









# The Value of Biomarkers in Disease Prevention for a Better Quality of Life

AICUBE
INTELLIGENCE INSIDE

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## INTELLIGENCE INSIDE

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# 1 - PROJECT OVERVIEW

## Main Goals

AICube wants to capture the opportunity the **health care sector** is offering in recent years, together with the important technological innovation provided by **artificial intelligence** and in particular Machine Learning. The costs for the community in patient care are becoming **unsustainable** for most industrialised countries; moreover, the increase in spending in the health care sector is not necessarily reflected in better care for patients.

The opportunity that has been presenting itself for some time now is to provide innovative solutions, in order to limit costs, in the treatment of diseases in order to redirect them to **prevention** with the aim of reducing the number of deaths linked in particular to **non-communicable diseases** (NCDs) by increasing people's life expectancy and quality of life. In addition, we are considering **undertaking** an evolution of the strategy, necessarily tied to recent pandemic events. **Covid-19** has changed the perspective on health and perceptions of safety dramatically. The possibility of contracting the virus and its consequences **changed the paradigm**. The possibility to develop with strategic partners the detection of Covid-19 on saliva has become one of our objectives while maintaining of course the **fundamental characteristics** of the original product. It is not an easy path, but universities, companies, and research centres are submitting daily publications about it. We are confident that by investing in this area we will soon be able to evaluate whether our **DOC.D©©** (Data Organized Collector Devices) device is implementable in the necessary features.

In AICube we believe that prevention and **predictive medicine** using new Machine Learning technologies are fundamental tools to operate in a market with the **highest expected growth** in which it is **mandatory to invest** now and in the coming years.

# GENERAL FRAMEWORK

## Financial crisis in the health system

The financial crisis in the health system is a significant concern as healthcare costs continue to rise and funding becomes increasingly limited. The high costs of healthcare can lead to limited access to care for some individuals and can also lead to financial hardships, such as medical debt, for both individuals and families. To tackle this crisis, prevention is considered as a key strategy. Investing in preventative measures such as promoting healthy lifestyles, providing access to affordable healthy food and physical activity options, and increasing access to preventive healthcare services can help to reduce the burden of chronic diseases, which are the main drivers of healthcare costs. Additionally, preventative measures can also help to reduce healthcare costs by reducing the need for more expensive treatments and hospital visits. Furthermore, prevention can also improve the overall health of the population, leading to increased productivity and a higher quality of life. By focusing on prevention, healthcare systems can become more sustainable, efficient and cost-effective, providing better care for all individuals.

The cost of healthcare is a significant concern around the world, as it continues to rise and become increasingly unaffordable for both individuals and governments. According to data from the World Health Organization (WHO), global health expenditure is projected to reach $18.3 trillion by 2040. The main drivers of healthcare costs include the aging of the population, the increasing prevalence of chronic diseases, and the high costs of new technologies and treatments.

In the United States, healthcare costs are among the highest in the world, with spending projected to reach $6 trillion by 2027. According to the Centers for Medicare and Medicaid Services (CMS), healthcare spending as a percentage of GDP is projected to increase from 17.7% in 2021 to 19.7% by 2040.

In Europe, healthcare costs are also a major concern, with spending projected to reach €1.2 trillion by 2040. According to Eurostat, healthcare spending as a percentage of GDP is projected to increase from 9.1% in 2020 to 10.4% by 2040.

In developing countries, healthcare costs are also a significant concern, with spending projected to reach $2.1 trillion by 2040. According to the World Bank, healthcare spending as a percentage of GDP is projected to increase from 4.8% in 2020 to 5.5% by 2040.

It's worth noting that these predictions are based on current trends and certain events such as pandemics, economic downturns, and changes in healthcare policies could significantly impact the forecasted figures.

## Population ageing

World population ageing is a growing concern as the number of older individuals increases globally. According to the United Nations, the proportion of older people (aged 65 years or older) is projected to increase from 7% in 2020 to 16% in 2050 and 29% in 2100.

This demographic shift is driven by factors such as declining fertility rates, increasing life expectancy, and improved healthcare. This presents both opportunities and challenges for society. On one hand, older individuals bring valuable experience, knowledge, and skills to the workforce and society. On the other hand, an aging population can put a strain on healthcare systems, pension schemes, and social welfare programs.

It also raises concerns about access to healthcare and support services, as well as housing and transportation for older individuals. World population ageing varies by country and region. Developed countries, such as

Japan and Italy, have a higher proportion of older individuals and a lower proportion of younger individuals. According to the United Nations, Japan had the highest proportion of older individuals (27% in 2020) and is expected to have the highest proportion of older individuals in 2050 (38%).

On the other hand, developing countries, such as India and Nigeria, have a lower proportion of older individuals and a higher proportion of younger individuals. India, for example, had only 8% of its population aged 65 or older in 2020 and is expected to reach only 12% in 2050. However, it's worth noting that all countries are experiencing an increase in the proportion of older individuals as the global population ages, and governments and organizations around the world will need to address the challenges and opportunities that come with an aging population.

### Population Growth

World population growth is a significant global issue. According to the United Nations, the world population reached 7.9 billion in 2020 and is projected to reach 8.5 billion by 2030, 9.7 billion by 2050, and 11.2 billion by 2100. This steady increase in population is driven by factors such as decreasing infant mortality rates and increasing life expectancy. However, this growth also puts pressure on resources and the environment, and raises concerns about food security, access to clean water, and the ability to provide adequate housing and healthcare for all. Additionally, population growth can exacerbate issues such as poverty, unemployment, and overcrowding in urban areas. It is important for governments and organizations to address these challenges and implement sustainable solutions to manage population growth and its effects on society and the planet.

## Life expectancy

Global life expectancy in 2015 was 71.4 years. Estimates of life expectancy per country for 2015 are shown in Fig.1. Twenty-nine countries have an average life expectancy of 80 years or more. Life expectancy exceeds 82 years in 12 countries: Switzerland, Spain, Italy, Iceland, Israel, France and Sweden in the WHO European region; Japan, Singapore, Australia and the Republic of Korea in the WHO Western Pacific region; and Canada in the WHO Americas region.

At the bottom end of the list there are still 22 countries with life expectancy under 60 years - all in sub-Saharan Africa.

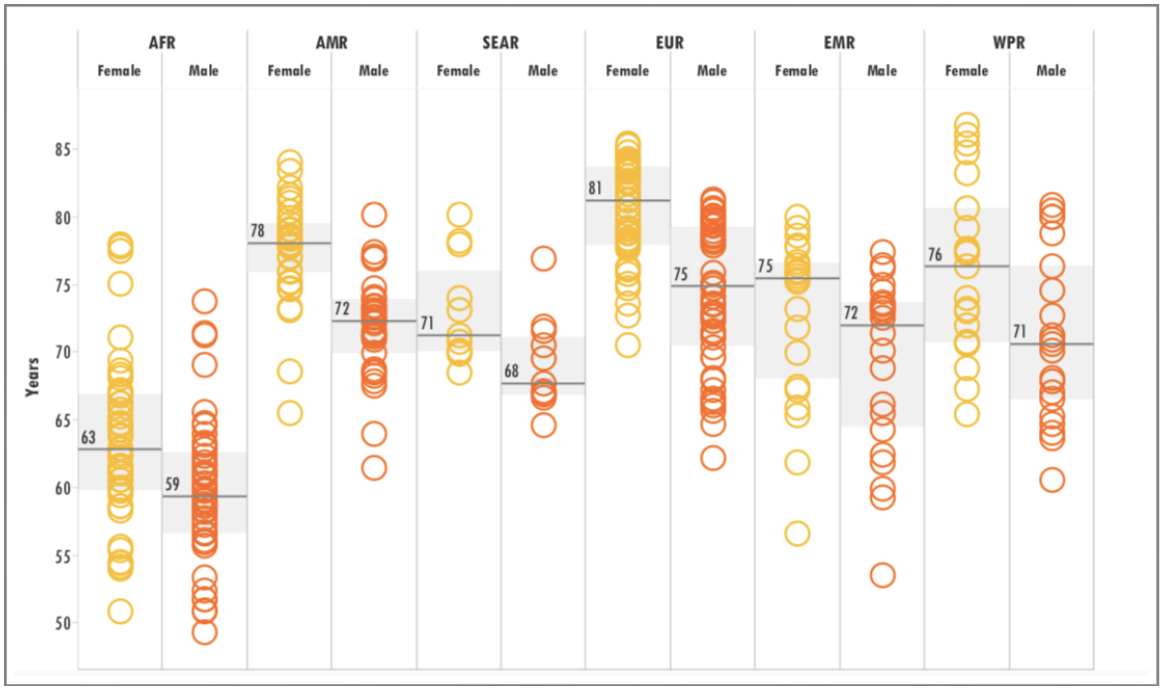



Fig.1

**Legenda:**

AFR - African Region ; AMR - Region of Americas; SEAR - South East Asia Region; EUR - European Region; EMR - Eastern Mediterranean Region; WPR - Western Pacific Region

## Quality care

Healthcare expenditure, in relation to its GDP, varies greatly by country (Fig.2). Unfortunately, higher levels of expenditure do not always produce better results for citizens' health.

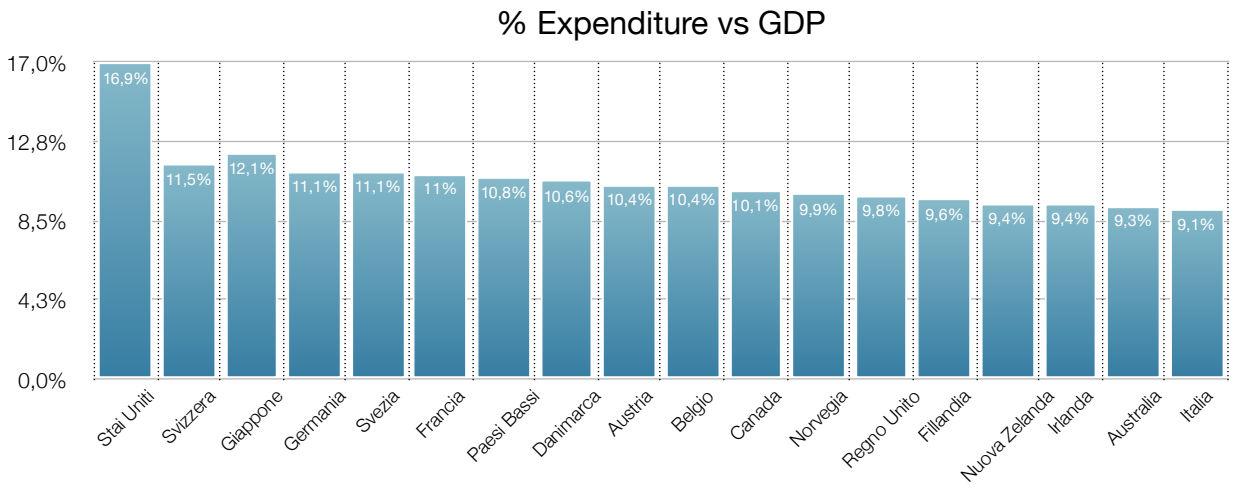



Fig.2

For example, the United States, with an expenditure of 16.9% of GDP in 2016, continues to spend much more on health care than other countries, but despite this, they are in the lower half of the Organisation for Economic Cooperation and Development (OECD) countries Fig.3 with a much lower life expectancy than European countries.

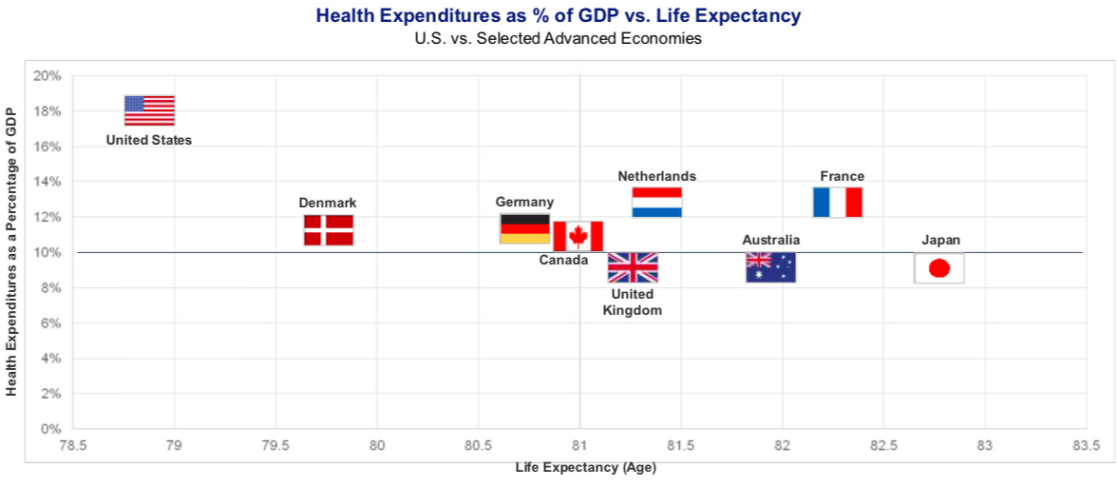



Fig.3

Healthcare spending in the United States now exceeds USD 3 trillion per year, with growth rates increasing in 2024. The main categories of spending are hospital care ($1 trillion), doctors ($635 billion) and prescription drugs ($329 billion).)[1] Fig.4.

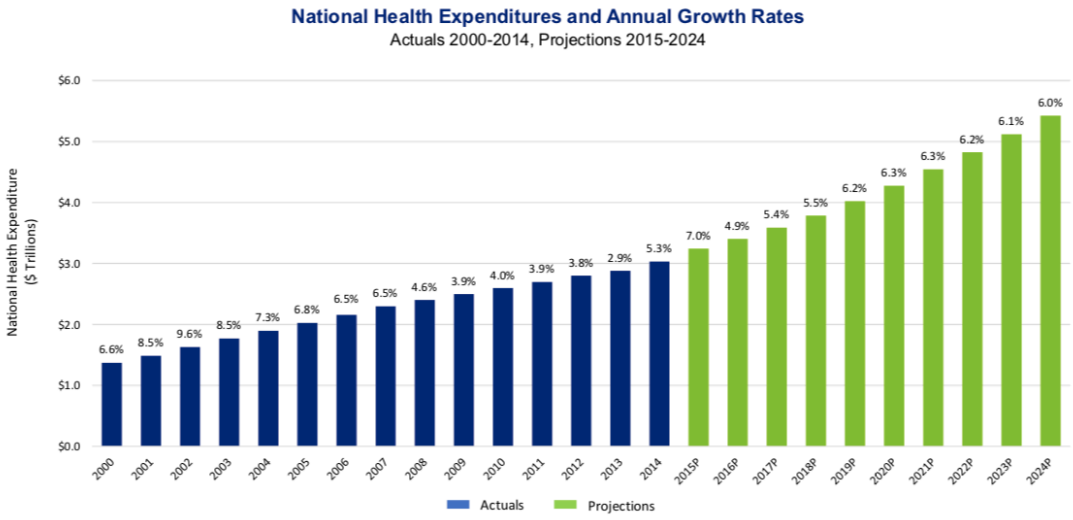
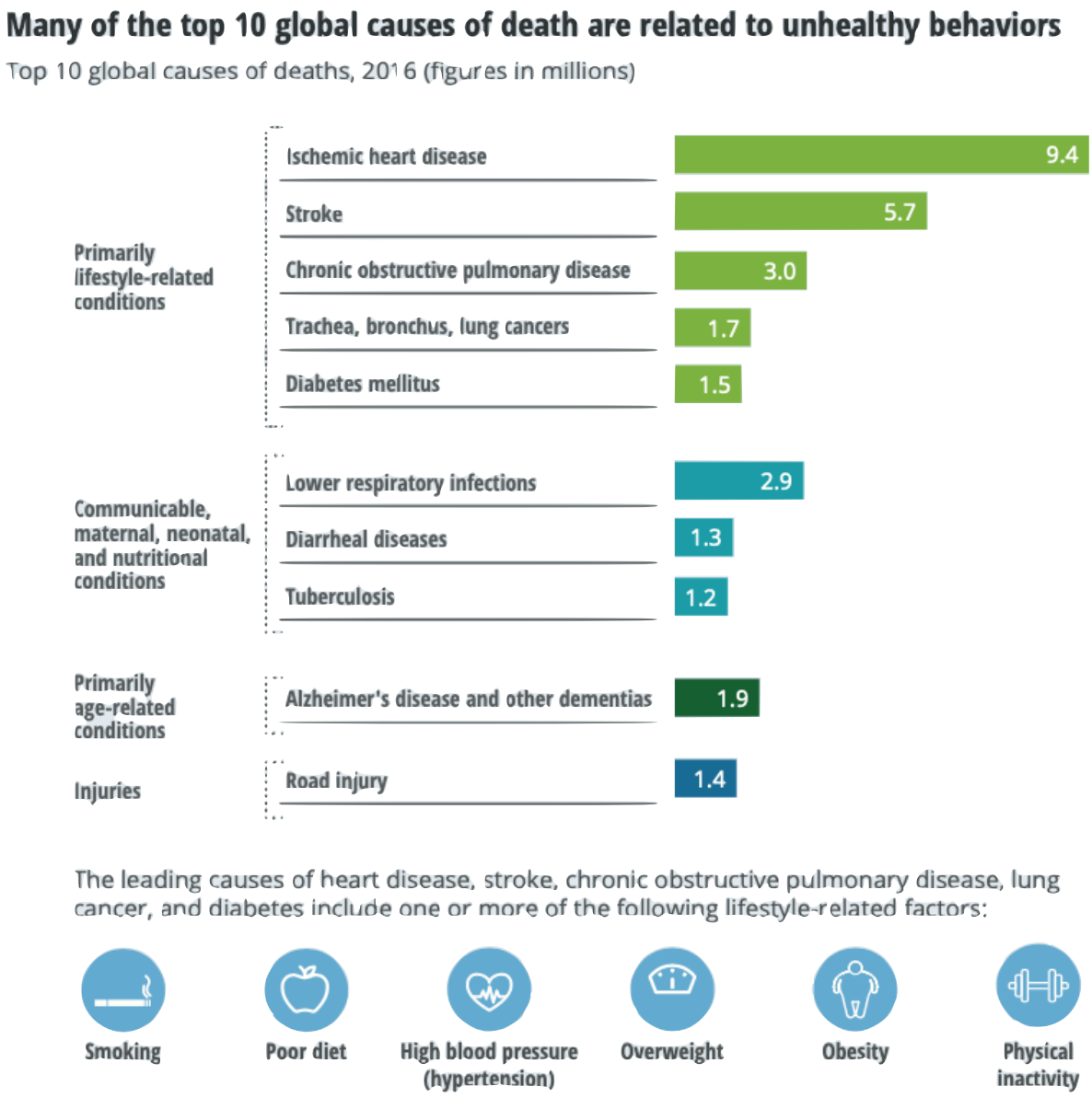



Fig.4

[1] Centers for Medicare and Medicaid Services (CMS) “NHE Tables” and “Historical and Projections 1960-2024” National Health Expenditure Projections, 2016–25: Health Affairs

## Non-communicable diseases (NCDs)

According to the World Health Organisation (WHO)[2] Non-communicable diseases (NCDs) caused 71% of deaths globally, rising from 37% in low-income countries to 88% in high-income countries. All but one of the top 10 causes of death in high income countries are non-communicable diseases. In terms of absolute number of deaths, however, 78% of total NCDs deaths occurred in low and middle income countries.




These statistics should help health authorities to determine the main objective of their actions in public health. A country where deaths from heart disease and diabetes increase rapidly within a few years, for example, has a strong interest in starting a major program to encourage better lifestyles that help prevent these diseases. Similarly, if a country recognises that many children die of pneumonia, but only a small part of the budget is dedicated to providing effective treatment, it can increase spending in this area.

[2] Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. World Health Organization; 2018.

In particular, the No. 1 cause of death in the world is Ischemic Heart Disease (IHDs), followed by Stroke and Dementia. Further back, but no less important is diabetes Mellitus.

Coronary heart disease (CAD), also known as ischemic heart disease (IHD), refers to a group of diseases that includes stable angina, unstable angina, myocardial infarction and sudden cardiac death. It is part of the group of cardiovascular diseases (CVD) of which it is the most common type.
16.6 % of deaths worldwide are caused by this type of disease. It has increased by 3.1 percentage points since 2000.

Stroke, also known as apoplexy, stroke, cerebrovascular insult, or brain attack, occurs when poor blood perfusion to the brain causes cell death. There are two main types of stroke, ischemic stroke, due to lack of blood flow, and hemorrhagic stroke, caused by bleeding; both result in a portion of the brain unable to function properly.
10.2% of deaths worldwide are caused by stroke. Since 2000 the index has increased by 0.3 points.

Dementia is an organically acquired disorder of the previously acquired intellectual functions: memory (short and long term) and at least one between abstract thought, critical capacity, language, space-time orientation, with preservation of the alert state of consciousness.
Dementia and associated diseases (Alzheimer's, etc.) have increased by 2 points, from 1.5% in 2000 to 3.5% in 2016.

Diabetes mellitus is a form of diabetes, a group of metabolic disorders that have in common a persistent instability of the blood glycemic level, passing from conditions of hyperglycemia, more frequent, to conditions of hypoglycemia.
Diabetes mellitus also increased over the same period of time, going from 1.8% to 2.8%.

These diseases together represent 33.1% of the most important causes of death in the world and are steadily increasing (6.4% since 2000).

# THE AICUBE PROJECT

## Prevention and Predictive Medicine

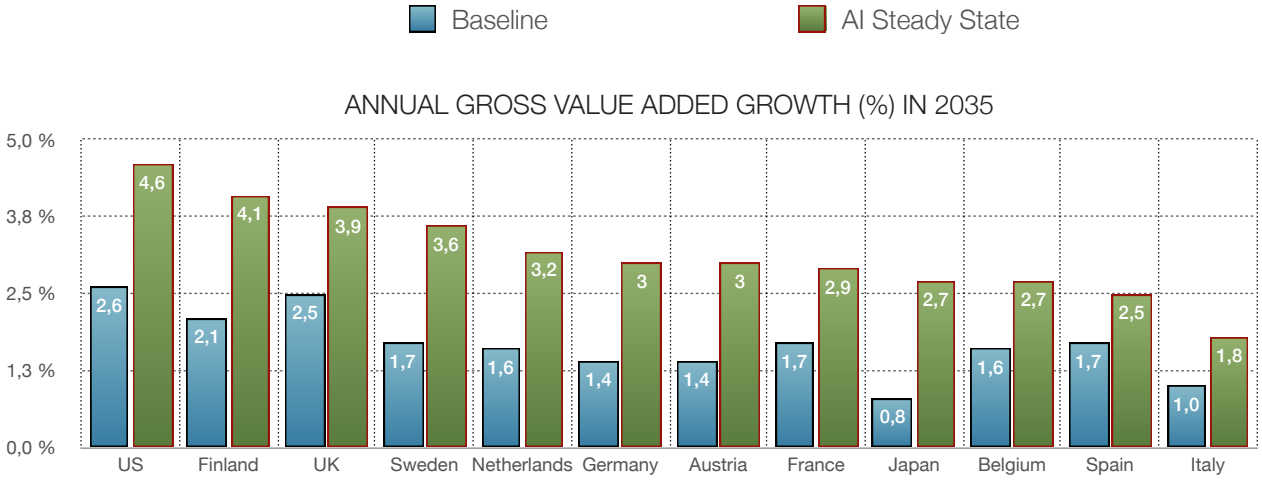
In this scenario, AICube wants to provide alternative and highly innovative solutions for the collection and analysis of specific biomarkers that, through Machine Learning algorithms, develop models of prevention and predictive medicine, suggesting personalised care treatments that improve people's quality of life, thus reducing the cost of associated health care.

The goal is to develop more devices that can collect and process clinical data to start preventing diseases that cause more deaths. Data collection should be daily or weekly, through the use of minimally invasive procedures. One of the key factors is the use of one or more commonly used devices already present in daily life (e.g. electric toothbrush, digital scale, wearable devices, etc.) integrated with specific sensors.

The Machine Learning process will provide, after a short training period, aggregated information and data to the patient / user or to a third party delegated by the user (e.g. General Practitioner, Hospital, Research Centre), but above all possible solutions to the pharmaceutical industry, insurance companies, or research centers.

The health sector is one of the largest and fastest growing segments of Artificial Intelligence application, mainly driven by innovation in clinical research, robotic personal assistants and big data analysis. Companies investing in AI/IV have the opportunity to accelerate their growth over the next three years.[3].

In an analysis conducted by Accenture Research[4] is expected to double GDP growth rates in countries investing in Artificial Intelligence. A significant number of evaluated countries double their additional growth (5 out of 12) and all (except Spain) increase their value by more than 50%.




The increase and accessibility of health data has led to a growing need for Artificial Intelligence technology to improve data mining and computing capabilities. Personalised treatments are reinforced by the growing application of AI in genomics and predictive medicine. It is expected that the emergence of new and promising applications for disease diagnosis and monitoring will further drive market growth.

[3] McKinsey Global Institute AI Adoption and Use Survey ; McKinsey Global Institute Analysis

[4] Accenture AI Economic Growth Infographic - 2016

## The value of Biomarkers

Serum or plasma biomarkers are the traditional "gold standard" for collecting physiological data, although each of them suffers from some drawbacks. Collecting and analysing bio-fluids such as blood can be expensive, time-consuming and invasive for individuals providing samples and professionals analysing samples.
Venipuncture (blood sampling) can induce a response to stress, as demonstrated by several laboratory studies, which may raise doubts about the results for studies that are based on the determination of biomarkers related to stress (e.g. Cortisol) or that work with individuals where a stress response may be high (e.g. Addison's disease) or where it is complicated to collect them (e.g. children and infants). The invasiveness of blood collection protocols also limits the ability of researchers to perform multiple bio-fluid collections, e.g. in studies requiring multiple or cross samples.

## Technological developments

It is important to note that biomarkers for saliva diagnostics are different from conventional serum biomarkers. One of the technical obstacles on the road to developing saliva diagnostics is the lower concentration (100 to 1000 times) of analytes detected in saliva compared to blood. Salivary tests for the screening of drug and alcohol use help to combat the abuse of these substances and are also used by some employers. In addition, the use of saliva analysis of hormones in many clinical and basic research fields has been described in numerous scientific papers.

The post-genomics era offers the opportunity for a simple and parallel approach to genomics and proteomics. Innovative miniaturization technologies, combined with the discovery of disease biomarkers, which goes hand in hand, open the door to the development of methods to detect diseases and monitor health and disease status. There is a great need for practical and accurate diagnostic tools for point-of-care (POC) examinations, which can be used non-invasively. This is of particular importance in developing countries, where many public health risk factors and many diseases remain poorly defined and patients receive inappropriate diagnosis and treatment. In addition, there is little information available on the impact of diseases that can guide health care decisions. Salivary POCs could represent a great opportunity. Currently, there are no specific POC systems for saliva that allow rapid diagnosis and/or screening of diseases. However, in this area, when saliva was used as a biological matrix on portable instruments, interesting results have been recorded.

Saliva is a physiological liquid of increasing importance with a significant number of applications for clinical and research use.[5],[6],[7]. Saliva has grown in popularity in recent years, balancing the potential strengths and weaknesses of this bio-fluid. Saliva is different from other common biological fluids such as blood, urine or tears in that it is easily available, with minimal risk to the donor and reduced costs for its collection, transport and analysis. Salivary tests can be performed quickly, providing the opportunity to evaluate biomarkers in real time with lower costs, faster response times and minimum training requirements.

Saliva is an aqueous substance secreted by the salivary glands. Human saliva is 99.5% water, the other 0.5% electrolytes, glycoproteins, hormones, enzymes and antibacterial compounds such as type A immunoglobulin (IgA). In saliva we can find important biomarkers such as: cortisol, glucose, glycoprotein α-Amilase and

[5] ibid

[6] Clin Chem. 2011 May;57(5):675-87. doi: 10.1373/clinchem.2010.153767. Epub 2011 Mar 7.

[7] Potential applications of human saliva as diagnostic fluid - M.Castagnola, P.M.Picciotti, I.Messana, C.Fanali, A.Fiorita, T.Cabras, I.Calò, E.Pisano, G.C.Passali, F.Iavarone, G.Paludetti, E.Scarano

molecules containing information relevant for the prevention of certain cardiovascular diseases (CVD).[8] e.g., C-reactive protein (PCR), myoglobin, sICAM-1 (Soluble intercellular adhesion molecule-1)[9].

[8] Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Aug;114(2):207-14. doi: 10.1016/j.oooo.2012.03.003.

[9] ibid

## Patent

AICube has patented its DOC.D© (N° 102018000006925) and extended it through a PCT procedure (N° WO2020008336 - PCT/IB2019/055598) to 150 other countries. We apply local for registration in US, China and Europe.

DOC.D© is the first device to acquire a sample of physiological liquid (saliva), consisting of a device (Fig.6) that collects several biomarkers on a daily and non-invasive basis, a POP (Point of Prevention) analyzer with a disposable cartridge with a number of tests included and a server called "The Cube" connected wirelessly that processes data using a proprietary Machine Learning algorithm.

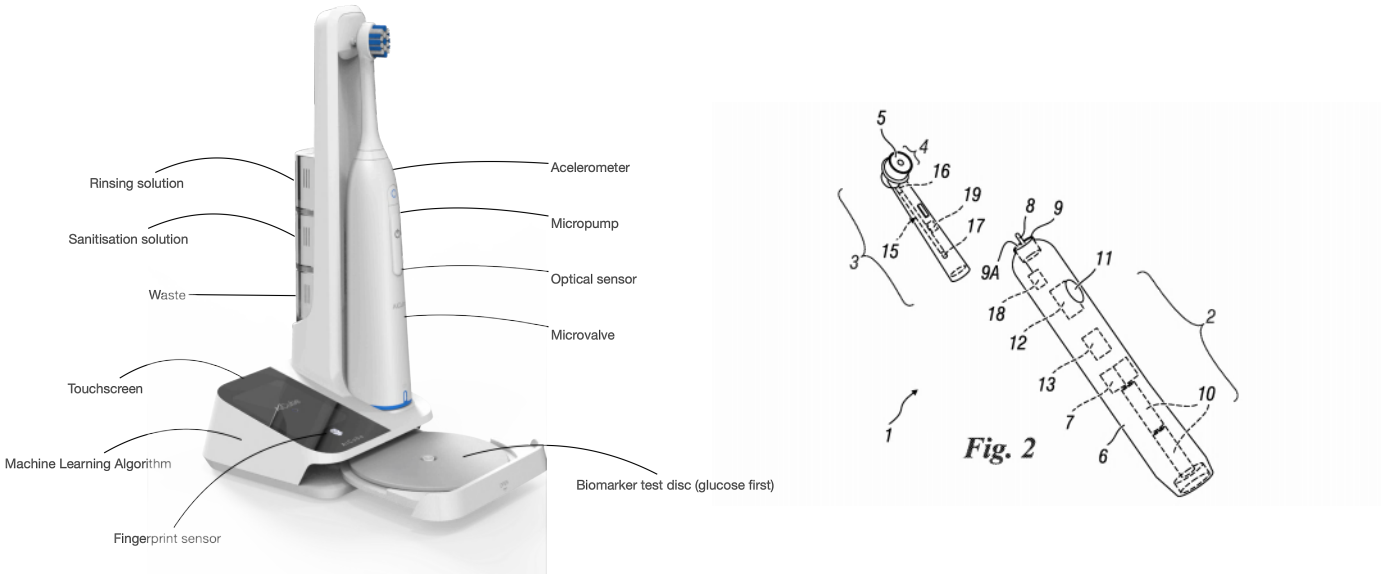



Fig.6

DOC.D© is basically an “augmented” electric toothbrush in which a saliva sample is collected and subsequently analysed in the analyser (POP). The system involves the identification of the user through the use of a fingerprint reader. This prevents the wrong association of the analysed sample to an incorrect user. In addition, an accelerometer is inserted into the toothbrush to determine the occurrence or worsening of diseases such as Parkinson's disease.

The system consists of several sensors and alarms (visual and audible) to alert the user to the correct sample collection. Once the sample has been collected, and brushed, the toothbrush will return to the (POP) for analysis and recharging.

The device will quickly analyse the saliva sample by evaluating the different biomarkers chosen by the user through a specific app provided during the installation of the device. In fact, it will be able to select, for example, a daily glucose analysis (if diabetic), while it may decide to check the best time to have a child (estrogen) or evaluate its risk factor of cardiovascular disease by measuring the C-Reactive protein.

The principle behind the AICUBE system is to develop individual devices that collect clinical data in order to prevent the most common diseases. Data collection must be daily or weekly, through the use of minimally invasive procedures. One of the key factors is the use of one or more common devices already present in daily life (e.g. electric toothbrush, digital bathroom scale, wearable devices, etc.) integrated with specific sensors. The data collected by the devices will be stored in a server called “The Cube" with an automatic learning algorithm inside. The Machine Learning process will provide, after a reasonable training period, suggestions to the patient / user or delegated members by the user (e.g. relatives, MD, Hospital). The data collected through the devices will be included anonymously within an encrypted and secure database with the aim of greatly increasing the quality level of the prediction process through machine learning. The Cube server itself has been loaded with a specific data set for each bio-marker and is continuously updated.

## Technology adopted

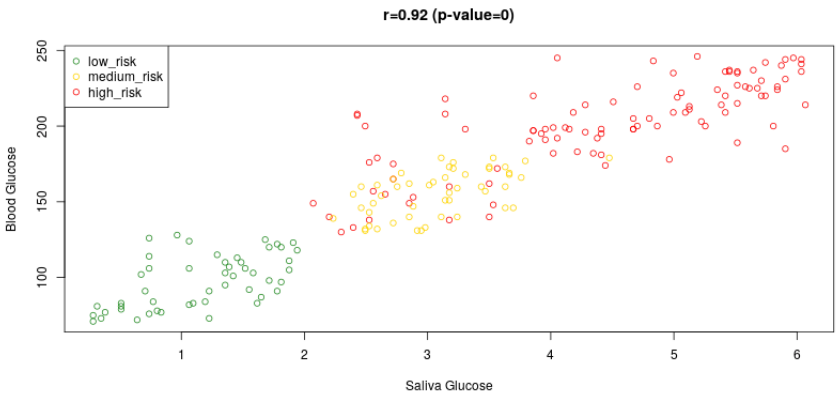
Within the device several technologies are adopted. As the unique patient recognition, the measurement of the different biomarkers and their processing through Machine Learning algorithms.

The patent filed bases its technology on existing systems, but used to date independently and unrelated to each other. The finger print sensor uses ultrasound technology offers the ability to uniquely identify the Patient / User who has previously registered access to the device. Recognition is also possible in non-optimal conditions such as presence of water, soaps, creams on surfaces that can get between the finger and the sensor.

Biometric sensors for the measurement of some biomarkers have been developed and validated by research centers, but not yet commercialized.[10].

The publication (Noninvasive glucose monitoring using nano-biosensor saliva) shows how it is possible to build a sensor that detects glucose in saliva for diabetic patients.

The graph shows the correlation (necessary) for the evaluation of glucose in the two fluids (blood and saliva).




In addition, the collection of samples, salivary and non-salivary, almost always takes place in analysis centers or in the presence of a doctor. The real innovation therefore lies in the aggregated collection of data in a non-invasive way, their processing through Machine Learning algorithms, the possibility of elaborating lifestyles and guidelines for the prevention of the most common diseases.

AICUBE is collaborating with the Italian Institute of Technology (IIT) to develop our sensor for the measurement of glucose in saliva based on nanotechnology. An article on the effectiveness[11] of the system has been published. Moreover, in 2020 we have confirmed the principle through a clinical trial conducted at the University of Pavia. So far a sensor platform based on gold nanostructures has been developed that can recognize a hyperglycemia condition from a small saliva sample within minutes. Thanks to the use of a special design of the nanoparticles and a calibrated mix of reagents, it was possible to exploit an original and very efficient colorimetric mechanism based on the structural reorganization (shape change) of the nanoparticles themselves. The first steps towards the realization of a portable device that has been validated on real samples of saliva from diabetic patients have also been successfully carried out.

[10] Noninvasive glucose monitoring using saliva nano-biosensor - Wenjun Zhang, Yunqing Du, Ming L. Wang

[11] Donati Paolo, Pomili Tania, Boselli Luca, Pompa Pier P. - Colorimetric Nanoplasmonics to Spot Hyperglycemia From Saliva - Frontiers in Bioengineering and Biotechnology

Further tests on decompensated patients (medium-high blood glucose values) are scheduled to complete the validation of the prototype. In addition, a series of further developments on the prototype (aging, scalability, reagent optimization, etc.) will be necessary in order to obtain a more advanced prototype that approaches a sensor system of practical applicability.

AICUBE has also developed, with the support of a specialised company in Artificial Intelligence (RES), the Machine Learning algorithm that defines a risk index for the development of type II Diabetes based on the patient's medical history and the collection of glucose data in saliva.The system will be validated shortly during the clinical Trial at the University of Pavia. (see graph for preliminary results)

In addition, we are developing a machine learning algorithm for creating a tremor severity index in parkinsonian patients using an accelerometer in the body of the toothbrush.

# 2 - MARKET ANALYSIS

The markets in which AICube competes are healthcare, mainly focused on prevention and predictive medicine, insurance market with the need to better profile customers and Pharma providing specific expertise in development of new drugs or checking the therapeutic adherence as the degree to which the patient follows the physician's recommendations regarding doses, timing and frequency of medication intake for the entire duration of therapy.

## Healthcare costs

Looking in detail at trends over the last decade, the average share of GDP related to health care jumped sharply in 2009 as overall economic conditions rapidly deteriorated in many countries, but health spending growth was generally maintained. (Fig 7a)

On a country-by-country basis there have been differing patterns in the health-to-GDP ratio in recent years. In the United States, after a number of years (2009-14) when the ratio of health spending to GDP remained stable at around 16.4%, this rapidly increased to 17.1% with the onset of a number of coverage changes, before falling to 16.9% in 2018 as overall economic growth in the US economy outpaced the growth in health spending.

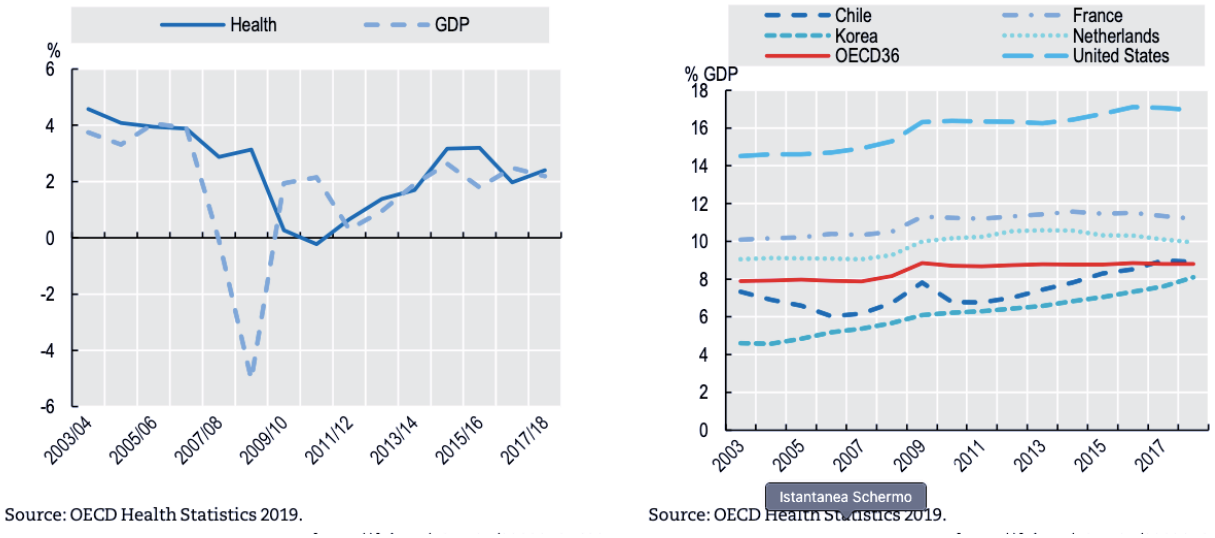



Fig.7

Health expenditure has outpaced economic growth across OECD countries over most of the past half century. This additional spending has contributed to improvements in health outcomes and been an important source of economic growth and jobs. Nevertheless, financial sustainability is becoming an increasing concern, as most countries draw their funding largely from public sources (OECD, 2015[1]). Projections of health expenditure growth can give countries a perspective regarding how quickly, and by how much, health expenditure could rise compared to general economic growth, or with respect to a country's population (Lorenzoni et al., 2019[2]).

Over the long run, health expenditure has largely outpaced GDP growth across all OECD countries, even taking into account the volatility following the financial crisis of 2007-08 Over the period 2000-15, annual health spending growth across the OECD was 3.0%, compared to GDP growth of 2.3%. By comparison, for the period 2015-2030, health expenditure per capita is projected to grow at an average annual rate of 2.7% across the OECD under a base scenario (with GDP growth averaging 2.1%). Average growth is projected to be as low as 2.2% with greater cost control, but as high as 3.1% in a cost pressure scenario. These scenarios reflect diverging assumptions such as countries' economic growth, productivity and healthy ageing. However, across OECD countries health expenditure is projected to outpace GDP growth in the next 15 years in all scenarios.

## Public Governance

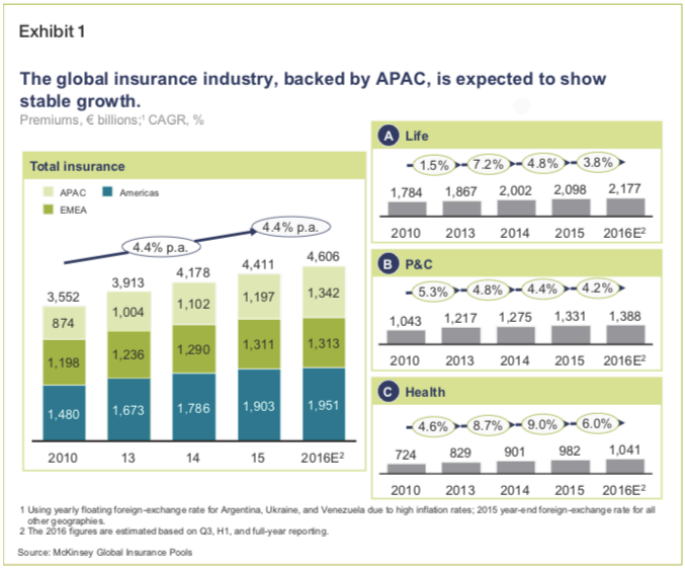
Only 37.63% of countries have regularly monitored the progress of their health policy / strategy / national health plan.

Governments around the world know that to continue to provide quality services, they must transform them by innovating. Populations are ageing, putting enormous pressure on health and social services; education systems need to provide young people with the skills for a technology-driven world; and the changing cities we live in are creating new demands on infrastructure. Many government services do not meet the growing expectations of citizens. These trends are contributing to public discontent.

The failure rate of governmental change is too high. It represents a huge missed opportunity to more effectively address major societal challenges, so that limited public resources can be used more productively. If governments around the world could provide new and innovative services, they could save up to $3.5 trillion a year by 2021, while maintaining today's levels of service quality. Alternatively, they could release resources for the needs of the citizens they care most about, keeping government overheads constant.

## Insurance

The insurance sector is a key component of the economy by virtue of the amount of premiums it collects, the scale of its investment and, primarily, the essential social and economic role it plays in covering personal and business risks.

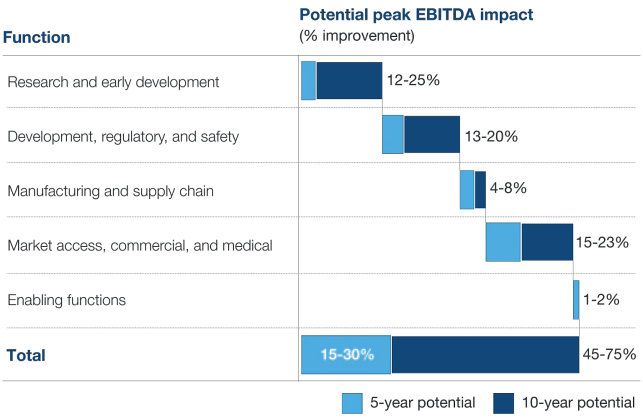



Gross premiums grew on average in both life and non-life insurance in real terms in 2016. In 2016, gross premiums increased on average by 3.7% in life and 2.0% in non-life insurance between 40 reporting countries.

Several factors can influence sales of life insurance products, which in turn influence premium volume. Customer demand for insurance products can be influenced by taxes on these products, their commissions, the returns offered to policyholders, the availability of alternative financial products and customer perception of these products.

Both life and non-life insurance can have scope for expansion as penetration of these sectors is still relatively low compared to the size of the economy (measured by GDP). Therefore, in the long term, depending on the economic environment, further expansion of insurance markets and gross premiums can be expected.

Advanced analytics could improve EBITDA for pharmaceutical companies by 45%–75%




Source: McKinsey analysis of potential based on blinded client information

McKinsey&Company

## Pharma

The increasing availability of real data has generated enormous interest in health care. According to some estimates, health data volumes are increasing by 48% per year and the last decade has seen a boom in the collection and aggregation of this information. Among these data, electronic health records (EHR) offer one of the greatest opportunities to produce new solutions and increase the current level of patient care.

Undoubtedly, the use of advanced analysis represents a real and significant opportunity for the pharmaceutical industry. Estimates of the operational efficiencies that can be achieved by reducing the impact of advanced analysis range from 15 to 30 % of EHR over five years, accelerating from 45 to 70 % over a decade given the potential impact of predictive modeling in the discovery and optimization of successful new therapies. In increasingly cost-constrained global healthcare markets, medicines that use analysis to make advanced data-based decisions over the next 1-3 years will gain a decisive advantage over their competitors.

With the right data, organizational processes and applied clinical knowledge, machine learning and artificial intelligence can now make a significant difference in the pharmaceutical and healthcare sector despite some remaining limitations.

## Competitors

The main competitors in this market are "traditional" service providers for disease prevention and treatment. Diagnostic centers and hospital care units usually respond to the needs of users/patients who need to make a preventive diagnosis or assess the status of their disease. The general practitioner suggests the best path of prevention or treatment for each individual patient based on the electronic health record (EHR). Moreover, for some pathologies that we want to refer to in terms of prevention and/or treatment there are portable devices that use blood as biological fluid for testing.

The main biomarkers currently in the AICube system development pipeline are Glucose, Cortisol and C-reactive protein, but other sensor and biomarkers are already available in the market to be included.

## BIOMARKERS :

## GLUCOSE

As far as glucose and the associated disease (Diabetes) are concerned, today AICube competes with two systems: blood sampling with cartridges and the new continuous monitoring system (CGM). The reference market is that of diabetic patients (Type 1 and 2) who need a precise measurement of glucose levels.

**Prediabets:**

Prediabetes is a condition in which blood sugar levels are higher than normal, but not yet high enough to be diagnosed as type 2 diabetes. According to the World Health Organization (WHO), prediabetes affects 1 in 3 adults worldwide, and is a major risk factor for the development of type 2 diabetes and associated complications such as heart disease and stroke. The good news is that prediabetes is preventable and can be reversed through lifestyle changes.

The primary risk factors for prediabetes are obesity, physical inactivity, and unhealthy diet. Therefore, the cornerstone of prediabetes prevention is lifestyle modification, including a healthy diet, regular physical activity, and weight management.

A healthy diet is essential for preventing prediabetes. A diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats, and low in added sugars and saturated fats, can help lower blood sugar levels and improve insulin sensitivity. The use of a food pyramid is an easy way to understand what to eat and how much of it. The pyramid shows the different food groups in descending order of recommended intake, with the foundation of the pyramid being fruits, vegetables, and whole grains.

Regular physical activity is also crucial for preventing prediabetes. Exercise helps to improve insulin sensitivity, lower blood sugar levels, and promote weight loss. The American College of Sports Medicine recommends at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity per week, in addition to muscle-strengthening activities at least 2 days per week.

Weight management is also an important aspect of prediabetes prevention. Being overweight or obese increases the risk of prediabetes and type 2 diabetes. Achieving and maintaining a healthy

**Diabetes Type 1 and 2:**

The causes of Type 1 diabetes are immune-based and therefore have no connection with eating habits. Type 1 diabetes is caused by insufficient or no insulin production due to the suffering - and destruction - of the beta cells of the Langerhans Islands of the pancreas, the cells responsible for producing the hormone insulin.

In type 2 diabetes, the genetic component plays a more important role than type 1 diabetes, although DT2 cannot be considered a hereditary disease. Environmental and individual factors should obviously not be overlooked. The latter include, for example, overweight and obesity. There is a close relationship between body weight and the development of type 2 diabetes. Most patients with type 2 diabetes (about 80%) are overweight, with a typical accumulation of predominantly abdominal fat that is also considered associated with increased cardiovascular risk. Sedentary lifestyle and an unbalanced diet also contribute to the onset of type 2 diabetes in predisposed individuals.

In type 1 diabetes, therapy with injectable insulin is essential from the onset and diagnosis of the disease. Insulin is life, without it, one dies in a few days.

In type 2 diabetes, therapy is more scalar. Generally, it starts with substantial changes in lifestyle (diet and physical activity) and if these are not sufficient, therapy is associated with oral (oral drugs) and/or subcutaneous (non-insulin injections).

A lifestyle that conforms to the therapy prescribed by the doctor allows good control of the disease and exposes the patient to a lower risk of diabetic complications over time. It has now been widely demonstrated that a careful correction of glycaemia alterations can prevent or significantly reduce the onset or evolution of chronic complications of diabetes mellitus.

**The diabetes market**

It has been estimated that global diabetes market growth will more than double by 2030. Although the incidence rates of type 1 diabetes have remained fairly stable, the number of people diagnosed with type 2 diabetes is steadily increasing. Type 2 diabetes currently accounts for about 90% of all diabetes cases in the United States and Europe and 100% in Asia. In particular, insulin resistance is closely linked to obesity, as 60-70% of type 2 diabetics also suffer from this condition. Insulin resistance is believed to be a gateway to many diseases, including atherosclerosis, coronary artery disease, kidney failure and polycystic ovary syndrome. The market value for type 2 diabetes in the seven major markets of the United States, France, Germany, Italy, Spain, the United Kingdom and Japan will more than double from $26.8 billion in 2016 to about $64 billion by 2026.

The global market for blood glucose test strips was $10.6 billion in 2017. The size of the market is influenced by the prevalence of diabetes, awareness of self-monitoring of blood glucose and the reimbursement of test strips in some countries. This market grew from $9.4 billion in 2013 to $10.64 billion in 2017 at a compound annual growth rate (CAGR) of 3.15% and is expected to grow to $12.93 billion at a CAGR of 5% by 2021.

North America was the largest market for blood glucose test strips in 2017, accounting for 47.1% of the market, at $5.01 billion. This is followed by Western Europe, Asia, South America, the Middle East, Eastern Europe and finally Africa. The United States is the largest country in this market, followed by Germany and then Brazil. India was the fastest growing market during the period and is expected to grow at a CAGR of 8.49% between 2017 and 2021.

In Italy, therapies cost the national health system around 9% of the budget, or about €8.26 billion each year. These are extremely important figures, which make this condition one of the heaviest financial burdens on the health system.

Many of these expenses could be avoided by prevention, reducing the number of new cases of diabetes and preventing complications if diabetes is already present. While it is difficult to make such a calculation, it is certain that with proper lifestyles (good nutrition and regular physical activity) and targeted and carefully observed basic therapies, one could save perhaps as much as millions of euros in hospital and outpatient expenses to repair organ damage caused by poor disease control.

In fact, the cost of healthcare for a diabetic patient increases by 3-4 times if cardiac, vascular or kidney, vision and peripheral nervous system complications occur. It can be deduced, therefore, that the intensive and preventive treatment of the disease from the beginning not only improves the quality of life of the diabetic patient, but is also advantageous in economic terms.

The top four companies in the industry, Roche, Johnson & Johnson, Ascensia (Panasonic Health Care) and Abbott account for 50% of the total. Due to falling prices for blood glucose test strips worldwide and increased competition from local suppliers, the market shares of these companies are declining.

The average cost per test that a diabetic patient currently pays to measure his or her glucose level is €1.2 per test (excluding measuring devices).

## CORTISOL

Cortisol is also called "stress hormone" because its production increases precisely under rather severe conditions of psycho-physical stress. With its action, it inhibits body functions that are not essential in the short term, supporting the functions of vital organs.

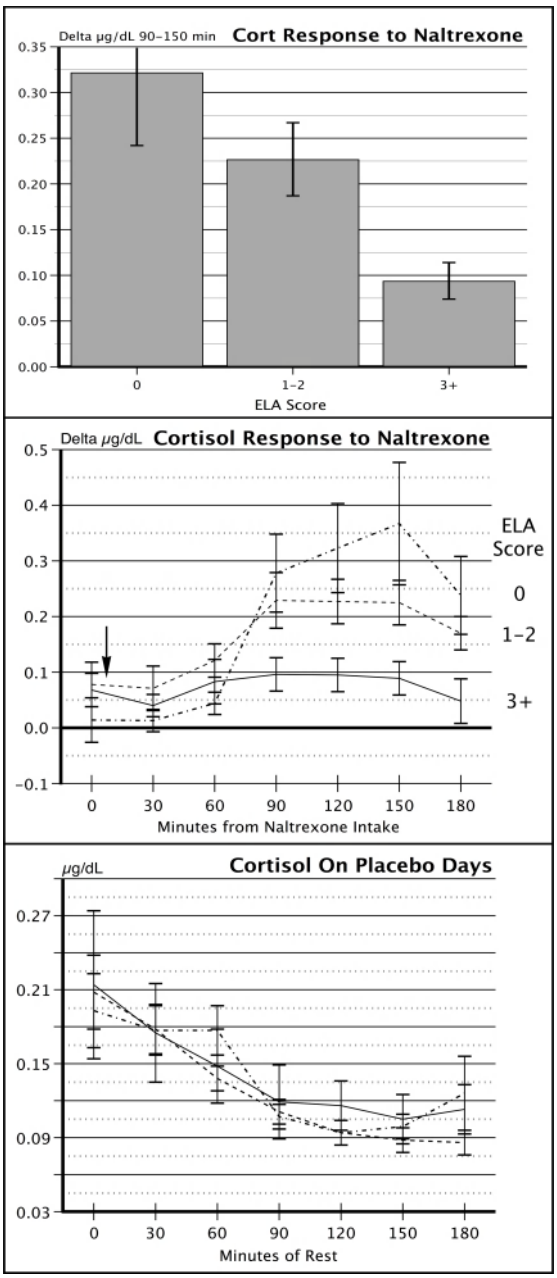
### Cushing's syndrome

Cushing's syndrome (CS) is a rare condition resulting from an excess of cortisol in the body. Cortisol is a hormone normally produced by the adrenal glands and is essential for life: it can respond to stressful situations, such as illness, and has effects on almost all tissues of the body. It is produced in peaks, more frequent in the morning and very low at night. When the body produces too much cortisol, whatever the cause, we are in the presence of Cushing's Syndrome.

### The development of specific drugs

Recently an article has been published announcing the passing of Phase 3 in the development of a specific drug for the treatment of Cushing's syndrome. The average cost of developing a drug is 1.5 billion USD and its duration is 5 / 7 years. During all the different phases it was necessary to monitor volunteers / patients by measuring cortisol. The possibility to do it in a NON-invasive, continuous, remote way together with other parameters could drastically reduce development costs and timing in the development of new drugs, not only related to cortisol.

**Cortisol as an index of cure for diseases of psychological origin.**




**Top panel:**

change in cortisol saliva from placebo day to naltrexone day, on average 90-150 minutes after administration of 50 mg naltrexone or placebo.

**Central panel:**

variation in saliva cortisol on naltrexone day at each collection interval. The arrow indicates the time of administration of naltrexone or placebo.

**Bottom panel:**

Saliva cortisol per day placebo for the three ELA groups.

**Alzheimer**

Recent studies by some Australian researchers have shown that a drug that reduces cortisol production could be the key to slowing the progression of Alzheimer's after finding that high levels of stress contribute to the progression of this devastating disease.

**The market for degenerative diseases**

Dementia-related diseases are expected to increase in all regions of the world to double every 20 years, reaching 74.7 million patients with degenerative diseases by 2030.

The global market for dementia drugs is expected to grow to a CAGR of 8.4% over the period (2018-2026), due to the introduction of innovative, more effective drugs and government initiatives to provide better palliative care to patients.

Some of the major players in the global dementia drug market include Eisai, Inc., Janssen Pharmaceuticals, Inc., Biogen Pharmaceuticals, Forest Laboratories, Inc., Eli Lilly and Company, Novartis AG, Sanofi SA, AstraZeneca GmbH, F. Hoffmann- La Roche, Merck & Co., Valeant Pharmaceutical International, Pfizer Inc. and Teva Pharmaceuticals Industries Ltd.

**Stress**

The adrenal glands are responsible for the synthesis of numerous hormones called steroids, but it is also the glands that regulate our response to acute and chronic stress. In response to acute stress, they release catecholamines (adrenaline and norepinephrine) which are responsible for the "fight or flight" response and provide the energy and metabolic acceleration needed to deal with an immediate dangerous situation.

In response to chronic stress, they produce cortisol (cortisone) which is essential in the metabolism of carbohydrates and proteins (catabolic action) and also has a powerful anti-inflammatory action.

A moderate amount of stress does not have negative effects, on the contrary, it is considered a positive stimulus, but when the stress becomes continuous, as often happens in today's hectic life where we add work, family, relational, financial and emotional stress, the load on our adrenals becomes excessive, and they begin to lose their efficiency.

Adrenal fatigue is therefore a condition in which the adrenal glands function at a sub-optimal level when the patient is at rest, under stress or in response to occasional, intermittent or continuous stimuli. The amount of cortisol produced will therefore be less than normal.

The existence of such intermediate states of adrenal insufficiency is practically ignored by modern medicine, which only recognizes Addison's Disease (i.e. complete exhaustion of adrenal function) while it was well known by doctors of the past who defined it in various ways: "Non-Addisonian Hypoadrenia", "Subclinical Hypoadrenia", "Adrenal Neurasthenia" and "Adrenal Apathy". In Anglo-Saxon countries, and especially in the United States, this state of partial adrenal insufficiency is beginning to be recognized, at least in non-conventional medicine, and is generally defined as "adrenal weakness" (adrenal weakness), "low adrenal reserve" (low adrenal reserve) but especially "adrenal fatigue" (adrenal fatigue).

**The cortisol market**

The global Cushing's diagnostic and treatment market is expected to increase to a CAGR of 8.28% to reach a total market volume of $405 million by 2023, rising from $251 million in 2017.

**The social cost of stress**

Workers' stress not only has a cost for their health but also a significant cost: every year, according to the estimates of the European Foundation for the Improvement of Leaving and Working Condition, about 20 billion euros are spent on social and health costs linked to stress which, by undermining workers' health, increases absences and accidents.

The economic crisis could also detonate the phenomenon because of the greater tension to which workers are subjected, with a risk of job loss. According to Steven Sauter, of the US Institute for Occupational Safety (Niosh), the costs could even explode. Referring to a study of 46 thousand people carried out in the U.S., Sauter reports that each worker subjected to stress costs about $600 more. And the current economic situation will increase workplace stress by 25 percent. If you multiply the $600 by this increase, the figures become exorbitant.

## C-REACTIVE PROTEIN

C-reactive protein (PCR or CRP) is a detectable blood protein produced by the liver and is part of the so-called acute phase protein, a group of proteins synthesized during an inflammatory state.

### Cardiovascular disease

Inflammation has been identified as the cause of atherosclerosis, a condition associated with the deposition of lipids in the inner lining of the arteries, which progressively leads to acute myocardial infarction (AMI), also referred to as a heart attack. A considerable number of patients with heart disease have no established risk factors (hyperlipidemia, hypertension and familiarity). Unlike subjects with increased LDL-cholesterol, subjects with increased plasma concentrations of C-reactive protein (PCR), an acute phase protein produced by the liver during inflammatory processes, are often unaware that they are at risk of developing CVD and, therefore, may not require medical consultation to lower their risk. An increased concentration of PCR requires further investigation because it may be attributable to CVD. Clinicians are currently considering whether to include PCR determination as an additional risk factor in the Framingham cardiovascular risk charter.

It is important that two recent studies have shown that PCR can be detected in saliva. The presence of PCR molecules in saliva offers an opportunity to develop a non-invasive approach to cardiovascular risk definition. However, the saliva PCR reference ranges and their correlation with serum concentrations have not yet been examined in detail. The low concentration of PCR in saliva requires the availability of high sensitivity measurement technologies.

### The market for cardiovascular disease (CVD)

CVD is the leading cause of death worldwide, with about 17.7 million deaths in 2015, with about 7.4 million (over 41%) specifically due to CHD (Coronary Hearth Disease) and about 6.7 million (just over 39%) specifically due to heart attack (WHO , 2017). The overall economic impact of CVD, including direct costs such as treatment and indirect costs such as loss of productivity, is considerable and varies from country to country. In the UK, total health care costs of CVD exceed $11 billion per year, with annual economic costs of CVD exceeding $24 billion per year (Townsend et al., 2012). In the United States, total costs associated with CVD were estimated at $656 billion in 2015 and could rise to $1.2 trillion by 2030.

## COVID-19

We're considering taking an evolution of the strategy, necessarily linked to recent pandemic events. The Covid-19 has changed the perspective of health and safety perception in a dramatic way.

Until a few months ago, prevention and early diagnosis through different biomarkers such as glucose for diabetes (for example) was a priority, monitoring one's own health was in our daily goals and fear did not guide our behaviour.

The possibility of contracting the virus and its consequences changed the paradigm.

Verifying the possibility of developing with strategic partners the identification of Covid-19 on saliva could become one of our primary objectives while obviously maintaining the fundamental characteristics of the original product.

It is not an easy path, but universities, private companies and research centres are presenting daily publications on the subject. We are confident that by investing in this area we will soon be able to assess whether our DOC.D© device can be implemented with the necessary characteristics.

# 3 - MARKETING STRATEGY

The company AICube was founded to promote the optimisation of investments in the health system, giving a part in the field of prevention and predictive medicine. The sooner we will be able to predict certain diseases, the sooner we will be able to reduce treatment costs by increasing the effectiveness of treatments. DOC.D© (Data Organized Collector Device) technology will help to acquire data on a daily basis and analysis through Machine Learning algorithms will provide guidelines / treatments suggested to patients.

## Mission

The mission of AICube is to equip every home with a biometric parameter acquisition device in order to monitor the health of the user / patient and, through Machine Learning technology, to predict the development

| | 2018 | 2019 | 2020 | 2021 | YTD 2022 |
|---|---|---|---|---|---|
| Funding | | 297.551 € | 537.182 € | 210.148 € | 1.044.881 € |
| Founder | 100% | 88,54% | 74,4% | 70,53% | |
| Crowdfunding campaign | | 11,46% | 9,62% | 9,12% | |
| I° Capital Increase | | | 15,98% | 15,16% | |
| II° Capital Increase | | | | 5,19% | |
| Total | 100% | 100% | 100% | 100% | |
| Enterprise Value | | 2.597.551 € | 3.360.607 € | 4.050.842 € | |

of possible diseases.

## Vision

We have built the foundation of AICUBE based on the ability of a team of experts with a business oriented attitude, proven results, knowledge of high-level domains in strategic areas. We want to leverage innovation. The difference between invention and innovation lies in execution. We have taken an idea and we will turn it into reality using a specific machine learning algorithm integrated in the AICube server. We want to reduce healthcare costs through prevention. Non-communicable diseases (NCDs), such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes, are the leading cause of mortality in the world.

## Business Model

The business model we are referring to is the multi-sided one. A model that brings together two or more distinct but interdependent groups of customers. In our case the customer groups are patients / users (B2C) and different stakeholders (B2B) such as insurance companies, pharmaceutical companies, Oral care company. AI Cube creates value by generating interaction between the two groups through the collection, analysis and processing of data from individual users in order to provide domain knowledge. Its value grows in a non-linear way as it attracts new customers and the data collected is potentially exponential with the continuous addition of new biomarkers. The most important choice is of course to correctly identify the Business to start from. B2C that provides data in a long time with better operating margins but higher investments, B2B2C that gives us immediate access to a pool of users immediately available (insurance, Oral Care) with lower margins.

In any case we will start with an MVP (Minimum Viable Product) approach and then implement the device with other biomarkers. In the development of an innovative product like ours, it is necessary to start from the product with the highest return on investment compared to the risk. The method involves the interaction with the market from the idea phase in order to validate the problem/customer binomial before making any form of prototype; with the initial validation it is possible to follow a structured process in order to arrive quickly, and at a lower cost, to the first objective of validation or invalidation of the hypothesis.

It is a strategy aimed at avoiding building products that customers do not want, which seeks to maximize the information learned about the customer for every euro spent. An MVP is not, therefore, a minimum product, but a strategy and a process directed towards the creation and sale of a product for certain customers. It is an iterative process of idea generation, prototyping, presentation, data collection, analysis and learning.

## Pivoting

A change of strategy is planned in relation to the different market response to the launch of our product, once the clinical validation phase is over. The pivoting will then take place after AICube has tested its initial product (equipped with Glucose sensor), already knowing that implementing it will give better results. In fact, we will be able to access new markets and the proposal of new guidelines for better lifestyles as well as diagnostic proposals to be validated by medical specialists and based on results derived from data processing through artificial intelligence.

# 4 - ORGANISATIONAL STRUCTURE

**AICube srl**

Aicube was established as an innovative limited liability company. In order to be able to access the benefits of an innovative startup in the establishment phase we have at least one of these requirements:

- We have allocated more than 15% of our annual costs to research and development in past fiscal year.
- AICUBE holds a registered patent and is owner of a Machine Learning Algorithm.

After the raising of capital through the Crowdfunding campaign and two capital increases the company is constituted as follows:

## Board of Directors

**Stefano Russano - Founder & CEO**

Graduated in Engineering at the Politecnico di Milano, specializing in Bioengineering in 1992, he has been working for more than 25 years in the "health" sector, contributing significantly to the development of the business entrusted to him. In the last 5 years he has directed a leading company, 20 Mil USD as CEO, developing quality strategic plans, ensuring their alignment with the company's short and long term objectives.

**Paolo Carmassi - Co-Founder & Board Member**

With a contagious leadership style, it combines experience in materials analysis, Artificial Intelligence directed to precision medicine, aerospace and automotive industries to create a unique and compelling vision supported by a viable strategy. Born in Italy, he has lived and worked in Italy, France, UK, USA, China, Netherlands and Switzerland, describing himself as "Anglo-Saxon software, operating on Mediterranean hardware".

**Matteo Giuffrida - Academic Fellow of the Department of Management and Technology at Bocconi University**

Successful entrepreneur, currently teaching the Global operations and Supply chain management course at Università Bocconi, as well as teaching in the MBA faculty of the School of Management.

## Advisory Board - Artificial Intelligence

**Dante Degl'Innocenti, PhD**

Dante is a Data Scientist and Software Engineer with expertise in Natural Language processing and Knowledge Representation. He is founder of 2 ICT startups.
Dante also has interest in Social Network Analysis, System Integration, and Robotics with specific application in the industrial field. He enhanced his knowledge in Machine Learning obtaining certifications from international courses on Data Science and Statistical Learning.
Dante holds a PhD, MSc, and BSc in Computer science from the University of Udine.
He also achieved the qualifying examination to engineers register from Ca' Foscari University of Venice.

**Christos Klement - CSTS Health Care**

Christos received his BASc in Engineering Science from the University of Toronto specializing in Aerospace in 2006 and then worked for 10 years in the aerospace industry in technology development, business development and strategic marketing. In his role as a chief marketing leader for a $900M international aerospace fortune 100 company, he consistently developed strategic marketing plans that delivered on growth objectives across Europe, Middle East, Africa and India.

Christos is dedicated to making the world a better place. He co-founded CSTS Health Care with the mission of applying the latest science, mathematics and artificial intelligence technologies to improving quality of life for cancer patients. His role leverages both his passion for technology and his professional experience in strategic marketing, product management and business development.

**Marco Pavan, PhD**

Marco is a Data Scientist and Software Engineer with expertise in Natural Language processing and User Modeling. He is founder of 2 ICT startups.
Marco also has interest in Information Retrieval, Context Aware computing, and Network Science to design and develop models and algorithms for profiling and similarity computation.
He has got international experience working as research fellow in Astrazeneca, UK, addressing research problems in the bio-medical domain, and at the Department of Information Science of Georg-Eckert-Institut, Germany.
Marco holds a PhD, MSc, and BSc in Computer Science from the University of Udine.

## Institutional Relations

**Anna Carmassi**

Entrepreneur for over 30 years in the field of multilingual communication and internationalisation services. In charge of corporate institutional relations, she has built and managed a network of companies in the sector, operating throughout Europe and in some non-European countries. She has been president of the national trade association. She has always carried out associative activities within the industrial system and is Project Leader of the STEAMiamoci project in Assolombarda.

## R&D

**Antonio Bosetto**

Gained consolidated experience in the management of projects, products, research and development facilities and production facilities in the field of bioengineering and in particular in the field of biomedical equipment and disposable devices, working for multinational companies of global level. He has been holder of the course of Artificial Organs at the Faculty of Engineering of the University of Bologna and of Medical Informatics at the School of Specialisation in Cardiology of the University of Ancona. He is author of international scientific publications and patents related to bioengineering.

## Scientific Advisory Board

**Dario Alimonti**

Dario Alimonti - Graduated in Medicine and Surgery at the University of Pavia, he specialized in Neurology in the same university. In 2004 I obtained a Master of Science in Clinical Neuroscience at the Institute of Neurology in London, with a thesis on the role of retinoic acid signaling system on neuronal regeneration. In 2011 I obtained a Master's degree in "Diagnosis and Treatment of Movement Disorders and other Neurodegenerative Diseases" at the Institute of Neurology "Carlo Besta" in Milan.

**Fabio Gorni**

Graduated in Dentistry and Dental Prosthesis at the University of Milan in 1984. Professor of Perioral Aesthetics, Degree Course in Dentistry and Dental Prosthetics (University Vita e Salute San Raffaele Milan). Former A.C. Professor in Endodontics at the University of Milan, H. San Paolo. In collaboration with Dr. Clifford J. Ruddle, he has published a video-series entitled The Endodontic Game", distributed in Europe, USA, Canada, Australia and Asia.

**Mariangela Rondanelli**

Since 1 June 2007 Associate Professor in “Applied Dietary Sciences and Techniques” (Disciplinary Scientific Sector MED 49) at the Faculty of Medicine and Surgery of the University of Pavia, Department of Public Health, Neuroscience and Experimental and Forensic Medicine, Section of Food Science and Human Nutrition and affiliated with the Personal Services Company (ASP), Pavia Institutions, Geriatric University Center, with the qualification of Director of the complex metabolic-oriented rehabilitation facility.
In December 2017 qualified as Full Professor in Applied Dietary Sciences and Techniques “(Scientific Disciplinary Sector MED 49) director of the School of Specialization in Food Science of the University of Pavia since January 2018 has published 170 scientific articles in indexed international journals and with Impact Factor.

**Paolo Donati**

Paolo Donati - Currently holding a Post Doc position at Italian Institute of Technology, where leads two projects focused on the development of Lateral flow assays for biomarker assessment based on a novel method that I developed and patented. Post Doc researcher Istituto Italiano di Tecnologia, IIT Center for Convergent Technologies, research Line Nanobiointeractions & Nanodiagnostics. Project: Colorimetric nanodiagnostics for Point-Of-Care detection of salivary biomarkers and environmental contaminants  Fellow PhD Student Istituto Italiano di Tecnologia, IIT Center for Convergent Technologies, research Line Nanobiointeractions & Nanodiagnostics. Research fellow Center for Micro-BioRobotics IIT@ Scuola Superiore Sant’Anna di Pisa. Project: synthesis and characterization of shaped platinum nanoparticles for application in imaging and radical scavenging in oxidative stress- mediated diseases.

## Business Partners

### BIOMARKERS

We developed with the **Italian Institute of Technology (IIT)** the salivary glucose sensor to be included in our AICUBE device. This sensor coupled with a **proprietary Artificial Intelligence algorithm** will produce an index risk of development Type II diabetes.

Glucose salivary test is a non-invasive method for measuring blood sugar levels. It is a relatively new technology that has gained attention as a potential tool for prediabetes prevention. The test measures the glucose content of saliva, which reflects the blood glucose levels. The procedure is simple, painless, and does not require fasting or a blood draw, making it more comfortable for the patient.

One of the main advantages of the glucose salivary test is its potential to detect prediabetes at an early stage. Early detection is crucial for preventing the progression to type 2 diabetes, which is associated with serious complications such as heart disease and stroke. The test can also be used to monitor the effectiveness of lifestyle changes, such as diet and exercise, in preventing prediabetes.

A study published in the Journal of Diabetes Research found that glucose salivary test can accurately detect prediabetes in obese individuals. The study included 100 obese individuals and found that the glucose salivary test had a sensitivity of 89% and a specificity of 85% for detecting prediabetes.

Another study published in the Journal of Oral Science found that glucose salivary test can also detect prediabetes in non-obese individuals. The study included 60 non-obese individuals and found that the test had a sensitivity of 86% and a specificity of 92% for detecting prediabetes.

There are also a few limitation of this method, one of them is the accuracy of the test can be influenced by factors such as oral hygiene, medication use, and salivary flow rate.

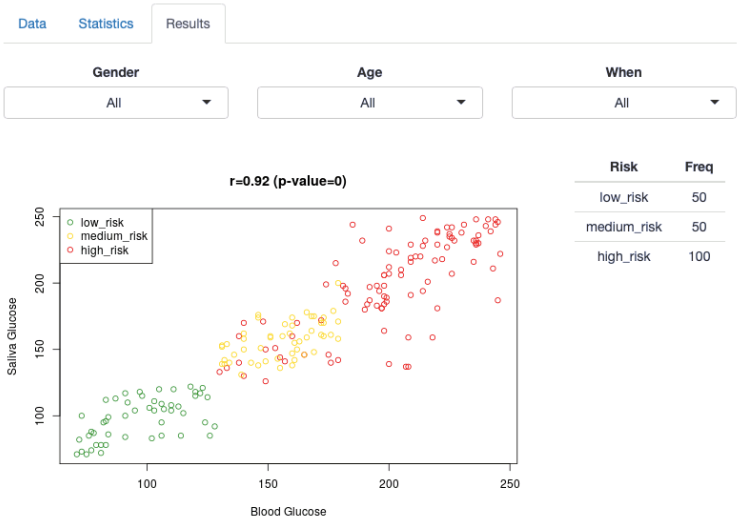
In conclusion, glucose salivary test is a non-invasive method for measuring blood sugar levels that has the potential to detect prediabetes at an early stage. The test is simple, painless, and does not require fasting or a blood draw, making it more comfortable for the patient.

## ARTIFICIAL INTELLIGENCE

### CSTS Health Care Inc.

CSTS is a next generation company in the oncology industry, a biotechnology company driven by artificial intelligence, which uses artificial intelligence to accelerate scientific discovery and commercialization. CSTS offers targeted anticancer therapies and through the use of specific drugs.

CSTS has two main products, Aiomic and Cytesia. Aiomic is a software platform that integrates multiomic information to create interactive models of cancer biology for each individual, for therapy design and clinical trial enhancement. Cytesia is a new drug delivery mechanism that uses platelets to deliver drugs to primary and metastatic cancer sites.




### RES-IT

RES IT is an Italian-based company that, since 1987, develops and markets software, services and consulting for Enterprise Management with offices and representation, in Italy and abroad, under the corporate name of RES Srl. To interact with the educational and university research, in 2017 RES set up together with the University of Pavia the RIDS – RES Institute for Data Science, a methodological and applied research laboratory in Data Science.

### Datamantix

Datamantix S.r.l., founded by PhDs in Computer Science with international experience in Artificial Intelligence and Software Engineering, develops advanced technological systems to enable its customers to exploit the potential of their data, knowledge, and skills. Datamantix designs and develops innovative solutions to support demanding and knowledge intensive tasks such as planning, quality control, monitoring, forecasting, and optimisation.

## INDUSTRIAL DESIGN

### PQ -Design

In 2020 AICUBE reached important goals in research, device development and capital raising. It has therefore begun the path of industrialisation that will lead it to the next stage of industrial prototyping. The relationship with Pq Design Group comes from an intense period of evaluation of different companies in the field of industrial design with the aim of finding the best partner for this important phase of the society.

Pq design Group is an Italian industrial design company specialised in product design and development of hi-tech products. They provide solutions to create successful products. Theirs is a consultancy that produces value, quality and innovation;

## MICROFLUIDICS

**Bartels Mikrotechnik**

Bartels Mikrotechnik is a globally active manufacturer and development service provider in the field of microfluidics. In the microEngineering division, the company supports industrial customers in the modification, adaptation and new development of high-performance and market-oriented product solutions through the innovative means of microsystems technology. The second division, microComponents, produces and distributes microfluidic products and systems, especially for miniaturized and portable applications. Our key products are micropumps that convey smallest quantities of gases or liquids and are used in a variety of ways in biotechnology, pharmaceuticals, medical technology and numerous other applications.

## ELECTRONICS

**DAOS**

DAOS Group is an Italian company formed by a group of professionals in the sector, active for over 30 years and with skills and recognition at an international level, which has created an avant- garde reality made up of specialized technicians. Able to innovate in terms of methodology and organization. Together with our partners DAOS has created a network capable of proposing original ideas and high-quality services: conceiving, designing, and implementing innovative solutions. The activities of the DAOS Group are divided into four macro areas of intervention: hardware design, software design, mechanical design, prototyping and production.

## Recruitment Plan

The growth plan provides for the inclusion of various professional figures who contribute significantly to the growth of the company in their areas of expertise. In the first two years after its establishment, the inclusion of these resources will also be linked to the company's operating result through the use of convertible financial instruments. In this way we want to encourage those who believe in the project from its early stages to bring much more of their expertise and professionalism. We want people who are strongly motivated to develop an innovative project with a great impact on people's health.

Recruitment plan table:

| Head Count | YTD | Y1 | Y2 | Y3 | Y4 | Y5 |
|---|---|---|---|---|---|---|
| **Sales** | 0 | 1 | 2 | 4 | 4 | 4 |
| **Marketing** | 0 | 1 | 1 | 1 | 1 | 1 |
| **Eng. / Clinical** | 0 | 1 | 1 | 1 | 1 | 1 |
| **Product Manag.** | 0 | 0 | 1 | 3 | 3 | 3 |
| **Supply chain** | 0 | 5 | 5 | 5 | 5 | 5 |
| **G&A** | 1 | 2 | 4 | 4 | 4 | 4 |
| | | | | | | |
| **Total** | **1** | **10** | **14** | **18** | **18** | **18** |

# 5 - ECONOMIC AND FINANCIAL FORECASTS

## Provisional Budget

| | Y1 | Y2 | Y3 | Y4 | Y5 |
|---|---|---|---|---|---|
| **Total Revenue** | **292.500** | **2.089.123** | **6.679.788** | **16.680.803** | **30.688.549** |
| | | | | | |
| **Total Cost of Revenue** | **(176.773)** | **(1.211.204)** | **(3.744.167)** | **(9.115.165)** | **(16.263.115)** |
| | | | | | |
| **Gross Profit** | **186.057** | **894.941** | **2.952.830** | **7.583.039** | **14.644.543** |
| | | | | | |
| **Operating Expenses** | | | | | |
| **Sales** | (55.833) | (242.859) | (398.793) | (408.477) | (408.477) |
| **Marketing** | (212.553) | (565.056) | (184.894) | (188.161) | (188.161) |
| **Eng. / Clinical / R&D** | (732.597) | (177.318) | (179.262) | (181.265) | (168.765) |
| **Product Management** | 0 | (101.560) | (253.628) | (259.797) | (259.797) |
| **Supply Chain** | (155.303) | (236.381) | (242.992) | (249.802) | (249.802) |
| **Warehouse & Distribution** | (8.775) | (329.944) | (133.596) | (333.616) | (613.771) |
| **G&A** | (183.558) | (329.944) | (357.437) | (366.570) | (366.570) |
| **Royalties** | (17.319) | (28.794) | (83.935) | (179.033) | (179.033) |
| **Total Direct Op. Ex.** | (1.365.938) | (2.011.856) | (1.834.537) | (2.166.721) | (2.434.376) |
| **Total Indirect Op. Ex.** | (35.703) | (40.701) | (47.620) | (60.036) | (75.447) |
| **Total Oper. Expen.** | **(1.401.641)** | **(2.052.557)** | **(1.882.157)** | **(2.226.757)** | **(2.509.823)** |
| **EBITDA** | **(1.215.584)** | **(1.157.616)** | **1.070.674** | **5.356.282** | **12.134.721** |
| **Net Income (Loss)** | **(1.065.459)** | **(1.013.607)** | **959.696** | **4.146.025** | **8.705.249** |

# 6 - FUNDING NEEDS

The value of the investments included in the plan is as follows:

- **2023 - 1,1 M€***
    - Fundraising to close the industrial design of the prototype, MDR (CE) certification of the device, and start development of the cholesterol sensor. Hiring strategic figures in the R&D area.

- **2024 – 1,5 M€**
    - Initiation of production and product launch in Italy, implementation of commercial distribution in selected countries (Europe), FDA certification, recruitment of senior level figures. Development of new sensors

- **2025 – 1,5 M€**
    - Completing the organizational structure and launching the international sales channel.

## Value of planned investments

The value of the investments foreseen in the plan, differentiated by type, is divided into several phases:

(*) Crowdfunding campaign close successfully. This include part of Friend& Family funding

(**) Two different capital increase launched in 2020 successfully.

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