HEARTGENETICS
GENETICS & BIOTECHNOLOGY

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INDEX

HEARTGENETICS
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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 SUPPORT PHYSICIANS IMPROVE HEART MEDICINE.

HEARTGENETICS
GENETICS & BIOTECHNOLOGY

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.

Oeiras, November 2013

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 have been 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, during 2014, we plan to start the commercialization of all the tests in described in table 2.

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.

Pathology	Number of associated genes
Hypertrophic Cardiomyopathy	Full panel - 53 genes *ACTA1, ACTC1, ACTN2, ANKRD1, BRAF, CALM3, CALR3, CASQ2, CAV3, COA5, COX15, CSRP3, DES, FHL1, FHOD3, FXN, GLA, JPH2, KLF10, MAP2K1, MAP2K2, MRPL3, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYO6, MYOM1, MYOZ2, MYPN, NDUFAF1, NDUFV2, NEXN, OBSCN, PDLIM3, PLN, PRKAG2, RAF1, SLC25A3, SLC25A4, SOS1, SRI, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TRIM63, TTN, VCL*
Genetic risk factors for Thrombophilia	Full panel - 10 genes *F13A*, FII, *FV, FBG*, *GP1BA*, *MTHFR*, *PAI1*, *PROCR*, *PROS1, SERPNIC1*
Molecular Risk Factors for Arterial Hypertension	Stage 1 - 35 genes *ACE, ACE2, ADD1, ADRA1A, ADRB1, ADRB2, AGT, AGTR1, AGTR2, CACNA1A, CACNA1H, CACNB2, CALCA, CLCNKA, CLCNKB, CYP4A11, ECE1, EDN1, EDNRA, FGF5, GNB3, GRK4, HSD11B2, NEDD4L, NOS2, NOS3, NPPA, NPPC, NR3C2, REN, SCNN1A, SCNN1B, SLC12A3, STK39, WNK1*
	Stage 2 - 33 genes *ACE, ADC, ADRA1A, ADRA2B, AGT, BDKRB2, CORIN, CYBA, CYP11B1, CYP11B2, CYP17A1, CYP2J2, DRD3, ECE1, EDN1, EDN2, HSD11B2, GCH1, KCNJ1, KCNJ5, KCNMA1, KCNMB1, NOS3, NPPA, NPR1, NR3C2, RETN, SCNN1A, SCNN1B, SCNN1G, SLC12A1, SLC12A3, VHL*
	Full panel – 56 genes *ACE, ACE2, ADC, ADD1, ADRA1A, ADRA2B, ADRB1, ADRB2, AGT, AGTR1, AGTR2, BDKRB2, CACNA1A, CACNA1H, CACNB2, CALCA, CLCNKA, CLCNKB, CORIN, CYBA, CYP11B1, CYP11B2, CYP17A1, CYP2J2, CYP4A11, DRD3, ECE1, EDN1, EDN2, EDNRA, FGF5, GCH1, GNB3, GRK4, HSD11B2, KCNJ1, KCNJ5, KCNMA1, KCNMB1, NEDD4L, NOS2, NOS3, NPPA, NPPC, NPR1, NR3C2, REN, RETN, SCNN1A, SCNN1B, SCNN1G, SLC12A1, SLC12A3, STK39, VHL, WNK1*

Table 1 – 2013 Cardiovascular genetic panel

Familial genetic studies 2013

The 2013 Cardiovascular Panel includes several familial genetic evaluations. These tests are based on the knowledge of the genetic alteration previously identified for the index case, for the following pathologies:

- Hypertrophic Cardiomyopathy
- Dilated Cardiomyopathy
- Long and Short QT Syndromes
- Brugada Syndrome
- Noonan Syndrome and associated syndromes
- Marfan Syndrome and associated syndromes

Pathology	Number of associated genes
Dilated Cardiomyopathy	45 genes *ABCC9, ACTC1, ACTN2, ADRB1, ADRB2, ADRB3, ANKRD1, ABG3, CRYAB, CSRP3, CTF1, DES, DMD, DSG2, EYA4, FKTN, FHL2, FKRP, ILK, LAMA2, LAMA4, LBD3, LMNA, MYBPC3, MYH6, MYH7, MYPN, NEBL, NEXN, PDLIM, PLN, PSEN1, PSEN2, RBM20, SCN5A, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, VCL*
Arrhythmogenic Right Ventricular Cardiomyopathy	12 genes *CTNNA3, DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, RYR2 TMEM43, TTN, TGFB3*
Long and Short QT Syndromes	15 genes *CACNA1C, CACNA2D1, CAV3, KCNQ1, KCNH2, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ5, KCNQ1, RYR2, SCN4B, SCN5A, SNTA1*
Leopard Syndrome	3 genes *BRAF, PTPN11, RAF1*
Brugada Syndrome	5 genes *CACNA1C, KCNE3, SCN1BB, SCN3B, SCN5A*
Noonan Syndrome and associated syndromes	9 genes *BRAF, CBL, KRAS, MAP2K1, NRAS, PTPN11, RAF1, SHOC2, SOS1*
Marfan Syndrome and associated syndromes	6 genes *ACTA2, FBN1, MYH11, SMAD3, TGFBR1, TGFBR2*

Table 2 – 2014 New cardiovascular genetic panel

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 112 genetic variations in 56 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). More than 900 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. HeartGenetics HCM genetic panel enables to test 53 genes related to HCM, in a very short time, up to five times faster and presenting an accuracy of 99%.

TECHNOLOGY/INNOVATION

Cardiovascular associated diseases are commonly considered multifactorial. The relative risk for these diseases results from genetic, environmental and lifestyle causes. Nowadays, the benefits of gene-based diagnosis of cardiovascular associated diseases for clinical medicine are severely limited by (1) considerable costs of current genetic testing strategies: automated sequencing and Next-Generation Sequencing (NGS), by (2) an incomplete screening of all disease genes and by (3) the time lasting for delivery of the results, that ranges from 4 to 12 months is most cases. HeartGenetics genetic diagnosis method, based on a **DNA MICROCHIP** (Fig1), makes use of a methodology that enables it to perform the analysis of a very large number of genetic alterations simultaneously, in a reliable, fast and cost-effectiveness manner.

The **innovation** at HeartGenetics, resulting from more than 7 years research, addressed all these current limitations. HeartGenetics is now able to provide a disruptive methodology that includes proprietary knowledge about genetic alterations associated to a number of cardiovascular pathologies and a method for the personalization of a state-of-the-art genomic technology, enabling very efficient and cost effective genetic tests. This technology is coupled with a new set of sophisticated bioinformatics tools that analyse and integrate large volumes of heterogeneous data, including genetic and clinical data. All together, this new methodology enables the company to develop a new service that is helping physicians to determine individuals and patients health at different stages, leading to a more accurate diagnosis, prognosis and risk stratification.

HeartGenetics technology is based on the integration of a set of known techniques and thus is not patented, but holds a trade secret that includes the data and the way it is managed. Our proprietary base of knowledge was validated by geneticists and medical cardiologists from the main Portuguese Hospitals, in the context of a number of scientific collaborations during seven years of research (Cardim et al., Revista Portuguesa de Cardiologia (Elsevier) 24 (12):1463-1476, 2005; Santos et al., BMC Medical Genetics 13:17, 2012; Santos et al., Revista Portuguesa de Cardiologia (Elsevier) 30:7-18, 2011).

HeartGenetics HCM genetic testing has been already proved to be a valuable tool. Portuguese cardiologists and Medical Geneticist had already take measures based on in their clinical diagnosis and on the genetic testing result. In these cases, genetics have played an important role in the final diagnosis and risk stratification.

The **DNA MICROCHIP** includes all the genetic variants that, to date, have been proved to be the main cause of a specific cardiac genetic disease. This is something that existing companies/genetic tests cannot cope with, due to technological limitations. The method also leads to the identification of genetic variants that are considered as molecular markers or genetic risk factors correlated with cardiovascular associated diseases. The knowledge about these genetic variants is obtained by merging a proprietary database of specific genetic mutations with the relevant data available at the Database of Human Gene Mutation Data (HGMD). All the genetic variants under analysis have been curated by medical geneticists and cardiologists.

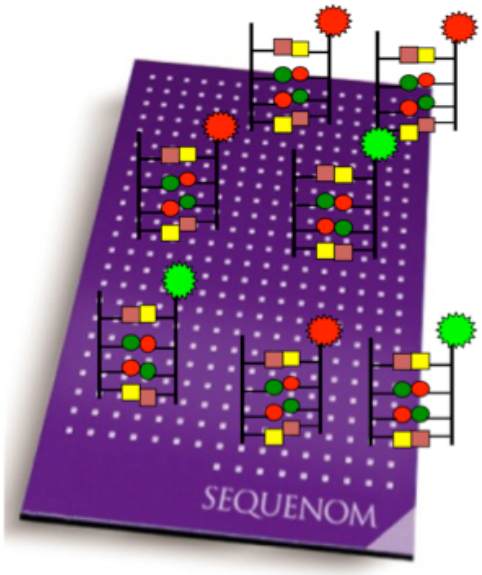

Fig1 – **DNA MICROCHIP (Courtesy of Sequenom®)**

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	4 weeks
Thrombophilia	10 days
Arterial Hypertension	10 days
Familial Studies	10 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

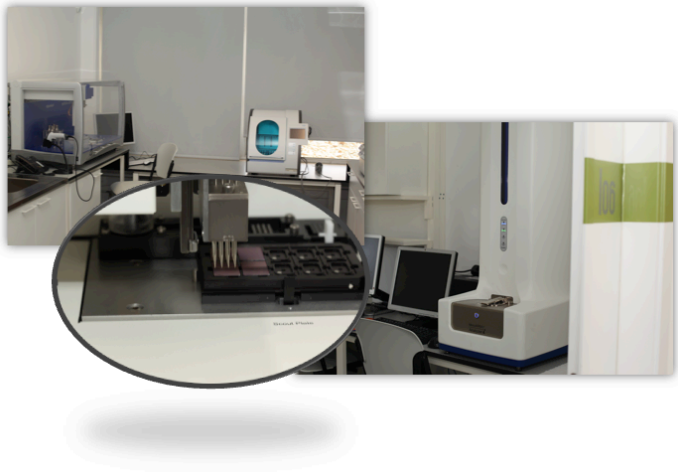

Fig 3 - Laboratory facilities and technology