There will be a greater integration of the diagnostics and pharmaceutical industries, which have historically operated very separately and been regulated quite independently.

Pharmacogenomics eventually can lead to an overall decrease in the cost of healthcare because of decreases in:

- The number of adverse drug reactions (ADRs).
- The number of failed drug trials.
- The time it takes to get a drug approved.
- The lengths of time patients are on medication.
- The number of medications patients must take to find an effective therapy.
- The effects of a disease on the body (through early detection).

Realizing the benefits of pharmacogenomics on a large scale still remains a long-term goal yet to be realized. To date, applications of pharmacogenomics in practice have been notable, but disappointingly few. Nevertheless experts, policy-makers and stakeholders still believe that current and emerging advances suggest that better targeted and more effective pharmacogenomics-based treatments have the potential to yield significant gains in personal health, population health, and cost-effective resource allocation.

The promise of pharmacogenomics has drawn great attention for its potential to redirect personal care and public health paradigms in the U.S. and abroad. It has begun to offer powerful tools for applying information about individual genetic variations and drug response for health care decisions, with the promise of "customizing" or "personalizing" health care.

It must be cautioned that pharmacogenomics is still an emerging field, and the instances of translating pharmacogenomics into clinical practice are very few to date. In a more realistic appraisal, some in the field consider that the promise of pharmacogenomics is still largely unfulfilled, with more modest expectations of benefits from pharmacogenomics, at least in the near term.

Pharmacogenomics also may help to improve the productivity of the new drug pipeline. The ability for pharmacogenomics based diagnostics to identify potentially high and low responders to investigational drugs may eventually improve the efficiency of clinical trials and lower their costs.