Company Profile

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XDx, Inc.

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XDx, Inc. is a molecular diagnostics company focused on the discovery, development and commercialization of noninvasive gene expression-based tests for the monitoring of transplant rejection and autoimmune diseases. The company has developed a proprietary new method for noninvasively monitoring immune system activity by measuring gene expression in a patient's peripheral blood. This work is the basis for AlloMap[®] molecular expression testing, which provides transplant physicians with a new tool to aid in the identification of the probability of acute cellular rejection for postcardiac transplant patient management. Some of the AlloMap molecular expression technology developed and implemented by XDx in heart transplant patient management may be applicable to other diseases that involve transplant rejection and the immune system.

Founded in 1998, XDx, Inc. is a molecular diagnostics company based in Brisbane, CA, USA. Setting the stage for a new era in personalized medicine, XDx is one of the first companies to develop and commercialize practical applications built on insights from the Human Genome Project.

In recent years, both high-throughput and high-sensitivity technologies have been developed to measure the levels of genes that are expressed in cells. The pattern of gene expression in a clinical sample reflects the specific population of cells that make up the sample, the genetic composition of the individual, and the conditions or disease states associated with the patient at the time that the sample was collected.

Microarray technologies allow gene-expression measurements to be made for thousands of genes at a time, including genes of both known and unknown function. PCR-based technologies provide a more sensitive, specific and reproducible gene-expression measurement of smaller numbers of genes. The emergence of these technologies, along with the development of statistical and database tools capable of storing

and analyzing gene-expression data, has made it possible to develop AlloMap[®] molecular expression testing for cardiac allograft rejection.

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AlloMap[®] molecular expression testing for heart transplant patients

Since the first successful cardiac transplant in 1967, approximately 40,000 such operations have been recorded by the Registry of the International Society for Heart and Lung Transplantation. Improved immunosuppressive agents, such as the introduction of ciclosporin in the early 1980s, have resulted in significant reductions in acute rejection rates, and improved survival. However, even with modern immunosuppressive therapy, acute rejection can still lead to graft dysfunction and is a cause of significant morbidity and mortality.

Endomyocardial biopsy is the standard method of monitoring for allograft rejection in heart transplant recipients. In this procedure, biopsy shears are inserted into a vein in the patient's neck and threaded through blood vessels into the heart. Small pieces of the heart

Figure 1. The immune-mediated inflammatory disease management challenge.

Provided by XDx, Inc.

muscle are clipped off and sent to pathologists to evaluate whether inflammatory patterns in the specimen indicate rejection. Most heart recipients have an endomyocardial biopsy procedure at least 12 times in the first year post-transplant, and periodic biopsies may continue thereafter. However, biopsy has significant limitations: it is invasive, associated with low-level risk of complications, expensive and not adequately sensitive for all types of rejection.

Immunosuppressive medications are effective at preventing and treating rejection episodes, but long-term exposure to these drugs can cause significant complications, such as infection and malignancy. The delicate balance between flare/organ rejection and damage caused by immunosuppressive therapy has made finding this quiescence 'sweet spot' a challenge since the advent of immunosuppressive therapy.

AlloMap molecular expression testing addresses this challenge by using gene-expression-based diagnostics to aid in the identification of organ rejection in heart transplant patients (see Figure 1). The AlloMap test is a noninvasive, quantitative, multigene molecular diagnostic test that applies a proprietary mathematical algorithm consisting of the expression

values, or RNA levels, of 20 genes and yields a single AlloMap score. This composite score is an integer ranging from 0 to 40 and discriminates between the absence or presence of moderate-to-severe acute cellular rejection.

A key benefit of the AlloMap test score is its negative predictive value (NPV). The NPV of the AlloMap test is the likelihood that a heart transplant recipient is at low risk for rejection. The NPV for patients with an AlloMap test score below the threshold range for one or more years post-transplant can be greater than 99% depending on the actual score. We believe the use of our test, in conjunction with other clinical indicators, may help physicians provide better care for their patients.

When an AlloMap test is ordered by a physician, a peripheral blood sample is drawn and processed to isolate the white blood cells, which are subsequently broken down, frozen and sent via overnight courier to the XDx reference laboratory in Brisbane, which is certified under the CLIA. All blood samples are tested in triplicate at the XDx reference laboratory and results are reported to the ordering physician by fax and mail within 1–2 business days of receipt of the sample (see Figure 2). Test samples that fail to meet

quality-control criteria are immediately retested, and the ordering physician is notified of the need to retest if turnaround time will be affected.

The AlloMap test may be used for stable patients aged 15 years or older at any time after the second month post-transplant, unless the heart transplant recipient is receiving high levels of specific steroids that interfere with gene expression. AlloMap testing assays the RNA levels of 11 rejection biomarker genes and nine control genes. The test involves 7–8 h of hands-on time by a clinical laboratory scientist. In order to maintain tight control of these processes, the tests are currently performed only at the XDx reference laboratory.

XDx launched the AlloMap HTx molecular expression test in January 2005. The company estimates that there are approximately 190 centers managing heart transplant recipients in the USA and, as of September 2007, the AlloMap test has been used in approximately 50 of them.

XDx is in the process of developing its second gene-expression-based test, the AlloMap LTx molecular expression test, to aid in the identification of the probability of acute cellular rejection in lung

Figure 2. Overview of the XDx Allomap® testing process.

Provided by XDx, Inc.

transplant recipients. This lung transplant rejection test is the focus of the ongoing Lung Allograft Rejection Gene Expression Observation (LARGO) study.

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Beyond transplant: opportunities in autoimmune & inflammatory diseases

Beyond the response to a transplant, the immune system is causative of very prevalent autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, diabetes, lupus and Grave's disease, to name a few. In addition, a myriad of chronic inflammatory diseases, such as Crohn's disease and ulcerative colitis, are accompanied by chronic or intermittent immune activity, which may be assessed using gene-expression technologies.

The cellular components of the immune system that circulate in the peripheral blood are ideal clinical samples for the development and implementation of multigene molecular tests for

these diseases. The XDx technology was designed with breadth and flexibility to assess immune mechanisms associated with multiple disorders. Clinical validation studies of molecular tests in autoimmunity are underway and XDx recently initiated a clinical study, the Systemic Lupus Erythematosus Activity Gene Expression study, to create a gene-expression test to monitor for disease flares in patients affected by systemic lupus erythematosus.

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Financial & competing interests disclosure

The authors are employed by XDx, Inc. and Pure Communications. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Highlights

- Immune-mediated inflammatory disease is an important field.
- Since 2002, XDx, Inc. has focused on improving patient care by developing molecular diagnostics that translate an individual's immune status into clinically actionable information.
- In 2005, XDx launched the first commercially available genomic-based test for immune-mediated conditions: AlloMap® HTx.
- The noninvasive technology offers the potential to decrease healthcare costs and significantly improve the quality of life for patients with a variety of life-threatening or life-altering immune-mediated diseases.
- XDx is well positioned to deliver innovative molecular diagnostics for immune-mediated inflammatory disease.