HEARTGENETICS
GENETICS & BIOTECHNOLOGY

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OUR MISSION

TO PLAY A LEADING ROLE IN CHANGING THE STATUS QUO OF GENETICS, BY BRINGING UP INNOVATIVE KNOWLEDGE THAT WILL HELP PHYSICIANS IMPROVE HEART MEDICINE.

HEARTGENETICS
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OUR SOLUTION

A DISRUPTIVE METHODOLOGY BASED ON THE INTEGRATION OF ADVANCED GENOMIC TECHNOLOGIES AND SOPHISTICATED COMPUTATIONAL METHODS.

EXECUTIVE SUMMARY

Molecular diagnostics is the fastest growing segment in the Diagnostics related HealthCare Market Worldwide. Key factors fostering growth include increasing awareness about the human genome, newer technologies for accurate detection and faster screening and powerful computational tools for data analysis and processing.

Currently, most of the genetic based diagnostic-testing companies in the world use sequencing approaches, namely the Sanger method or Next-Generation Sequencing (NGS), that are time consuming, expensive, difficult to use for larger genes and in some cases require complex computational approaches for data analysis.

HeartGenetics, a Spin-off from Instituto Superior Técnico, is a new company that has developed a revolutionary methodology that includes (i) a **DNA MICROCHIP** array platform optimized for genetic analysis and (ii) efficient and scalable algorithms for data processing. This new methodology is particularly relevant for improving significantly cardiovascular diagnostics.

Based on **DNA MICROCHIP** array platform for genetic analysis, our team of investigators has developed genetic tests for eleven cardiac pathologies, e.g.: Hypertrophic cardiomyopathy, Dilated cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy, Long and Short QT syndromes, Brugada Syndrome, genetic risk factors for thrombophilia, molecular markers for arterial hypertension, among others.

On top of our core competences on the subject of cardiovascular genetic testing, we are developing new high-tech bioinformatics technologies that support highly accurate analysis and integration of both genetic and clinical data. We plan to launch by the end of 2014 an innovative clinical decision support system, allowing clinicians and practitioners to perform a more accurate diagnosis, prognosis and risk stratification.

HeartGenetics is a VC-backed company since April 2013, by Portugal's unique world-class VC player. We believe having them on board will give us a strong support to achieve our goals. We are headquartered in Arruda dos Vinhos, Portugal, with laboratory facilities at the TagusPark Incubator, a leading technological center in Portugal where major biotechnology start-ups are located.

PRODUCTS OVERVIEW

HeartGenetics has developed a comprehensive panel of genetic tests for cardiac pathologies shown in Table 1. This cardiovascular genetic panel covers the needs of patients and clinicians concerned with cardiovascular inherited disorders. All the diseases included in the cardiovascular genetic panel can be tested in an individual way if prescribed by the clinician. One of the main distinctive factors of the tests is the coverage of all the genetic alterations that have been described to be associated with each pathology. This key factor is still a limitation for the existing sequencing technologies, given the need to dramatically increase the delivery time (and thus cost) to obtain a comparable result.

Currently Existing Tests Panel

The three exams described below are to the ones that will be initially launched in the market, by July 2013. These tests have been selected due to its high demand by the hospitals and clinics we have contacted. In a second phase, by the end of the year, we plan to start the commercialization of all the tests in the panel.

All these tests are unique in the market since they include all the genetic alterations that have been reported and known to be associated with the pathology. However, it should be stressed that the Arterial Hypertension test is a pioneer test, as there is currently no possible comparable offer in the market.

Table 1 – Cardiovascular genetic panel

Pathology	# Genes	# Mutations / Genetic Variants
Hypertrophic Cardiomyopathy	53	957
Dilated Cardiomyopathy	53	463
Arrhythmogenic Right Ventricular Cardiomyopathy	12	308
Long and Short QT Syndromes	18	1281
Brugada Syndrome	5	357
Marfan Syndrome	5	1317
Noonan Syndrome	8	177
Leopard Syndrome	3	14
Genetic risk factors for arterial hypertension	45	80
Genetic risk factors for thrombophilia	10	14
Genetic predisposition	**# Genes**	**Genetic Variants**
Sports Performance	30	40

Current Main Tests Panel

Arterial Hypertension (HTA) or high blood pressure is common, but too often goes undetected and constitutes a major risk factor for stroke, heart attack and heart failure. Determining the genetic cause of essential hypertension has been difficult, because the level of blood pressure is the result of the interplay between heredity and environment factors.

HeartGenetics implemented a high quality genetic test suitable for screening a large number of patients for the most relevant genetic markers associated with

HTA. The genetic test covers 80 genetic variations in 45 genes being, to the best of our knowledge, the most complete genetic test in the market and an important tool to support medical doctors in their diagnosis of genetic forms of arterial hypertension. Moreover this arterial hypertension genetic test will provide guidance to patients with a family history of HTA who wish to know if they should modify their lifestyles to help prevent the debilitating consequences of high blood pressure such as heart failure and stroke.

Thrombophilia is a disease characterized by an increased tendency of the blood to clot leading to possible serious and/or life-threatening complications. It is considered a multicausal disease due to the interaction of genetic and environmental risk factors. The thrombophilia genetic test has become useful for patient management supporting clinicians in deciding specific items such as the duration of anticoagulant therapy, risk stratification for primary or secondary prophylaxis, and family studies.

HeartGenetics has developed an accurate and reliable genetic test based on a DNA microchip that allows the detection of the most relevant genetic risk factors (14 genetic variations in 10 genes) associated with thrombophilia.

Current laboratory testing of thrombophilic disorders incorporates only a few of the most relevant genetic risk factors and in consequence it will not possible to provide truthful risk stratification. Testing for all the genetic risk factors that encompasses HeartGenetics panel it is possible to address in a more accurate manner specific issues of patient management such as the duration of anticoagulant therapy, risk stratification for primary or secondary prophylaxis, and family studies.

Like for any case, having a genetic predisposition does not mean that the individual will definitely have a blood clot. However, it is particularly important to

be aware of this information to control the factors that may promote a blood clot. This test allows clinicians to predict the risk of increased tendency to form abnormal blood clots in blood vessels providing to each individual a personalized interpretation of the associated genetic risk for developing thrombophilia.

Cardiomyophathies are an important group of cardiovascular pathological conditions prevalent in the World population and that are associated with heart dysfunction which can vary from an asymptomatic course to heart failure.

Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium that can lead to mild symptoms as well as to sudden cardiac death. HCM is a common genetic cardiovascular disorder. Moreover considerable interest has been raised regarding the athletes screening for early identification of cardiovascular diseases that are responsible for athletic field deaths and for disqualification of athletes at risk.

HeartGenetics has developed a very accurate and sensitive diagnosis test specially designed for HCM. This test is the most accurate test in the market, covering 100% (53 genes, known to date). A total of 957 mutations are analyzed using the **DNA MICROCHIP** allowing their detection in about four weeks. The proposed genetic test is a cost-effective gene-based diagnostic that is considered appropriate for clinical diagnosis of HCM.

HCM genetic test is already implement in the market. However for the majority of the companies only a few genes (5-18) are evaluated from a total of about 55 already known to be related with this pathology. HeartGenetics HCM genetic panel allows to perform this test up to 20% more accurate because encompasses all the genetic causal mutations in 53 genes related to HCM, in a very short time, up to five times faster.

TECHNOLOGY

Cardiovascular associated diseases are considered multifactorial. Risk factors, that increases the relative risk for these diseases, result from genetics, environment and lifestyle. Nowadays, the benefits of gene-based diagnosis of cardiovascular associated diseases for clinical medicine are limited by (1) the considerable costs of current genetic testing strategies: automated sequencing and next generation sequencing (NGS), (2) by an incomplete screening of all disease genes and (3) by time for delivery of the results, from 4 to 12 months is most cases.

HeartGenetics genetic diagnosis method, the **DNA MICROCHIP** (Fig1), makes use of a methodology that enables us to perform the analysis of a very large number of genetic alterations simultaneously, in a reliable, fast and cost-effectiveness manner. The **DNA MICROCHIP** includes all the genetic variants that, to date, have been proven as the cause of a specific cardiac disease.

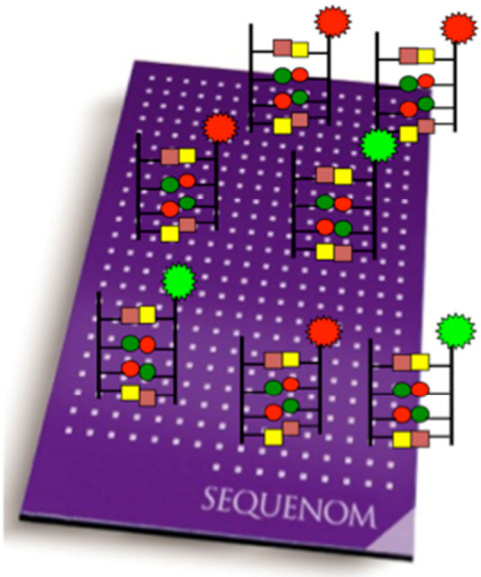

Fig1 – **DNA MICROCHIP (Courtesy of Sequenom®)**

HeartGenetics technology is based on the Sequenom MassArray system. The MassARRAY system is a DNA Microchip array platform optimized for genetic analysis that provides unparalleled sensitivity and specificity using MALDI-TOF mass spectrometry.

This new technological process is very accurate when compared with the sequencing approaches. The accuracy of a test is measured by its sensitivity and specificity, and to compute these parameters, it is important to consider the incidence of the pathology within a population.

The DNA MICROCHIP Sensitivity and Specificity

Regarding the HCM pathology, the prevalence in the general US population is estimated to approach 1 in 500 persons (Maron et al., Circulation, 1995).

The **DNA MICROCHIP** is the most accurate test in the market for the HCM pathology, covering 100% of the genes identified to be involved in this disease (53 genes, known to date) providing an overall estimated sensitivity of 80% and a specificity of 99%. The sequencing approaches that are commonly available at present, for single nucleotide identification, have a sensitivity and specificity up to 75% depending on the sequencing coverage.

The DNA sequencing limitations for single nucleotide mutations identification is due to technological errors that can be introduced during the sequencing process. These small errors can easily be interpreted as pathological changes in the genome. It is possible to avoid this problem by increasing the sequencing coverage of the DNA regions of interest. However, this approach dramatically increases the delivery time of the results. Another important aspect that must be considered is the total cost of the process. If sequencing is used in the analysis of the 53 genes associated to HCM, the final cost of the exam can be in an order of 10 times higher than that performed with the **DNA MICROCHIP.**

Regarding the **DNA MICROCHIP** technology, the sensitivity is only limited by the scientific knowledge of the pathology. With the increase of the scientific knowledge about this pathology, it is expected that this method sensitivity will increase remarkably.

Due to the importance of this test to high performance athletes, mostly healthy athletes, all positive DNA regions for all POSITIVE samples are double check. This procedure gives close to a 100% guaranty that no FALSE POSITIVE is reported.

Advisory board

HeartGenetics has been supported during the years by a strong team of well-known scientists and medical doctors. These members of the advisory board are internationally recognized as experts in their own field and have been working in a close collaboration with the company.

ARLINDO OLIVEIRA

- PhD in Computer Science from UC Berkeley
- CO-founder of ALGOS and KDBIO research groups at INESC-ID
- President of Instituto Superior Técnico

ISABEL MARIA MARQUES CARREIRA

- PhD in Human Genetics and Patology
- Director of Laboratório de Citogenética e Genómica at Universidade de Coimbra

NUNO CARDIM

- Medical doctor (PhD) on Cardiology
- Director of Laboratório de Ecocardiografia at Hosp. da Luz
- Member of the European Society of Cardiology

DOMINGOS GOMES

- Medical doctor on sports medicine
- Member of CESPU

REPORTS DELIVERY TIME

Currently, the tests from the main panel can be performed in days or weeks.

Pathologies	Normal Time Delivery
Cardiomyopathies: HCM/DCM/ARVD Brugada/Noonan Syndromes	4 weeks
Marfan/QTs Syndromes	6 weeks
Thrombophilia/Leopard Syndrome	5 days
Arterial Hypertension/ Genetic Predisposition: Sport Performance	5 days

** In case of an emergency, all exams can be performed in 5 days.

LABORATORY FACILITIES

Located at Taguspark Business Incubator (http://www.taguspark.pt), a science and technology park, Portugal, HeartGenetics new lab facilities are managed according to the highest standards of quality. With the goal of being a reference

laboratory with high volumes, the company is implementing LEAN principles to meet growing demand for faster turnaround times.

HeartGenetics enrolled several external European quality control panels regarding cardiovascular disease genetic diagnosis and has started ISO9001:2008 certification. Regarding the legal environment, there are no special concerns and for now there is no licensing requirements concerning genetics laboratories in Portugal. Nevertheless, HeartGenetics has already submitted a license application as a regular laboratory.

Fig 2 – Taguspark Business Incubator, Oeiras, Portugal

Fig 3 - Laboratory facilities and technology