Biomarkers in Parkinson’s Disease is focused on the biomarker identification and development in patients with Parkinson's Disease. This report focuses on the Parkinson's Disease space featured in the parent report, highlighting several biomarker targets under investigation and the progress that has been made in the industry. With regards to employing the use of biomarkers for Parkinson's Disease, Biomarkers in Parkinson’s Disease captures market growth of biomarkers, advantages, disadvantages, and validation techniques.

Experts interviewed in this report include:

- Dr. Andrew West, Associate Professor of Neurology and Neurobiology and Co-Director, Center for Neurodegeneration and Experimental Therapeutics
- Dr. Xuemei Huang, Professor and Vice Chair, Department of Neurology; Professor of Neurosurgery, Radiology, Pharmacology, and Kinesiology Director; Hershey Brain Analysis Research Laboratory for Neurodegenerative Disorders, Penn State University-Milton, S. Hershey Medical Center Department of Neurology
- Dr. Andreas Jeromin, CSO and President of Atlantic Biomarkers

Also available in this report is extensive survey data exclusively conducted for this report. Illustrated by 30 figures captured in an in-depth analysis, this section features insight into targets under investigation, challenges, advantages, and desired features of future diagnostic applications.

Insight Pharma Reports also engineered a table of clinical trial information and pipeline data from multiple databases related to Parkinson’s Disease. This table features companies, targets, clinical phases, and brief target/product descriptions.
Executive Summary

Biomarkers have been a heavily studied topic of interest, and recently on the rise is the interest in neurodegenerative disorders, particularly Parkinson's Disease. Although there are many techniques used to track Parkinson's Disease progression, this report will primarily focus on blood-based and cerebrospinal fluid-based biomarkers currently under investigation. In addition to covering extensive background information, this report will also highlight market growth and outlook, and feature clinical trial and pipeline information.

After the introduction, Chapters 2 and 3 highlight background information on neurodegenerative disorders and include definitions and elaborate examples of different types of biomarkers used in the clinic. Chapter 2 concludes with market growth, advantages of biomarkers, disadvantages of biomarkers, and validation techniques. Chapters 3 gives a brief overview of neurodegenerative disorders, also speaking to the market growth and rise in interest in biomarkers over the years.

Chapter 4 gives specifics on Parkinson's Disease, featuring definitions, symptoms, genetic markers, and current research. As the second leading cause of neurodegeneration in the aging population, researchers are scrambling to find biomarkers that will provide enough information for therapeutic action. Featured in this chapter is an interview with Dr. Andrew West, who speaks about his research and successes with the gene LRRK2. This chapter also provides an extensive amount of detail speaking to genetic targets and their use as biomarkers. Furthermore, Chapter 5 features Dr. Xuemei Huang (Professor and Vice Chair, Department of Neurology; Professor of Neurosurgery, Radiology, Pharmacology, and Kinesiology Director; Hershey Brain Analysis Research Laboratory for Neurodegenerative Disorders, Penn State University-Milton, S. Hershey Medical Center Department of Neurology) and Dr. Andreas Jeromin, CSO and President of Atlantic Biomarkers. These chapters provide insight to utilizing biomarkers as a diagnostic for Parkinson's Disease.

Chapter 6 includes an elaborate survey analysis exclusively done for this report. Qualifying participants worked with neurobiomarkers, neurodiagnostics, or both. With over 30 survey figures depicting the general R&D group working in this space, this section provides information including: research demographics, targets under investigation, challenges, advantages, and desired features of future diagnostic applications.

Finally, Insight Pharma Reports also created a table of clinical and pipeline information related to Parkinson's Disease.
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**Table 2.1:** Clinical Applications of Biomarkers as Surrogate Endpoints
About Insight Pharma Reports

CHI’s Insight Pharma Reports are written by experts who collaborate with CHI to provide a series of reports that evaluate the salient trends in pharmaceutical technology, business, and therapy markets.

Insight Pharma Reports are used by senior decision makers at life sciences companies to keep abreast of the latest advances in pharmaceutical R&D, their potential applications and business impacts. Our clients include the top 50 pharmaceutical companies, top 100 biotechnology companies, and top 100 vendors of life science products and services. Typical purchasers are managers, directors, and VPs in business development, discovery research, clinical development, strategic planning, portfolio management, new product planning, and marketing.

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- Expert insight based on interviews with key personnel in companies at the forefront of technological advances who share their views on their technology's current status, applications, future direction, and market environment.

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CHAPTER 1: The Focus of this Report

Biomarker in Parkinson’s Disease features current research revelations on several targets for Parkinson’s Disease (PD). The report covers the following areas: Introduction/background information, biomarkers under investigation, diagnostics in development, survey analysis, and exclusive complementary data on ongoing clinical trials and drugs in the pipeline. This report will focus on biomarkers for Parkinson’s Disease therapeutics and diagnostic applications in R&D.

Neurodegeneration is increasing among aging adults. Next to Alzheimer’s Disease, Parkinson’s Disease is the most common form of dementia in the aging population. These disorders affect cognitive function and motor ability, respectively, due to loss of neurotransmitter development and function. For both of these diseases, several genetic risk factors have been identified and are now being studied as potential biomarkers for early onset detection and proactive treatment. This report also highlights research activity currently in the diagnostic space.

Furthermore, Insight Pharma Reports (IPR) also conducted interviews with several experts in the field whose research involves Parkinson’s Disease biomarkers and diagnostics. Having gathered information on 15 survey questions, IPR generated an in-depth analysis regarding research tactics, challenges and pitfalls, targets under investigation, and desired features of future technologies.
What are Biomarkers?

According to the FDA, biomarkers are “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Marking key molecular and cellular events of specific environmental factors to health outcomes, biomarkers play a significant role in understanding several relationships between environmental chemicals and chronic human diseases, and based on data from Figure 2.1, interest in biomarkers has been on an exponential incline since the ’70s.

Figure 2.1: Growth of Interest in Biomarkers

PubMed results

50000 —

40000 —

30000 —

20000 —

10000 —

0 —


Year

Figure Source: PubMed; Search details: “biological markers”[MeSH Terms] OR (“biological”[All Fields] AND “markers”[All Fields]) OR “biological markers”[All Fields] OR “biomarkers”[All Fields]
Biomarkers have not only established a number of properties in both disease assessment and treatment monitoring, but also significant utility with regard to diagnosis, prognosis and physiology. Each of these applications directly affects the other; biomarkers can relay information on disease and disease subtype, determining prognostic outcomes. Thus, biomarkers can resultantly maximize efficacy and reduce toxicity when applying therapeutics; this course of action also enables researchers to monitor outcomes for physiological responses. Furthermore, biomarkers also have the ability to accurately measure biological activity and have repeatedly demonstrated correctly predicting relevant outcomes across a variety of treatments and populations. These features expedite therapeutic development, enabling researchers to explore the world of personalized medicine and opening up more applications in genomics and proteomics. The utility of biomarkers has shown great precedence in clinical research, so much that their use has been widely accepted without question. Figure 2.2 depicts research activity in biomarkers as diagnostics compared to therapeutics. Although both have been on the incline, researchers have made more progress in biomarkers as diagnostics.

Figure 2.2: Biomarker Presence in Diagnostic Development vs. Therapeutic Development

PubMed results

Year

0 10000 20000 30000 40000 50000

Diagnostic Therapeutic

Advantages of Biomarkers

Biomarkers serve a number of advantages to researchers, particularly when used strategically in the clinic. Some of the main advantages include cost effectiveness and easier detectability than true clinical endpoints. This is especially useful in studies that would normally take years to collect proper data for analysis. Another advantage is the effectiveness of biomarkers in decreased sample sizes. Because biomarkers are a direct measurement of a characteristic, they can be detected much more quickly and earlier than standard clinical data; this enables researchers to understand certain drug or disease effects faster than if chosen to proceed with clinical trials, which would have otherwise taken years to be completed. Furthermore, biomarkers can also determine whether or not treatment is required for certain diseases. This is not only supports cost effectiveness, but also affords physicians the opportunity to act on diseases that may impact vital organs before clinical evidence is available.

Clinical Endpoints vs. Surrogate Endpoints

Currently, researchers are exploring several applications and properties of biomarkers to expedite therapeutic development and diagnostic approaches. However, this process isn’t as easy as it sounds. There are several challenges that exist within biomarker discovery and development, the basics of which include validation, technological malfunctions, and biomarker identification. However, an even more important factor that renders itself problematic to discovery is determining therapeutic efficacy, specifically if there is a relationship between the measurable biomarker and relevant clinical endpoints.

A clinical endpoint is a variable that reflects specific traits of a subject in a study or clinical trial. These traits include how the subject “feels, functions, or survives,” representing health and wellbeing from the subject’s perspective. Clinical endpoints are related to a desired effect, particularly when measuring efficacy in response to potential therapeutics, with the goal of improving morbidity and mortality.

A surrogate endpoint is a biomarker used as an outcome in clinical trials to substitute for a clinical endpoint. In order to be considered a surrogate endpoint, there must be strong evidence demonstrating a biomarker’s ability to consistently and accurately predict a clinical outcome that is either beneficial or harmful. That said, it must also be recognized that although a surrogate endpoint can substitute a clinical endpoint, it does not serve as a replacement for one. As is often the case, even statistically validated biomarkers used as surrogates may only measure a process or product of a key pathway stage, misleading researchers to believe their presence is affiliated with the pathophysiological pathway when in fact it is not.

Because biomarkers are a measurement of biological processes, they do not always correlate to a patient’s experience and sense of wellbeing in response to treatment. Hence, not all biomarkers are affiliated with clinically relevant outcomes; their utility ranges beyond that of clinical outcomes, and they are therefore intended for much more application than patient wellbeing.

Advantages of Biomarkers as Surrogate Endpoints

Although validating and trusting the validation of biomarkers as surrogate endpoints can be a hassle, several published works provide a handful of examples citing advantages these endpoints bring to the healthcare industry. In fact, expert recommendations suggest “biomarkers can and should be applied throughout the drug
development process for novel agents.” The FDA further confirms this by suggesting and supporting the use of biomarkers as surrogate endpoints: “The use of these markers to obtain information early in drug development that may be critical to further development seems self-evidently appropriate.” Common advantages of markers as surrogate endpoints are described below. This is followed by Table 2.1, which identifies several applications biomarkers and surrogate endpoints possess for optimizing therapeutic development, clinical efforts, and patient benefits.

First, surrogate endpoints come in handy with respect to clinical endpoints that occur so infrequently that their use in clinical trials can be highly impractical or even unethical. An example of such a scenario is with regard to diseases that take years to establish a clinical endpoint (such as survival, or recurrence of, a cardiovascular event). The use of biomarkers can provide researchers with adequate evidence about the safety and efficacy of treatments for such ailments while more definitive data is collected. Thus, biomarkers as surrogate endpoints have proven to be a valiant solution to expedite clinical trials.

Furthermore, biomarkers as surrogate endpoints also possess the quality of early detection, which has the potential to reduce the risk of harm to subjects that would otherwise be detected later in trials using clinical endpoints. Still, other advantages include enabling researchers to design small, more efficient studies, which not only reduces the number of subjects exposed to an experimental treatment, but also shortens the time approval for said treatments; this expedites the drug development process, enabling researchers to generate and distribute therapeutics sooner than anticipated, all while conserving materials and resources for other potential projects.

**Table 2.1: Clinical Applications of Biomarkers as Surrogate Endpoints**

- Identify and validate therapeutic targets
- Screen and optimize candidate targeted agents
- Provide proof of concept for agents and models
- Enhance mechanistic understanding of drug or drug combination effects (such as clear indicators of target engagement, cell death, and changes in tumor biology)
- Identify optimal target populations
- Predict response, resistance, and toxicity
- Rapidly distinguish responders from nonresponders to therapeutic intervention

**Disadvantages to Biomarkers as Surrogate Endpoints**

Although surrogate biomarkers have established a notable reputation in the healthcare industry, which has slowly coaxed research institutions to adopt this method in substitution of clinical endpoints, there are several noteworthy challenges that have proven arduous in advancing patient care. One of the major setbacks in the development of surrogate biomarkers is that a standardization process does not exist. Although in most cases, acceptance is based on long-term clinical use and adequate data from clinical trials, other cases have forcibly driven researchers to accept potential biomarkers based on epidemic crises.

With regard to pitfalls, they are likely to occur if the pathophysiology of the disease in question and the mechanism of action of allotted intervention are not well understood. Here, the FDA also points out that “in some cases, the proposed clinical benefit (for example, an effect on survival) might not be detectable in trials of reasonable duration or size.” These are the cases in which clinical effects (such as mortality) are
crucial to the development and advancement of therapeutics.4

Furthermore, markers that happen to correlate with patient wellbeing aren’t always indicative of it. This can lead to unintended pursuit of markers, which can easily get prioritized in R&D, and the development of insufficient therapeutics with an increased risk of adverse effects.3,4 Such an example of this is with ventricular arrhythmias. In a Cardiac Arrhythmia Suppression Trial, antiarrhythmic drugs were hypothesized to prevent sudden death, a complication often caused by ventricular arrhythmias.3 Because antiarrhythmic drugs are so well known for their prevention of ventricular arrhythmias, researchers in this trial expected nothing but positive results from their application in the prevention of sudden death. However, it turned out that in patients who experienced asymptomatic ventricular arrhythmias after a myocardial infarction, antiarrhythmic drugs significantly increased the risk of sudden death; the trial was terminated prematurely.3

Further evidence speaking to the importance of fully understanding a disease and its mechanics is exampled by a trial comparing angiotensin-converting enzyme (ACE) inhibitors (enalapril) and vasodilators (hydralazine-isosorbide dinitrate). This study measured changes in hemodynamic effects from these two drug classes and its association for the treatment of heart failure. Based on the results, researchers observed a greater improvement in left ventricular function from vasodilators than ACE inhibitors; however, a greater improvement in reduced mortality was observed with ACE inhibitors.3,6 Although changes in hemodynamic measurements were associated with improved ventricular function for both drug classes, it is clear this improvement is unrelated to mortality. Therefore, hemodynamic effects are a poor choice of a surrogate endpoint because they are not guaranteed to improve the patient’s quality of life.3,6

How are Biomarkers Validated?

Biomarkers go through an extensive discovery process, and the FDA has issued guidance for the research industry in classifying various types of genomic biomarkers.5 According to the guide, there are three degrees of validity: exploratory biomarkers, probable valid biomarkers, and known valid biomarkers.5,7 According to the Biomarker Task Force, exploratory biomarkers do not meet the criteria for probable or known valid biomarkers.8 As a result, they assume the role of a working scaffold and provide researchers with incentive to explore these markers with the expectation they will one day gain relevance.5 To discover this relevancy, researchers confide in exploratory biomarkers in a number of applications including: to fill in gaps of uncertainty about disease targets or variability in drug response, to bridge the results of animal model studies to clinical expectation, or even to be used to select new compounds.5

In order to be considered for a probable valid biomarker, sources say that exploratory biomarkers need to establish their value via an analytical testing system with well-established performance characteristics. They need to demonstrate a “scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.”5 According to Chau, et al., “A probable valid biomarker appears to have predictive value for clinical outcomes but has not been independently replicated or widely accepted.”5 Once the biomarker has repeatedly demonstrated the same outcome at multiple locations, and these locations are in agreement with the results of this outcome, the previously known “probable biomarker” becomes a “valid biomarker”. In fact, legitimate validation of a biomarker is completely dependent on “widespread agreement in the medical or scientific community,”8 and these biomarkers are accepted at-large for their abilities to predict clinical and preclinical outcomes.5
Not only should there be a large amount of epidemiological evidence supporting the biomarker as a risk factor, but the marker should also be consistent with pathophysiology, on a causal pathway, and indicative of changes in prognosis when experiencing changes of its own. Further statistical criteria includes changes within the biomarker should correlate with changes in clinical outcomes; although, these correlations do not necessarily link to changes in causation.
**Figure 6.20**: What is the Clinical Status of Your Target(s) for PD?*

- Pre-discovery: 14%
- Discovery: 57%
- Preclinical: 29%
- Phase I Clinical Trials: 0%
- Phase II Clinical Trials: 0%
- Phase III Clinical Trials: 0%
- Phase IV Clinical Trials: 0%
- FDA Approved: 0%
- Other: 0%

*Multiple responses allowed

Source: Insight Pharma Reports

**Figure 6.21**: When Do You Expect Your Targets for PD to Enter Into Clinical Trials?

- <1 year: 14%
- 1-5 years: 29%
- 5-10 years: 14%
- >10 years: 0%
- Other: 0%

N=7

Source: Insight Pharma Reports

**Figure 6.22**: When Do You Expect Your Targets for PD to be an Available Therapeutic?

- 14%<1 year
- 43% 1-5 years
- 43% 5-10 years
- 0% >10 years
- 0% Other

N=7

Source: Insight Pharma Reports

**Figure 6.23**: How Would You Describe Your Line of Research?

- Developing neurodiagnostics: 18%
- Developing biomarkers: 32%
- Identifying biomarkers for therapeutics: 33%
- Clinical Research: 5%
- Other: 12%

N=60

Source: Insight Pharma Reports
# Clinical Trials and Pipeline Information in Parkinson’s Disease*

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