

**How the Genetic Diagnostics Market  
is Revolutionizing Medicine...**  
**and the one phantom micro cap stock laboratories,  
hospitals and doctors are turning to.**

**Our Number One Diagnostics Company is: Nanosphere (NSPH: \$4)\***



Nanosphere Inc develops, manufactures and markets an advanced molecular diagnostics platform, which is known as the Verigene System. This system enables simple, low cost and highly sensitive genomic and protein testing on a single platform.

*(from the Nanosphere's prospectus rule)*

Nanosphere's proprietary "nanoparticle" technology simplifies the ability to perform molecular diagnostic tests, achieves ultra-sensitive protein detection at limits beyond current diagnostic technologies. It provides the ability to multiplex, or run multiple tests at the same time on the same sample, and enables the development of a broad menu of test assays to be performed on a single platform.

The company is currently developing diagnostic tests for a variety of medical conditions including:

- Cancer;
- Neurodegenerative;
- Cardiovascular and infectious diseases;
- As well as pharmaco-genomics, or tests for personalized medicine.

There is a growing demand among laboratories to implement molecular diagnostic capabilities, but the cost and complexity of existing technologies and the need for specialized personnel and facilities have limited the number of laboratories with these capabilities.

The company states that the Verigene System's ease of use, rapid turnaround times, relatively low cost and ability to support a broad test menu will simplify work flow and reduce costs for laboratories already performing molecular diagnostic testing and allow a broader range of laboratories, including those operated by local hospitals, to perform molecular diagnostic testing.

Nanosphere's ability to detect proteins, which is at least 100 times more sensitive than current technologies, may enable earlier detection of and intervention in diseases associated with known biomarkers and the introduction of tests for new biomarkers that exist in concentrations too low to be detected by current technologies.

NSPH received 510(k) clearance from the United States Food and Drug Administration for commercial sale of the Verigene System in September 2007. The company also received clearance for two diagnostic tests in September 2007 and October 2007, respectively.:

1. Their warfarin metabolism assay, which is a pharmaco-genomic test to determine how an individual metabolizes the drug warfarin, including Coumadin, the most-prescribed oral anticoagulant in North America and Europe.
2. The company's hyper-coagulation test: This test is one of the highest volume genetic tests currently performed, which determines an individual's risk for the development of blood clots.

Upon receipt of the FDA clearance, Nanosphere commenced sales to hospital-based laboratories and academic research institutions in the United States, which the company believes is the primary market for their products.

Nanosphere has established a direct sales organization within the United States and is focusing their initial commercial efforts on the hospital-based laboratory market. Nanosphere's revenues to date have been derived from the sale of the Verigene System, including cartridges and related products, within the U.S to research laboratories and pursuant to government contracts.

The company anticipates that they will submit applications to the FDA for clearance of tests for cystic fibrosis, herpes, cervical cancer, respiratory illness, recurrent prostate cancer and cardiovascular disease during the next 36 months, and it is anticipated that NSPH will submit two of such tests within the next 12 months.

Additionally, Nanosphere has an active program to develop protein tests based on established biomarkers and to validate new biomarkers where their ultra-sensitive protein detection technology may enable earlier detection of a broad range of diseases.

Through their biomarker validation program, they are working to confirm novel protein targets for Alzheimer's disease, stroke, sepsis and kidney disease, which the company believes will lead to new protein-based diagnostic tests.

Nanosphere's technology is broadly applicable beyond the clinical diagnostic market in both research and industrial applications. For over two years the company's "Verigene System" has been in use in research laboratories supporting collaborations and independent research in areas including ovarian cancer, mad cow disease and HIV.

They are currently working with the FDA on a joint research program to develop an H5N1 avian flu assay. NSPH has developed and delivered a biosecurity platform for the detection of various bioterrorism agents to the Technical Support Working Group, an agency affiliated with the U.S. Department of Defense.

Currently, the company's patent portfolio is comprised, on a worldwide basis, of 80 issued patents and 150 pending patent applications which, in either case, they own directly or for which we are the exclusive licensee.

NSPH exclusively licensed their initial core technology from the International Institute for Nanotechnology at Northwestern University in May 2000. This formed the basis for a sustained relationship with Northwestern whereby they have rights to future developments in the field of biodiagnostics.

This relationship provides the company with access to ongoing research and innovation which they utilize in their research and development of new applications and products.

## **Industry Background**

In-vitro diagnostic tests are used to detect the presence and quantity of certain substances in biological samples to diagnose disease, monitor and guide treatment, and assist in managing chronic conditions.

The global market for in-vitro diagnostic products was estimated to be \$34 billion in 2006 according to Boston Biomedical Consultants. Molecular diagnostics is a new and expanding part of the in-vitro diagnostics market that emerged in response to a need for

more rapid, sensitive and specific diagnostic tests than were previously available using traditional techniques, such as immunoassays.

Nanosphere's current market opportunity is more than \$3 billion, including the \$2.3 billion molecular diagnostics market and their estimated market for their initial protein assays.

The genomic market growth has been driven primarily by conversion of traditional testing methods to molecular methods. In addition to the continuation of this conversion, NSPH believes that four primary trends will expand the market for molecular and other advanced testing:

- *Expanded Human Genetic Testing.* Advances in the understanding of the role genes play in disease have led to the emergence of human genetic tests that today, are primarily used in prenatal screening for inherited diseases, such as Down Syndrome or in perinatal testing for diseases like cystic fibrosis. As technology advances, NSPH expects a growing number of genetic tests will emerge that will be able to establish an individual's predisposition to a wide range of diseases, such as cancer.
- *Pharmaco-genomics.* There is growing recognition of the role that genetics plays in how well individuals tolerate and respond to many drugs. As a result, NSPH expects growing use of genetic testing to guide personalized medicine.
- *Protein Testing.* As in the field of molecular diagnostics, the introduction of more sensitive testing technologies is expected to revolutionize protein testing by enabling physicians to detect target proteins at lower concentrations than can be detected using traditional technologies. This is expected to expand the market for tests associated with existing biomarkers and drive the emergence of new tests for biomarkers that cannot be detected using current technologies.
- *Convergence of Genomic and Protein Testing.* The growing medical understanding of the inter-relationship between genetics and proteins in disease states will drive a convergence of genomic and protein testing.

## **The Genomic Testing Market**

Nucleic acids, DNA and RNA, are molecules found inside cells and viruses that contain genes, the unique blueprint of each living creature.

The diversity of living organisms results from variability in genetic content, which is determined by the sequence of four nucleotide bases that form the chemical building blocks of DNA and encode an organism's genetic instructions.

Variability can also be the result of differences in gene expression, the process by which a gene's DNA sequence is converted into proteins that in turn regulate or perform most of the physiological functions of the body.

Variations or mutations in the sequences of genes may be introduced by environmental or other factors, such as errors in the replication of genes. Mutations in individual genes have been associated with diseases like cystic fibrosis, and mutations in multiple genes have been associated with diseases such as cancer, cardiovascular disease and drug metabolism. Most molecular diagnostic tests target only one or a few genes.

### ***The Limitations of Current Genomic Testing Methods***

Over the past 20 years, scientists have developed a variety of genomic analysis methods, including DNA sequencing, gene expression analysis and genotyping, to measure an ever-increasing number of genomic biomarkers and to more effectively detect diseases.

The most widely used method for genetic testing is polymerase chain reaction, or PCR, which involves amplifying, or generating billions of copies of, the DNA sequence in question and then detecting the DNA with the use of fluorescent dyes.

Due to the complexity, susceptibility to contamination and significant costs related to PCR and other existing technologies, the genomic testing market remains limited to reference laboratories, research facilities and laboratories associated with the top 200 to 300 hospitals; primarily at academic teaching institutions.

A typical molecular diagnostics laboratory in a hospital or research laboratory setting is a dedicated facility that employs highly skilled technologists and is supervised by a technician with a Ph.D. or M.D./Ph.D.

To guard against contamination, which is a common result of target amplification, a typical laboratory will require at least three separate rooms, or isolation areas, to perform PCR-based assay methods for genomic testing.

Due to the limited capability of many existing technologies, numerous testing platforms are required to perform even a limited menu of tests. Also, due to the complexity of test procedures and the cost of reagents and supplies, tests are typically batch processed, often only on a weekly basis.

These issues require molecular diagnostics laboratories to maintain multiple pieces of equipment, each with a very limited testing menu. This creates a laboratory model that is complex, costly and one that demands a significant commitment of highly specialized and skilled laboratory technologists (due to the training required to utilize the numerous

techniques and pieces of equipment and the significant amount of technologists time required by current test systems).

Furthermore, these target amplification technologies continue to lack the capacity to run multiple tests at the same time on the same sample, or multiplex, in a cost effective manner.

## **The Protein Testing Market**

Proteins are one of the primary structural and functional components of the human body. While genes are typically associated with presence or absence of disease states, proteins often reflect the activity of a disease state.

That being said, many diseases are both diagnosed and monitored at the protein level, rather than at the genetic level. Proteins often serve as the primary biomarkers for detecting disease states, such as post-surgical recurrent prostate cancer or cardiovascular disease, and monitoring the progress of these diseases during treatment. As a result, the simultaneous detection of both protein biomarkers and genomic biomarkers is emerging as a way to more comprehensively diagnose and monitor the entire disease process.

### ***The Limitations of Current Protein Testing Methods***

Protein detection methods have been evolving over the last 40 years. The most widely used method for protein testing is enzyme-linked immunosorbent assay, or ELISA, which was the first method that allowed for widespread use of protein detection for discovery and diagnostic applications.

ELISA and similar predecessor technologies have proven effective in detecting many of the common protein markers associated with diseases including some forms of cancer, cardiovascular disease and various infectious diseases.

However, they are often not sufficiently sensitive to detect the protein biomarkers until the disease has progressed to an advanced stage. And the need for greater sensitivity has become apparent in protein detection for biomarkers, drug discovery and diagnostics.

Moreover, biomarkers for medical conditions such as stroke, various forms of cancer and neurodegenerative diseases, like Alzheimer's, have not been validated or commercialized because they exist in concentrations too low to be detected by current technologies.

As a result of this limitation, an alternative approach to protein detection called mass spectrometry has been used in research laboratories to detect protein biomarkers undetectable with ELISA technology.

Mass spectrometry systems first purify the sample and then break the proteins down into pieces. Each protein constituent is then injected into the mass spectrometer, where it is ionized and information regarding mass and charge data is then extracted from the system.

Although mass spectrometry is highly sensitive, it is extremely costly and requires significant time and effort by highly trained personnel. Additionally, mass spectrometry is not able to detect long peptide chain proteins or misfolded proteins, which are biomarkers for diseases, such as mad cow and Alzheimer's, and therefore is not practical for commercial molecular diagnostics.

## **Nanosphere's Solution**

*"We are commercializing a platform based on our proprietary nanotechnology that we believe will significantly advance and expand the market for molecular diagnostic testing. Our technology makes possible the combination of direct genomic detection and ultra-sensitive protein detection on one simple to use, low cost platform.*

*Our technology will enable faster and simpler genomic detection than other currently used genomic testing technologies. In addition, our ultra-sensitive protein detection technology, which is at least 100 times more sensitive than ELISA, will enable earlier detection of disease and the validation and commercialization of new biomarkers where no test exists today."*

### ***The Verigene System***

The Verigene System is a bench-top workstation, which is comprised of a microfluidics processor, a touch screen reader and disposable test cartridges.

With a prepared sample, the Verigene System completes tests in 45 to 90 minutes and requires less than 20 minutes of technician time. Specifically, the system incorporates several key features, which the company believes will make it attractive to a wide range of laboratories, including:

- ***Low Cost and Complexity.*** The Verigene System is a low cost platform without the need for sophisticated instrumentation or complex reagent kits. The versatility of the cartridge-based design eliminates the need for multiple testing platforms. Automation of key process steps eliminates manual intervention and algorithms provide test results without the need for operator interpretation or data manipulation. By eliminating the need for skilled technicians and multiple complex platforms, costs are reduced, work flow is simplified and molecular diagnostic testing can be decentralized to a greater number of laboratories around the world.

- *On Demand Testing.* The Verigene System allows laboratories to economically run tests at the time they are ordered, unlike other systems where laboratories must process patient samples in batches to control reagent and labor costs. This results in faster turn-around times and potentially improved patient care.
- *Multiplexing.* The Verigene System enables high count multiplexing, or the ability to identify a large number of target molecules on the same sample in a single assay. Potential applications include combination genomic and protein test panels and cartridges that allow for the simultaneous detection of multiple genetic mutations associated with complex diseases, such as cystic fibrosis.
- *Direct Genomic Detection.* The Verigene System utilizes a proprietary method to detect nucleic acids with greater specificity and without the complexity and risk of contamination inherent in the use of amplification techniques such as PCR, thereby increasing the reliability of test results.
- *Ultra-Sensitive Protein Detection.* The Verigene System allows ultra-sensitive detection of proteins with at least 100 times greater sensitivity than current technologies such as ELISA. This may enable earlier detection of disease, potentially improving clinical outcomes and enabling the development of completely novel tests.
- *Target Key Customer Segments.* NSPH will focus their sales efforts on hospital laboratories, where there is large and growing demand for molecular diagnostic testing, but where cost, complexity and resource requirements of existing technologies have limited their ability to process tests in-house. The company will emphasize the ease of use, bench-top convenience and high quality and consistent results of their system, as well as the flexibility afforded by a broad test menu on a single platform.
- *Employ a Direct Sales Force Model.* They are currently marketing and selling the Verigene System through their own sales and marketing organization, which is currently comprised of 19 people, including sales representatives, clinical support staff and product managers. In the company's experience, technical sales of new technologies, such as their own, are best accomplished directly through an in-house organization, which allows them to control the pace of commercialization.
- *Market FDA Cleared Products.* Nanosphere will seek FDA clearance for all of their products. Many tests currently on the market are sold as analyte specific reagents, or ASR, assays, which laboratories use to create "home-brew" tests. The company believes that there is strong market demand for FDA cleared tests because FDA cleared tests require less skilled laboratory technician time and do not subject the laboratory to the additional regulatory requirements imposed on laboratories using "home-brew" tests. Marketing only FDA cleared products will expand diagnostic testing into smaller hospitals and other laboratories that lack the capability to develop their own "home-brew" tests or do not have laboratories

that meet the higher quality standards imposed on laboratories performing “home-brew” tests.

- *Establish a Broad Test Menu.* Nanosphere is developing a broad genomic and protein test menu for the Verigene System, focusing on assays that are either already in high demand or projected to experience rapid growth. This will maximize the value of the Verigene System and support placements of systems in those laboratories that demand a broad testing menu before implementing a new testing platform. Likewise, for those laboratories that implement their system with a narrower initial test menu, an expanding range of tests will drive incremental cartridge sales.
- *Utilize heir Ultra-Sensitive Protein Detection Methods to Validate New Biomarkers and Commercialize New Diagnostic Tests.* Nanosphere is applying their ultra-sensitive protein detection methods to the development of established protein biomarkers and the validation of novel protein targets that may lead to earlier detection of medical conditions including cancer, neurodegenerative disorders including Alzheimer’s disease, sepsis and mad cow disease, for blood screening and veterinary applications.
- *Capitalize on Strong Intellectual Property and Development Capabilities.* Nanosphere will continue to develop their product capabilities based on our strong in-house and licensed intellectual property to expand the utility of established biomarkers and enable the creation of entirely new tests by validating new biomarkers. Their ongoing relationship with the International Institute for Nanotechnology at Northwestern University and their internal expertise will allow them to develop new genomic and protein assays for the Verigene System.

Currently Nanosphere has six tests in development beyond those recently cleared by the FDA.

We believe that with a strong patent portfolio and a feasible alternative to current methods, that Nanosphere has a unique solution to a prevalent problem.

Their products and services should be in high demand as they offer low costs, diversity of testing, proven products, innovative solutions, in-house capabilities, divergence from specialization and associated time and costs, and support that can potentially increase the survivability of patients, and revolutionize genetic diagnostics.

This is a critical market and Nanosphere is working each day to make it more productive and accessible, passing along the benefits to the doctors, which in turn can better provide accurate treatments to the patient.

*\*Initial Recommended Price*

