Biomarkers: Discovery and Development for a Diagnostic Approach to Neurodegenerative Disorders
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Biomarkers: Discovery and Development for a Diagnostic Approach to Neurodegenerative Disorders has a focus in biomarkers for neurodegenerative diseases and diagnostic applications in development. Biomarkers have been a heavily studied topic of interest, and recently on the rise is the interest in neurodegenerative disorders. Although there are many techniques used to track neurodegenerative disease progression, this report will primarily focus on blood-based and cerebrospinal fluid-based biomarkers. In addition to covering background information, this report will highlight several technologies that have been developed for employing the use of biomarkers for neurodegenerative disease detection, analysis and therapeutic development. Including substantial background information, illustrated with graphics and figures, this report captures market growth of biomarkers, advantages, disadvantages, and validation techniques.

Three neurodegenerative disorders that are heavily focused on in this report include: Alzheimer’s Disease/Mild Cognitive Impairment, Parkinson’s Disease, and Amyotrophic Lateral Sclerosis. Part II of the report will include all three of these disorders, highlighting specifics including background, history, and development of the disease. Deeper into the chapters, the report will unfold biomarkers under investigation, genetic targets, and an analysis of multiple studies investigating these elements.

Experts interviewed in these chapters include:

• Dr. Jens Wendland, Head of Neuroscience Genetics, Precision Medicine, Clinical Research, Pfizer Worldwide R&D
• Dr. Howard J. Federoff, Executive Vice President for Health Sciences, Georgetown University
• Dr. Andrew West, Associate Professor of Neurology and Neurobiology and Co-Director, Center for Neurodegeneration and Experimental Therapeutics
• Dr. Merit Ester Cudkowicz, Chief of Neurology at Massachusetts General Hospital
Part III of the report makes a shift from neurobiomarkers to neurodiagnostics. This section highlights several diagnostics in play and in the making from a number of companies, identifying company strategies, research underway, hypotheses, and institution goals. Elite researchers and companies highlighted in this part include:

- 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
- Julien Bradley, Senior Director, Sales & Marketing, Quanterix
- Dr. Scott Marshall, Head of Bioanalytics, and Dr. Jared Kohler, Head of Biomarker Statistics, BioStat Solutions, Inc.

Further analysis appears in Part IV. This section includes a survey exclusively conducted for this report. With over 30 figures and graphics and an in-depth analysis, this part features insight into targets under investigation, challenges, advantages, and desired features of future diagnostic applications. Furthermore, the survey covers more than just the featured neurodegenerative disorders in this report, expanding to Multiple Sclerosis and Huntington’s Disease.

Furthermore, Insight Pharma Reports also put together a generous amount of data compiling clinical trial information and pipeline data from multiple databases related to Alzheimer’s Disease, Parkinson’s Disease, and Amyotrophic Lateral Sclerosis. This is the fifth and final part of this report and it contains the most current information in the aforementioned disease areas.
Executive Summary

Bio-markers: Discovery and Development for a Diagnostic Approach to Neurodegenerative Disorders has a focus in biomarkers for neurodegenerative diseases and diagnostic applications in development. Biomarkers have been a heavily studied topic of interest, and recently on the rise is the interest in neurodegenerative disorders. Although there are many techniques used to track neurodegenerative disease progression, this report will primarily focus on blood-based and cerebrospinal fluid-based biomarkers. In addition to covering background information, this report will highlight several technologies that have been developed for employing the use of biomarkers for neurodegenerative disease detection, analysis and therapeutic development.

Part I of this report includes Chapters 2 and 3, highlighting background information relevant to the rest of the report. Chapter 2 will detail a definition of biomarkers, elaborating on different types used in the clinic, market growth, advantages, disadvantages, and validation techniques. Chapters 3 will give a brief overview of neurodegenerative disorders speaking to the market growth and rise in interest in biomarkers over the years.

Part II of this report includes Chapters 4, 5 and 6, which give great detail to Alzheimer’s Disease, Parkinson’s Disease and ALS, respectively. This part of the report features definitions of each disease, symptoms, genetic markers, and current research. These three neurodegenerative diseases are among the most common experienced by the aging population. Understanding the role of specific proteins, and therefore identifying core biomarkers, is crucial to combating these diseases and leading patients on the road to effective therapeutics and treatment options.

Chapter 4 will kick off with MCI and Alzheimer’s Disease. These two disorders generally go hand-in-hand and have had a significant impairment on the aging generation. Because of the growing number of cases and the detrimental effects of these diseases, there are many researchers tackling MCI and/or Alzheimer’s Disease from all different angles and perspectives. This chapter provides an extensive amount of detail speaking to genetic targets and their use as biomarkers. Experts interviewed for this section include: Dr. Jens Wendland, Head of Neuroscience Genetics, Precision Medicine, Clinical Research, Pfizer Worldwide R&D, and Dr. Howard J. Federoff, Executive Vice President for Health Sciences, Georgetown University. Each of these interviewees discusses their research and how they are advancing the MCI/Alzheimer’s disease field.

Similarly Chapter 5 details a considerable amount with regard to Parkinson’s Disease. As the second leading cause of neurodegeneration in the aging population, researchers are scrambling to find elusive 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.

Finally, Chapter 6 focuses on Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig’s disease. Following a similar style to the previous chapters regarding informative background information, this chapter garners a wide spectrum of history, symptoms, and biomarkers under investigation. In this chapter, Dr. Merit Ester Cudkowicz, Chief of Neurology at Massachusetts General Hospital, discusses her progress on discovering biomarkers for therapeutic development and understanding the biology of ALS.

Part III makes the shift from neurobiomarkers to neurodiagnostics. This section includes Chapters 7, 8, 9 and 10. Each chapter provides insight to developing technologies, recent research, hypotheses and institution goals. Elite researchers and companies highlighted in this part include:

- 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
- Julien Bradley, Senior Director, Sales & Marketing, Quanterix
- Dr. Scott Marshall, Head of Bioanalytics, and Dr. Jared Kohler, Head of Biomarker Statistics, BioStat Solutions, Inc.

Highlights in these chapters include technology status, advantages, pitfalls and exclusive interviews.

Part IV features a 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.

To add even more to the robustness of this report, Insight Pharma Reports put together a generous amount of data compiling clinical trial information pipeline data related to Alzheimer’s Disease, Parkinson’s Disease and Amyotrophic Lateral Sclerosis.
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PART I: INTRODUCTION AND BACKGROUND INFORMATION

CHAPTER 1:
The Focus of this Report

Biomarkers: Discovery and Development for a Diagnostic Approach to Neurodegenerative Disorders features current research revelations on several targets for Alzheimer’s Disease (AD), Parkinson’s Disease (PD), and Amyotrophic Lateral Sclerosis (ALS), and is broken up into five parts: Introduction and background information, biomarkers under investigation, diagnostics and technologies in development, survey analysis, and exclusive complementary data on ongoing clinical trials and drugs in the pipeline. This report will focus on the application of neurobiomarkers, diagnostics and technologies in neurodegenerative disorders.

Neurodegeneration is increasing among aging adults. Alzheimer’s Disease is the most common form of dementia in the aging population, followed by Parkinson’s Disease. These disorders affect cognitive function and motor ability, respectively, due to loss of neurotransmitter development and function. Due to extensive research, several genetic risk factors have been identified for these diseases and are now being studied as potential biomarkers for early onset detection and proactive treatment.

Amyotrophic Lateral Sclerosis is the third disease covered in this report. This disease, also called Lou Gehrig’s Disease, is not as common as AD or PD, but is similar to PD in that it also affects motor neurons. Researchers and physicians have taken an interest in ALS because of its rapidly progressive and ultimately fatal characteristics. Furthermore, the exact cause and internal mechanisms of the disease are still unknown, which makes it very difficult to develop therapeutics and diagnostics. By working to understand more about the process involved in patients with ALS, researchers can one day implement biomarkers for early onset detection.

However, although biomarkers provide a novel solution for early detection and diagnosis, current technologies aren’t as sensitive or specific, making it difficult to actually detect the presence of certain biologics, especially if they are in lower concentrations in a given sample. Alongside this, cerebrospinal fluid is currently the gold standard of sample collection, but due to its invasive properties, researchers have begun searching for an alternative solution, such as plasma analysis.

Furthermore, in an effort to provide as much information as possible and accurate snapshot of research in the AD, PD and ALS disease spaces, Insight Pharma Reports (IPR) also conducted interviews with several experts in the field relating to their progress towards biomarker and diagnostic applications. IPR also polled over 30 survey questions (supplemented with an in-depth analysis) regarding research tactics, challenges and pitfalls, targets under investigation, and desired features of future technologies.
Biomarkers and Their Clinical Utility

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,15 and based on data from Figure 2.1, interest in biomarkers has been on an exponential incline since the ’70s.
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.
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

Figure Source: Park, et al.7

### 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. 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. 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. 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.

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. 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.

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. According to the guide, there are three degrees of validity: exploratory biomarkers, probable valid biomarkers, and known valid biomarkers. According to the Biomarker Task Force, exploratory biomarkers do not meet the criteria for probable or known valid biomarkers. 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. 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.

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.” 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.” 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” and these biomarkers are accepted at-large for their abilities to predict clinical and preclinical outcomes.
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.
Biomarkers have made the greatest impact in cancer research. This is followed by inflammation, immunology, and neurology. Figure 3.1 shows a comparison between these four disease-categories based on the number of publication hits in the PubMed database. Cancer clearly surpasses all other disease forms. Inflammation closely paralleled cancer up until 2002, when it started plateauing, and research in cancer continued to increase. Following inflammation is immunology and then neurology. As depicted in Figure 3.1, neurology has had the least amount of research publications compared to the other disease spaces, but nonetheless has considerably increased over the last decade (Figure 3.2). Researchers have been making significant progress in biomarker discovery and development in this space, which has directly impacted therapeutics and diagnostics for neurodegenerative disorders, three of which are highlighted in Figure 3.3: Alzheimer’s Disease, Parkinson’s Disease and Amyotrophic Lateral Sclerosis.
Chapter 3: Biomarkers in Neurodegenerative Disorders

Biomarkers: Discovery and Development for a Diagnostic Approach to Neurodegenerative Disorders

Figure 3.2: Growth of Interest in Biomarkers for Neurology

Figure 3.3: Growth of Interest in Biomarkers for Alzheimer’s Disease, Amyotrophic Lateral Sclerosis, and Parkinson’s Disease


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