OVER DATA.

Research Project

HORIZON EUROPE PROJECT

PRAESIIDIUM

Physics-informed machine learning-based prediction and reversion of impaired fasting glucose management

INDEX

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Physics-informed machine learning-based prediction and reversion of impaired fasting glucose management

Spindox Labs srl (SPXL, project coordinator) is the research and development center of Spindox SpA. Its mission is to support the process of digital transformation of their customers, by developing new technology and providing consultancy in five strategic domains: cloud computing, hybrid and native mobile applications, artificial intelligence, big data & analytics and internet of things.

Introduction to the PRAESIIDIUM project

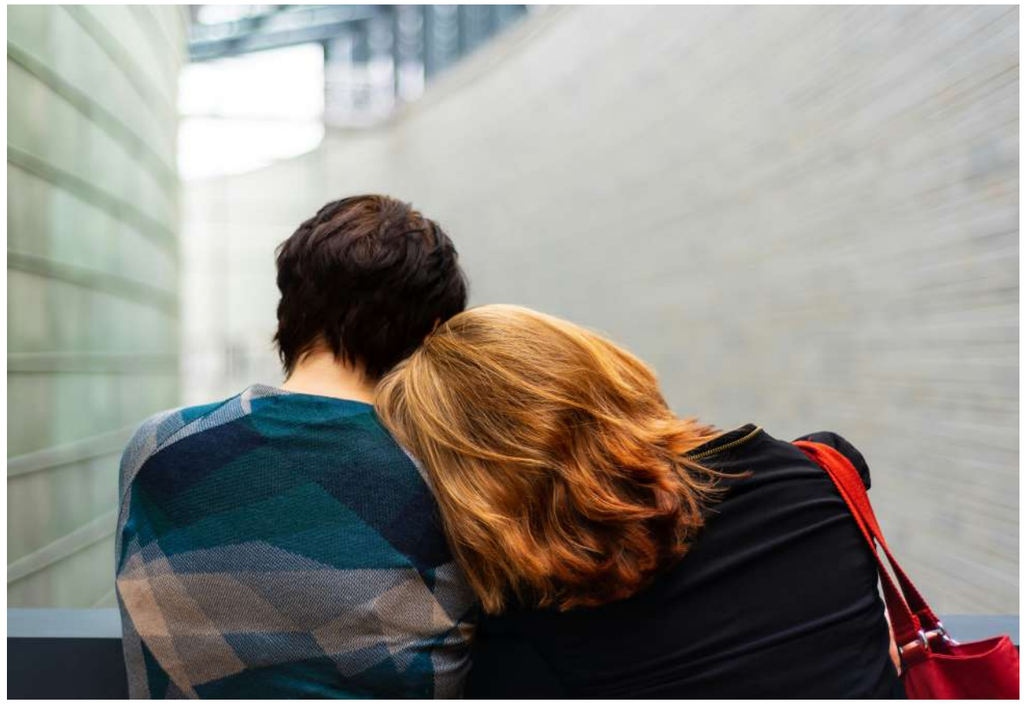
"Prevention is better than cure", a maxim that applies to many aspects of life, especially when facing the probability of developing a chronic and progressive disease. When it comes to Type-2 Diabetes (T2D) - which affects 540 million people worldwide (2022) - prevention is not only essential, but an early diagnosis is lifesaving. Worldwide, 541M adults have Impaired Glucose Tolerance (IGT), an important risk factor for further diabetes development. Along with Impaired Fasting Glucose (IFG), these are intermediate conditions within the "healthy-to-T2D transition" and are manifestations of the so-called **prediabetes**. Unlike overt diabetes, prediabetes is still an early-stage, intermediate condition that **can be reversed** with physical activity (e.g., a minimum of 30-54 minutes at least 2-5 days/week) and a **healthy diet**, as strongly recommended by the World Health Organisation (WHO) and the International Diabetes Federation (IDF).

Non-Invasive Risk Prediction Models for Prediabetes

As prevention is pivotal, **non-invasive prediabetes risk prediction models,** which can be used by healthcare professionals or patients themselves, may offer an interesting alternative to the typical glucose management practice. Although some models already exist, none functions as a consensus method in diabetology care. The onset of diabetes involves complex mechanisms acting on multiple scales, from molecular and tissue levels to organ dysfunction. Chronic inflammatory biomarkers play a crucial role in diabetes pathogenesis. Considering such a multi-level approach is also a step toward **personalized diagnosis** of the disease.

Mathematical Models to Understand Complex Biological Phenomena

The multi-level complexity of a biological phenomenon can be modeled through mathematical formulations, either continuous (i.e., ordinary or partial differential equations) or discrete (agent-based models). These models describe the functional relationships among entities and track changes over time and space. At a molecular level, complex biological systems can be represented and mathematically analyzed as computable networks. Based on these assumptions, a multiscale, hybrid computational model of the human metabolic and inflammatory status was developed by Consiglio Nazionale delle Ricerche (CNR) during the former EU-FP7 project **MIS-**



> **More than 500 million adults worldwide have Impaired Glucose Tolerance, which can lead to overt type-2 diabetes if not timely treated. Prevention now becomes essential.**

SION-T2D (MT2D) to provide an indication of the risk of T2D. While the MT2D prototype simulator is already functional, some fundamental and computational challenges still need to be addressed.

wProject: Innovation for Diabetes Prevention

The PRAESIIDIUM project (Physics-infoRmed mAchine lEarning-baSed predIction and preventIon of impaireD fastIng glUcose Management), contextualized within the Horizon Europe Cluster 1 Health framework, aims to optimize some outcomes of the MT2D project and integrate a new research area called "physics-informed machine learning" **(PI-ML)** to develop an easy-to-use and efficient tool for predicting prediabetes risk. The goal of the PRAESIIDIUM project is to develop a tool aimed at providing real-time prediction of an individual's prediabetes risk. The prediction algorithm will be based on a "physics-informed machine learning" approach: a rich dataset of **real-life data**, obtained from existing and new clinical studies with continuous data ingestion through **wearable sensors**, will be combined with mathematical models and **eXplainable AI (XAI) techniques** to overcome the limitations of "black-box" ML approaches while improving prediction performance and reducing computational time. The final algorithm will be implemented in a web-based platform, where medical doctors and patients can input data from multiple sources (acquisition from connected sensors and manual insertion) and obtain a real-time analysis of the risk of developing prediabetes over time.

Key Objectives of the PRAESIIDIUM Project

- To develop **physics-informed machine learning** for early-stage prediction of prediabetes risk within a specific timeframe.
- To develop and deploy a **web and mobile application** for healthcare professionals and patients: the PI-ML algorithm will generate a personalized real-time risk factor based on input from doctors and patients, predicting a time window for potential prediabetes development.
- To acquire retrospective and generate **prospective longitudinal datasets representing the "health-to-prediabetes transition**": two clinical studies will follow participants at risk of prediabetes for four months, collecting clinical and biological data to train the PI-ML.
- To ensure **ethical and regulatory compliance**, including GDPR and the EU AI Act.
- To propose a roadmap for **certification of AI medical device,** which is crucial for the future commercialization of the solution.

A Multidisciplinary Approach for Project Success

To achieve these goals, PRAESIIDIUM adopts a multidisciplinary approach involving humanities, medicine, biology, computer technologies, mathematics, and engineering. The European-based consortium includes healthcare professionals and diabetologists (Fondazione Italiana Fegato Onlus, University of Latvia, Graz Medical University), bioinformatics researchers (Consiglio Nazionale delle Ricerche), AI/machine learning experts (Scuola Universitaria Professionale della Svizzera Italiana-IDSIA, Spindox Labs, HK3-Lab), data analysts, wearable sensor developers (Latvia Institute of Electronics, Check Health Sweden), project managers (Spindox Labs), and ethics specialists (Scuola di Robotica).

Ethical and Regulatory Challenges in AI for Healthcare

The PRAESIIDIUM project requires deep insights into medical aspects, ethical considerations, and technical aspects of AI-ML approaches, such as bias elimination, robustness, and computer science. User experience and safety are also critical, especially concerning wearable sensors.

PRAESIIDIUM X OVERDATA

The **PRAESIIDIUM x OVERDATA** issue showcases all the aspects of the multidisciplinary nature of the PRAESIIDIUM project. The reader will be guided through the

clinical and biological description of prediabetes and the challenges faced by doctors and patients: prediabetes in fact is often accompanied by metabolic syndrome, obesity and liver diseases. When dealing with AI and e-health technologies, ethics and regulations are pivotal: here the novel ethics assessment adopted by the consortium is presented. Next, the reader will be guided through the core of the physics-informed machine-learning (PI-ML) with aspects and challenges of AI and math models in determining the risk of prediabetes. Real-life data is necessary for training and using the models: two articles present novel tools for patient's remote monitoring and data acquisition (e-health technologies) through wearable sensors and vocal assistant. In the end, the reference business market for e-health technologies is described.

About the Project

Did you know that the acronym of the project title derives from the latin word "praesidium" which means "to protect"?

The PRAESIIDIUM project started in January 2022 and will last 36 months, considering the project overall goals, to guarantee the objectives achievement and to manage the project efficiently and effectively. The project work-plan is organized through 7 work-packages (WPs), including project management and activities for dissemination, communication and exploitation of results. At the present, the project is in its final year, where results are being consolidated, and demonstrations are being prepared.

About the Consortium

The consortium consists of 12 members, four of which are companies, and the rest are universities or research institutes. The members come from five EU countries and one Swiss Associated Partner.

Spindox Labs srl (SPXL, project coordinator) is the research and development center of Spindox SpA. Mission of Spindox Spa is to support the process of digital transformation of their customers, by developing new technology and providing consultancy in five strategic domains: cloud computing, hybrid and native mobile applications, artificial intelligence, big data & analytics and internet of things. Spindox Labs collaborates with Italian and international universities and research centers carrying out innovation projects related to Artificial Intelligence and Artificial Vision, Internet of Things and 3D modelling.

The National Research Council of Italy (CNR) is a public organization; its duty is to carry out, promote, spread, transfer and improve research activities in the main sectors of knowledge growth and of its applications for the scientific, technological, economic and social development of the country. Two departments are involved within PRAESIIDIUM, both with strong expertise and research in diabetes prediction and prevention:

- **The Istitute IAC "M. Picone"** (Istituto per le Applicazioni del Calcolo (www.iac.cnr.it) is specialized in developing highly advanced mathematical, statistical and computational methods to solve problems with strong relevance to society and industry.
- **The Institute of Electronics, Information Engineering and Telecommunications** IEIIT (www.ieiit.cnr.it) performs research activity in the fields related to information technology, systems engineering, electronics, and biomedical engineering.

Euronet Consulting EEIG (Exploitation Manager) is a pan-European group of cutting-edge consultancy companies and a global network consisting of partners in Official Development Assistance (ODA) countries. The group was established in 1990 as a coordination hub for managing joint operations in a broad number of thematic sectors. Over time it evolved to become a means by which services of member companies have been made readily available to major international donors, primarily the Commission of the European Union.

ALPHA Consult is a European consultancy delivering tailor-made solutions supported by senior staff with significant strategic development, market assessment and business modelling experience. Alpha's key competences lie in: 1) Exploitation: business plans, impact assessments, market / competition assessments, go-to-market strategy, IPR; 2) Communication & Dissemination: on-site promotion (events, workshops), on-line promotion (websites, social media); 3) Support to Project Management: quality assurance plans, risk management, ethics. Alpha Consult plays a pivotal role in the project, defining the business plan and exploitation strategy, driving the PRAESIIDIUM's impact, and ensuring its

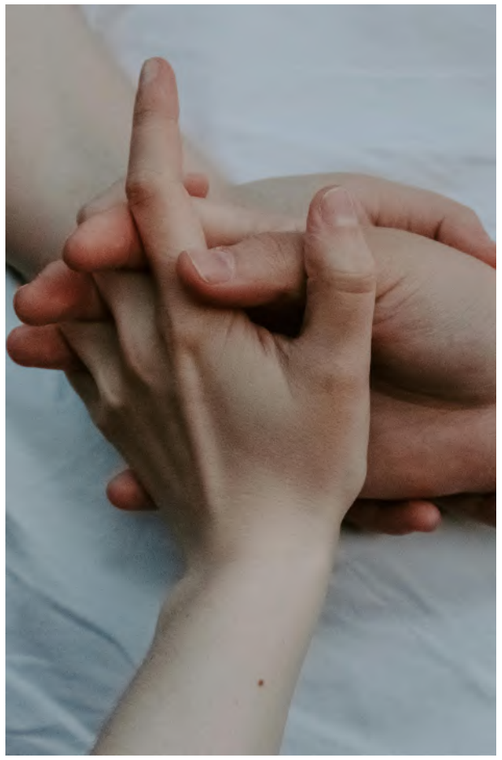
innovations transition from research to market.

SUPSI-IDSIA is a Swiss research institute - one of the most prominent European research institutes in AI - with pioneering expertise in mathematical modelling and optimization, machine learning, advanced statistics, distributed systems, control of swarm intelligence and Bayesian methods. optimization, and machine learning

The Medical University of Graz (MUG) is the second largest Medical University of Austria with over 2,500 academic and general staff members and around 4,500 students. The Division of Endocrinology and Diabetology offers extensive outpatient services and a 21-bed inpatient ward. Research areas of the Division are: analysis of real-world data, assessment of risk prediction tools, biomarker research, design, evaluation and use of diabetes technology incl. software, hypoglycaemic clamp experiments, new pharmaceutical approaches for the treatment of diabetes mellitus.

HKL Lab (HKL) develops research assets for the new season of AI, where the availability of predictive models is vital for any organization, from corporates to public agencies and individuals. HKL has expertise based on more than 20 years of international research in machine learning, including highly cited papers in deep learning, predictive biomarkers, model distillation, and model reproducibility. H3K Lab provides solutions & consulting services in machine learning, data science and their applications, with a focus on Life Sciences.

The Institute of electronics and computer science (EDI) is a Latvian public state research institute conducting fundamental and applied research in the broad area of Smart Embedde Cooperative Systems. Currently, EDI is the highest rated scientific institution in Latvia specializing in engineering research. The key driving force of EDI scientific activities is its economic and social impact; therefore we apply our expertise in mobility, industry, health, digital life and space domains. Meanwhile, we are focusing on following research directions: extremely precise event timing; remote sensing and space data processing; robotics and machine perception; signal processing and embedded intelligence; smart sensors and IoT.



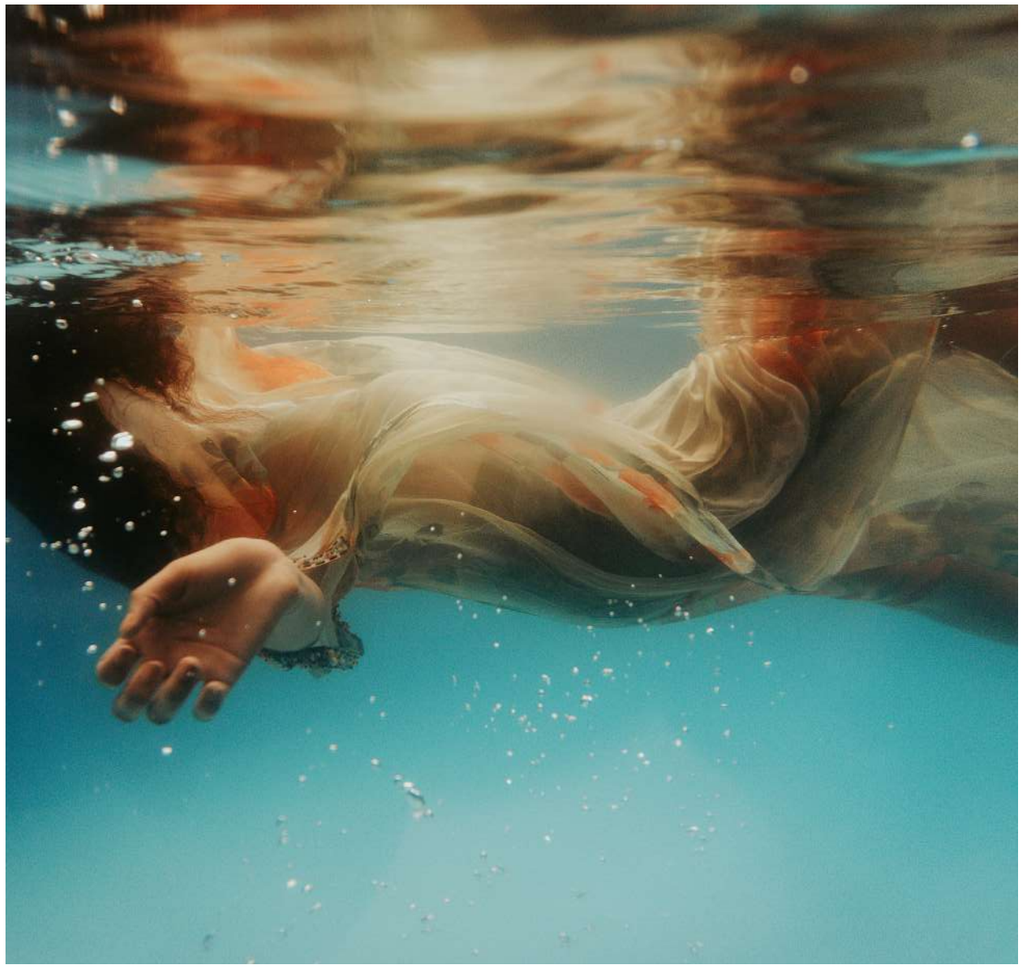
CheckHealth (CHK) is an innovative medtech company developing and marketing solutions to help care organisations implement customised remote patient monitoring programmes. CheckHealth offers LinkWatch, a cloud-based platform for patient data collection and self-monitoring, RheumaCloud a service for self-management of rheumatic patients with cardiovascular complications using our medical device gateway and federated cloud and VoiveRPM, an Intelligent Digital Voice Assistant for Remote Patient Monitoring.

Scuola di Robotica (SDR) is a non-profit association founded in 2000 by a group of robotics and human science scholars. The main objective of Scuola di Robotica is the promotion of culture through education, training, education and dissemination of the arts and sciences involved in the process of development of robotics and new technologies. Over the years Scuola di Robotica has become a national and international reference point for many research activities and application of robotics in the most varied sectors of society such as didactics, ecology and disabilities.

The Italian Liver Foundation (Fondazione Italian Fegato (FIF)–ONLUS) is a no-profit research center in Trieste, Italy, specialized in translational research and educational training of researchers and clinical personnel in liver-related diseases. Its additional strength lies in the

vast network of collaborators with research centers, universities, hospitals (more than 30) located worldwide (Italy, US, EU, Indonesia, Philippines, Argentina, Vietnam). The Foundation's staff ranges from senior scientists and researchers, PostDocs and PhD students, including the visiting researchers and a significant number of ungraduated students performing their daily research activity. One research line developed ten years ago is dedicated to studying metabolic associated liver disorders and chronic liver diseases, and currently, the team counts on expertise/skills/tools and models for the investigation of the liver diseases. Prof Claudio Tiribelli is the Scientific Director, FIF is scientific dissemination manager.

University of Latvia (UNIL) is one of the largest comprehensive and leading research universities in the Baltics. University of Latvia is continuously developing – expanding horizons of the academic work and scientific research by collaborating internationally, increasing the number of international study programmes, strengthening its cooperation with industrial partners. The laboratory for Personalized Medicine, Faculty of Medicine has experience in running national and international scientific projects in the area of diabetes and endocrinology. In addition, close collaboration of UNIL with Latvian Genome database (national biobank) allows for high-quality sample collection and preservation protocols.



Prediabetes: a silent warning

The Medical University of Graz

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Imagine going for a routine checkup, feeling perfectly fine, only to be told that your blood sugar levels are higher than normal. The doctor calls it pre-diabetes, a term that sounds harmless, even temporary. After all, it is not diabetes, right? Many people shrug it off, assuming it is just a minor issue. But that assumption can be dangerous.

Pre-diabetes is more than a warning, it is a turning point. At this stage, the body is struggling to regulate blood sugar in normal levels, and if left unaddressed, the road ahead leads to type 2 diabetes. Yet nearly 90% of people with pre-diabetes do not even know they have it. With no symptoms to warn them, millions remain unaware that their body is already in distress.

The statistics are alarming: More than 1 in 3 American adults – around 98 million people – have pre-diabetes. Without intervention, 5–10% will develop diabetes each year, and within five years, up to 50% may cross that threshold. The good news? It is not inevitable. In fact, for many, this moment is an opportunity to take charge of their lifestyle and prevent the progression to diabetes altogether.

Why Diagnosis Isn't Always Straightforward

Identifying pre-diabetes is not as simple as a single test. Doctors rely on three primary methods (according the American Diabetes Association):

- Fasting Plasma Glucose (FPG): A reading of 100–125 mg/dL (5.6–6.9 mmol/L) after fasting overnight suggests prediabetes.
- Oral Glucose Tolerance Test (OGTT): If blood sugar spikes between 140–199 mg/dL (7.8–11.1 mmol/L) two hours after drinking a glucose solution, it indicates prediabetes.
- Hemoglobin A1c (HbA1c): This test averages blood sugar over two to three months, with prediabetes ranging from 5.7–6.4% (39–46 mmol/mol).

Here is where it gets tricky: these tests

do not always agree. Studies have shown that only 12.6% of adults were diagnosed with pre-diabetes using HbA1c, while 28.2% tested positive with fasting glucose, more than twice as many. Even more surprisingly, only 7.7% of people met both criteria at the same time. This means that some individuals may be told they have prediabetes using one test, but not another.

Globally, diagnostic thresholds vary. The World Health Organization (WHO) sets a higher fasting glucose cutoff, 110–125 mg/dl (6.1–6.9 mmol/L) and does not use HbA1c for diagnosis, citing concerns about accuracy across different populations. The lack of uniformity adds to the confusion, leaving some at risk without realizing it.

Prediabetes: How harmful is it?

One of the biggest misconceptions about prediabetes is that complications only start after full-blown diabetes develop. The truth is damage can begin even in the prediabetic stage.

Studies have shown that 8% of prediabetic individuals already had signs of diabetic retinopathy, a condition most commonly associated with advanced diabetes. This means tiny blood vessels in the eyes were already being affected, despite these individuals never being diagnosed with diabetes.

The kidneys also show early warning signs. Studies have linked pre-diabetes to higher rates of microalbuminuria, an early marker of kidney stress. Over time, elevated blood sugar places a burden on the tiny filtering units in the kidneys, increasing the risk of chronic kidney disease.

The heart and blood vessels are not spared either. Prediabetes is often accompanied by insulin resistance, which triggers inflammation and arterial stiffening. These hidden changes raise the risk of heart disease and strokes, even before diabetes sets in.

The key takeaway? Prediabetes is not harmless. It is a slow-moving storm, and unless addressed early, the damage can quietly build up over time.

Why Does Prediabetes Happen?

To understand prediabetes, it helps to picture insulin as a key that unlocks the body's cells, allowing sugar (glucose) to enter and provide energy. But in insulin resistance, the underlying cause of prediabetes, the lock gets jammed. Cells stop responding properly to insulin, forcing the pancreas to produce more and more to compensate.

For a while, the pancreas can keep up. Blood sugar levels remain in check, but insulin levels are abnormally high. This is the silent phase of insulin resistance. Eventually, the pancreas starts to fall behind, and blood sugar begins creeping up, first after meals, then even during fasting.

At this stage, pre-diabetes is diagnosed. If nothing changes, diabetes develops. The cycle is driven by multiple factors, including:

- Excess body weight (especially around the abdomen), which worsens insulin resistance.
- Physical inactivity, reducing the body's ability to use glucose efficiently.
- Genetics, as some people are more prone to insulin resistance than others.

The progression is not inevitable, but it's common. Without intervention, many will advance to diabetes within a few years. However, there is hope. Pre-diabetes can often be reversed.

Turning the Tide: How to Prevent or Reverse Pre-diabetes

The most effective way to combat prediabetes is through lifestyle changes, which have been proven to significantly reduce the risk of developing diabetes. Research shows that even modest weight loss can have a profound impact, shedding just 5–7% of body weight lowers the risk of diabetes by 58%. The benefits are even more pronounced in individuals over 60, who experience a 71% risk reduction with similar lifestyle modifications. Additionally, engaging in regular physical activity, such as 150 minutes of moderate exercise per week, has been shown to improve insulin sensitivity, making it easier for the body to regulate blood sugar effectively. These findings highlight that even small, consistent ef-

forts can reverse prediabetes and prevent it from progressing to diabetes.

What Works Best?

The most effective way to combat prediabetes starts with a smarter diet. Cutting out sugary drinks and refined carbohydrates helps prevent blood sugar spikes and reduces insulin resistance. Instead, focusing on fiber-rich foods like vegetables, whole grains, and legumes can slow sugar absorption, keeping blood glucose levels stable. A Mediterranean-style diet, rich in healthy fats, lean proteins, and whole foods, has been particularly successful in improving blood sugar control.

Regular exercise also plays a crucial role. Experts recommend at least 150 minutes of moderate activity per week, such as brisk walking, cycling, or swimming, to improve insulin sensitivity. Incorporating resistance training helps build muscle, which enhances the body's ability to use glucose effectively. Even small lifestyle changes, such as walking more frequently and sitting less, can make a significant impact.

For individuals at very high risk, doctors may recommend metformin, a medication that helps regulate blood sugar. However, lifestyle changes remain the most effective approach and should always be the first line of defense against pre-diabetes and its progression to diabetes.

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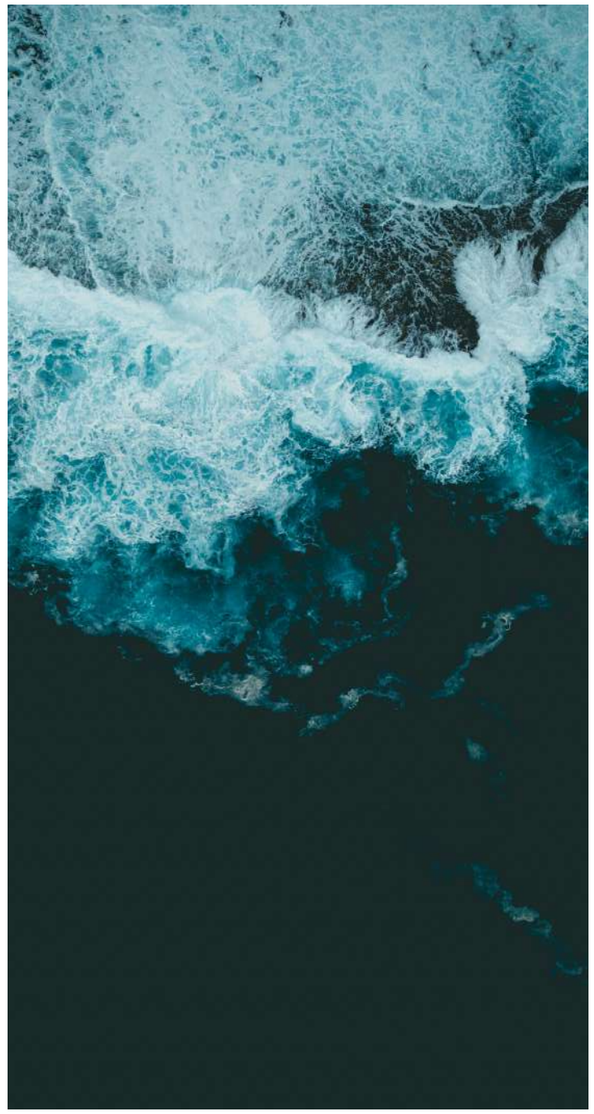
Obesity and metabolic syndrome: pandemic of the 21st century

University of Latvia

University of Latvia (UNIL) is one of the largest comprehensive and leading research universities in the Baltics. University of Latvia is continuously developing – expanding horizons of the academic work and scientific research by collaborating internationally, increasing the number of international study programmes, strengthening its cooperation with industrial partners.

World Obesity Day - 4th of March – aims to increase awareness and promote actionable solutions for tackling the global obesity crisis. Obesity has emerged as one of the most pressing public health challenges of the 21st century, with its prevalence reaching pandemic proportions globally. According to data, the projected rise in the prevalence of obesity among adults will increase from 0.81 billion in 2020 to 1.53 billion in 2035, representing an 88.9% increase. It is expected that 1 in 4 individuals will be living with obesity by 2035[1].

According to the Obesity Medicine Association[2], obesity is no longer considered a risk factor for the development of other diseases like cardiovascular, but as a chronic, relapsing, and neurobehavioral disease (abnormal condition or disorder), which is associated with increased accumulation of dysfunctional and

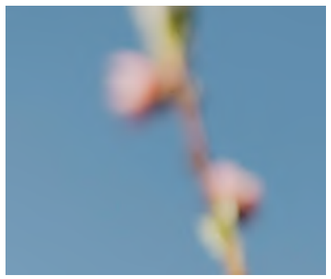


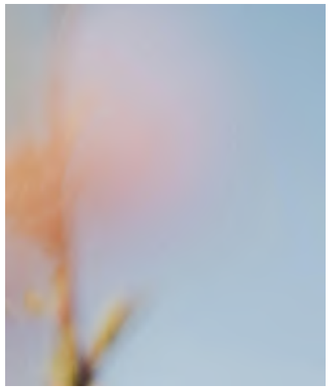
"Obesity is dramatically increasing: by 2035, 1 in 4 individuals will be afflicted."

abnormal fat mass, resulting in metabolic, biomechanical, and psychosocial health consequences. On the other hand, according to the World Health Organization, obesity is classified using the body mass index (BMI 25 – 29.9 kg/m^2 overweight, BMI > 30 kg/m^2 – obesity), which is not very accurate because it is not account for muscle mass.

It is important to emphasize that obesity and metabolic syndrome are different conditions. How do health professionals diagnose metabolic syndrome? At least three of the following criteria must be met[3]:

- central or abdominal obesity (elevated waist circumference ≥80 cm in female and ≥102 cm in male);
- high triglyceride levels in blood sample (>1.7 mmol/L or ≥150mg/dL);
- reduced high-density lipoprotein (HDL) (<1.3 mmol/L or <50 mg/dL in female and <1.0 mmol/L or <40 mg/dL in male);
- elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg or taking antihypertensive drugs);
- elevated fasting glucose levels (glycemia ≥5.6 mmol/L or ≥ 100 mg/dL or receiving glucose-lowering treatment).





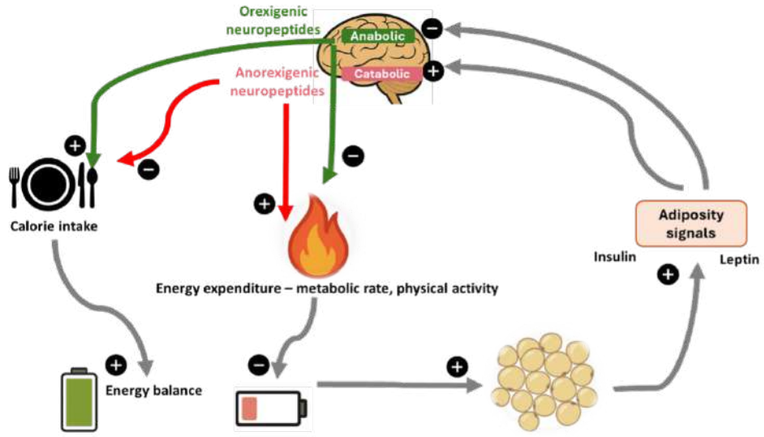


Figure 1. Neurobiological mechanisms of the central nervous system. Orexigenic neuropeptides: NPY/AgRP; anorexigenic neuropeptides: POMC/CART. Adapted from: Schwartz MW, Woods SC, Porte DJ, Seeley RJ, Baskin DG: Central nervous system control of food intake. Nature 404:661–671, 2000.

The energy balance is regulated by the neurobiological mechanisms of the central nervous system (Figure 1). It ensures a continuous balance between nutwrient intake on one side of the scale and energy expenditure through physical activity on the other side. The anabolic pathway includes neurons in the hypothalamic arcuate nucleus that coexpress neuropeptide Y (NPY) and agouti-related protein (AgRP) that stimulates food intake and suppresses energy expenditure. Ghrelin also called "hunger hormone" is secreted from the P/D1 cells in the fundus and upper intestine that activates NPY/AgRP neurons and stimulates food intake[4].

In contrast, a key catabolic pathway consists of specific neurons that produce **α**-melanocyte-stimulating hormone, derived from the precursor prepro-opiomelanocortin (POMC), which stimulates energy expenditure and suppresses appetite. POMC neurons also express cocaine-amphetamine-regulated transcript (CART), which, in collaboration with **α**-melanocyte-stimulating hormone, reduces food intake[4].

Leptin is also known as "a satiety hormone", its overproduction leads to insensitivity of the hypothalamus response to overfeeding and delayed satiety. Leptin and insulin concentrations in blood reflect body fat levels (higher adipocyte mass will lead to leptin and insulin resistance) and influence the hypothalamus by promoting the catabolic pathway and suppressing the anabolic pathway[4]. Leptin is not the exclusive "player" in satiety promotion, other incretins like glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), oxyntomodulin and peptide YY also play important roles in food intake regulation.

How do these signaling pathways promote energy balance?? When adiposity signal levels drop below normal during negative energy balance (promoting weight loss) anabolic pathway is strongly activated (e.g., increased food intake, reduced energy expenditure) and catabolic – opposite – suppressed. Since anabolic pathways are already inhibited by normal adiposity signal levels, further suppression has minimal impact on the response to increased adiposity signaling. As a result, the response to positive energy balance (weight gain) is less pronounced, primarily driven by increased catabolic pathway activity that leads to food intake inhibition and increased metabolic rate (POMC/CART secretion dominates over NPY/AgRP signalling)[4].

But can obese people be metabolically healthy and what does it mean? The answer is no. The so-called 'metabolically healthy obese" individuals have an increased level of subcutaneous white adipose tissue, without excessive intra-abdominal fat deposits (in the liver, skeletal muscles, heart, pancreas), normal levels of systemic inflammation markers, but increased levels of leptin, and resistin[5]. Resistin is associated with insulin resistance, which is one of the risk factors for the development of metabolic syndrome, prediabetes and diabetes. "Metabolically healthy" obesity reduces the risk of developing type 2 diabetes and CVD in the short term, still having an increased risk of cardiovascular disease - 49% increased risk of coronary heart disease, 7% increased risk of cerebrovascular disease, and 96% increased risk of heart failure, respectively[6].

It is impossible to modify genetics, neurobiological diseases, gender, age, and height, but still, a large portion of obesity risk factors can be modified – diet, physical activity, behavioral and environmental risk factors, and physical and mental health. And the sooner the modifiable risk factors are improved – the better.

If we discuss how much weight loss is potentially needed to improve obesity-related complications then already 1-5% of total body weight can normalize blood pressure and glycemia[7]. Of course, a higher reduction is a greater health improvement – for instance, a 5-10% reduction can reduce adipocyte accumulation in the liver (improve metabolic dysfunction-associated steatotic liver disease)[7].

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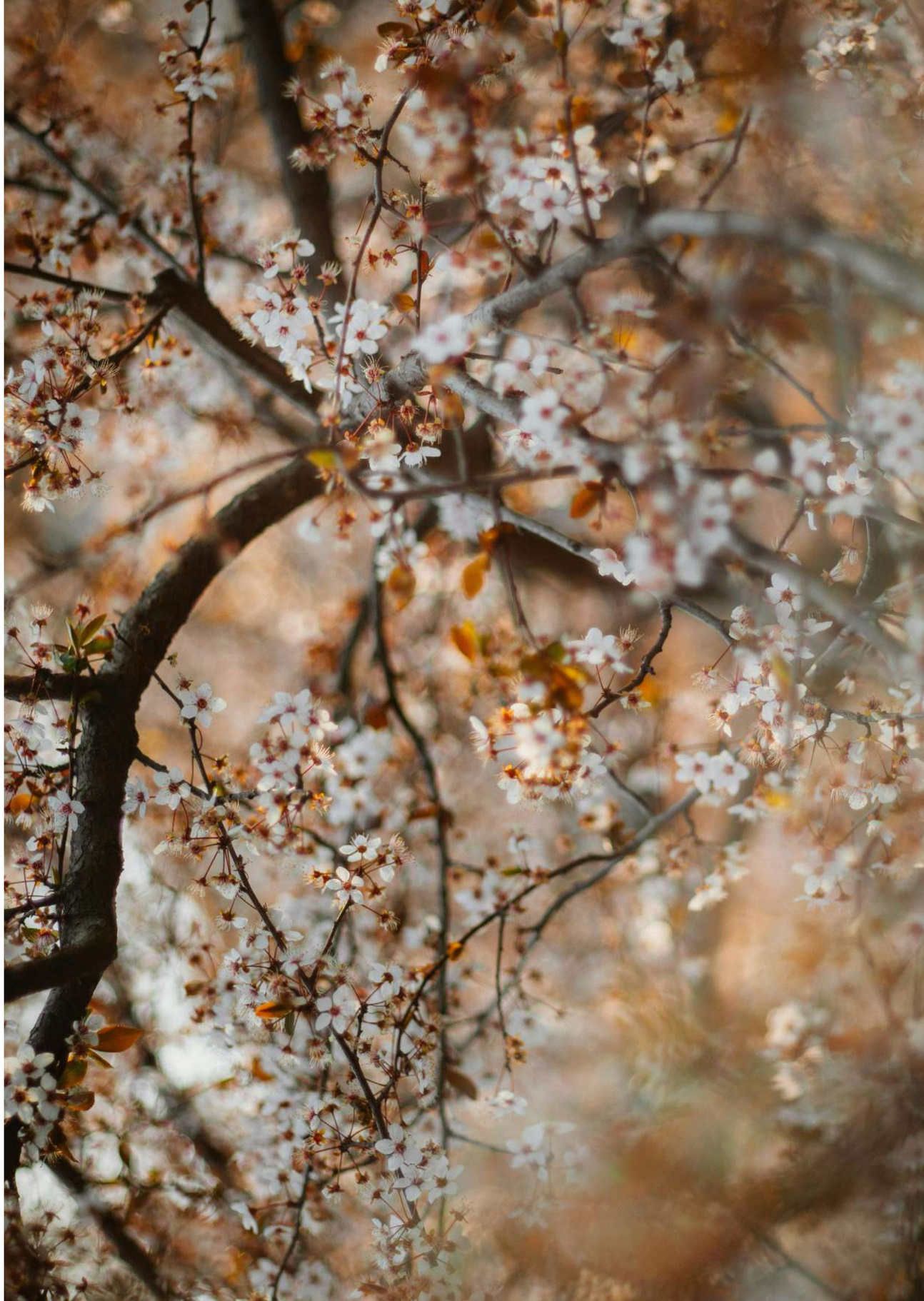

Exploring Type 2 Diabetes from a Hepatic Angle: What Your Liver Reveals

The Italian Liver Foundation

Fondazione Italiana Fegato ONLUS

The Italian Liver Foundation (Fondazione Italian Fegato (FIF)–ONLUS) is a no-profit research center in Trieste, Italy, specialized in translational research and educational training of researchers and clinical personnel in liver-related diseases.

The Growing Health Crisis

The global rise in obesity is fueling a silent but serious health crisis: **metabolic dysfunction-associated steatotic liver disease (MASLD)**[1]. This condition, which affects more than 30% of people worldwide, is expected to surpass 50% by 2040[2]. Among individuals with obesity, the numbers are even more staggering—over 70% are affected, and in cases of severe (morbid) obesity, it reaches up to 90%[3].

MASLD doesn't just affect the liver; it also increases the risk of heart disease, kidney problems, and even certain cancers. Many people with MASLD also struggle with diabetes, high cholesterol, and other metabolic issues[4]. The disease starts with fat accumulation in the liver (steatosis) and, in some cases, progresses to a more severe form called **metabolic dysfunction-associated steatohepatitis (MASH)**, which can lead to liver fibrosis, cirrhosis, or even liver cancer[5].

The Need for Better Diagnostic Tools

Detecting MASLD early is crucial to preventing these severe complications. Currently, the most accurate way to diagnose it is through a l**iver biopsy**, which is an invasive and sometimes painful procedure. Because

of this, researchers are looking for non-invasive ways to detect and track the disease, including **blood tests and imaging techniques like ultrasound and MRI**. While these methods are helpful, they are not always accurate, leading to the search for better alternatives.

Recent research has focused on identifying **specific proteins in the blood** that could serve as early warning signs of MASLD and MASH. Scientists use advanced proteomics techniques—such as the Olink®[6] and SomaScan®[7] platforms—to analyze blood samples for potential biomarkers. However, these findings have yet to be widely adopted in clinical practice.

Our Study: Identifying Key Biomarkers for Liver Disease and Diabetes

Our study examined **the blood of 90 individuals with severe obesity** who were undergoing bariatric surgery. We divided them into two groups: those with MASH (40 patients) and those without MASH (50 patients). We analyzed their blood samples to identify **specific proteins associated with liver disease** and explored how these proteins might relate to diabetes as well.

Key Findings

- **FGF-21: A Promising Biomarker for Liver Disease**

One protein, **fibroblast growth factor 21** (FGF-21), stood out as the most significantly increased in people with MASH.

This protein plays a crucial role in regulating metabolism, reducing fat buildup[8], and improving insulin sensitivity[9]. High levels of FGF-21 in the blood correlated with liver damage seen in biopsies, making it a strong candidate for a non-invasive diagnostic tool.

- **Diabetes and Inflammation Markers**

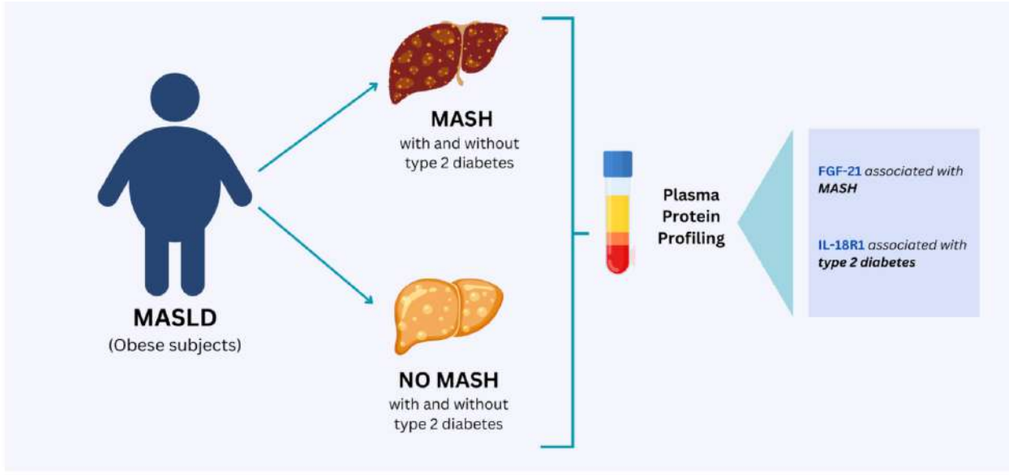

Figure 1 - Summary of the study design and the results

When we analyzed the blood samples based on the presence or absence of **Type 2 diabetes (T2DM)**, we found that seven proteins showed significant differences.

Interleukin-18 receptor 1 (IL-18R1), a protein linked to inflammation, was strongly associated with **high blood sugar (glycated hemoglobin levels)**, a key marker of diabetes progression.

Why These Findings Matter

Our research aligns with previous studies highlighting **FGF-21 as a potential biomarker for diagnosing and monitoring MASLD and MASH**. In fact, new drugs that mimic FGF-21—such as efruxifermin and pegbelfermin—are being explored as treatments for liver disease. Similarly, **IL-18R1 may play a key role in diabetes management,** particularly in controlling blood sugar and preventing complications like kidney disease.

The Future of Diagnosis and Treatment

Despite advances in research, current diagnostic methods for liver disease **are still not widely used in routine medical practice.** Our study highlights the need to integrate proteomics (blood protein analysis) into clinical settings to develop more reliable, non-invasive tests. A next step would be to validate these findings in larger patient groups and incorporate them into diagnostic models for both MASLD and diabetes.

Conclusion

Obesity, liver disease, and diabetes are deeply interconnected, and early detection is critical for preventing severe health complications. Our study shows that **FGF-21 and IL-18R1 could serve as valuable biomarkers** for these conditions, paving the way for better, non-invasive diagnostic tools. As research continues, we hope these findings will contribute t**o more effective screening, earlier treatment, and improved patient outcomes.**

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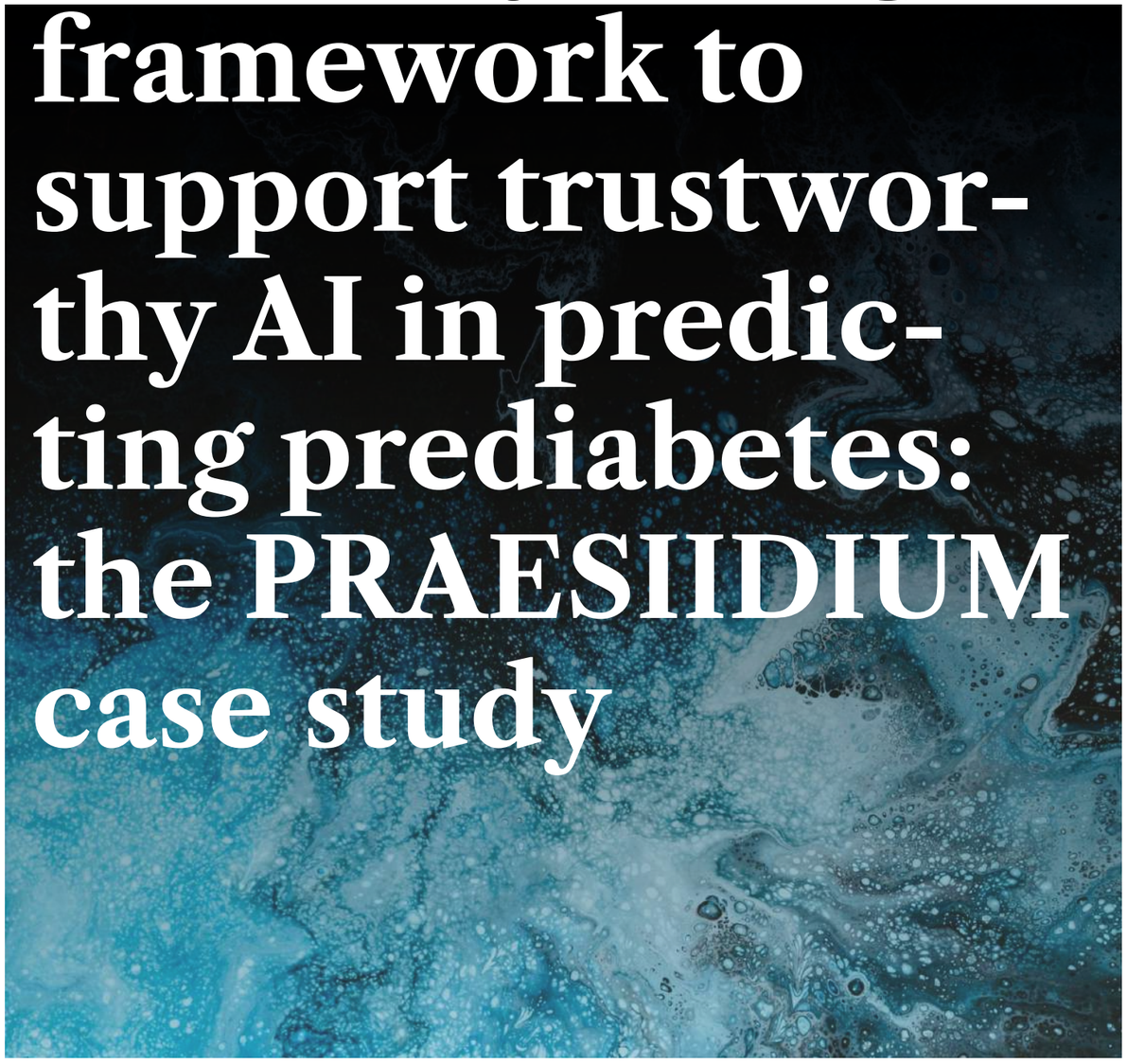
Ethics-by-Design framework to support trustworthy AI in predicting prediabetes: the PRAESIIDIUM case study



Scuola di Robotica

Scuola di Robotica (SDR) is a non-profit association founded in 2000 by a group of robotics and human science scholars. The main objective of Scuola di Robotica is the promotion of culture through education, training, education and dissemination of the arts and sciences involved in the process of development of robotics and new technologies.

The impact of the application of AI and Machine Learning technologies on health care is so decisive that there is now **no area of medicine and care delivery that has not been changed by AI technologies and programs** (1, 2). However, as in any other technology area, AI and ML applied to health raise ethical, legal, and social (ESL) issues in various domains, from concern for patients to the problem of data and AI reliability in the case of applications to predictive medicine, to the relationship between physicians, clinicians, patients, and AI. (3)

Ethical issues concern the application of European GDPR and of any other international regulation protecting patients' privacy, confidentiality and integrity of personal data; the effectiveness of informed consent; human wellness in the use of AI health technologies and programs, and the subsequent need for appropriate education in the use of technologies that are often unfamiliar to people. AI employed in healthcare must be reliable, transparent, trustworthy. The data used in model building and on which AI is trained must be secure and free of bias. The relationship between the healthcare professional, digital technologies, and AI tools must be carefully evaluated so as not to generate biased hierarchy models and to maintain the **health professionals as the ultimate decision responsibility** (4).

We present here the methodology adopted by the consortium of the Horizon Europe PRAESIIDIUM project, in which multi-scale mathematical models and eXplainable AI techniques are used to predict the individual risk of prediabetes in a personalised way. Large-scale real-life data, from retrospective and prospective clinical studies, including wearable devices, are employed for training the algorithms. To assess the ELS isues emerging from project actions, PRAESIIDIUM adopted an **Ethics by Design** methodology (EbD, 5) applying the

> **AI systems should support human agency and human decision-making, especially when applied into healthcare**

procedures recommended by ALTAI, Assessment List for Trustworthy Artificial Intelligence, the evaluation procedure recommended by the High-Level Expert Group on Artificial Intelligence (AI HLEG) at the request of the European Commission (6,7).

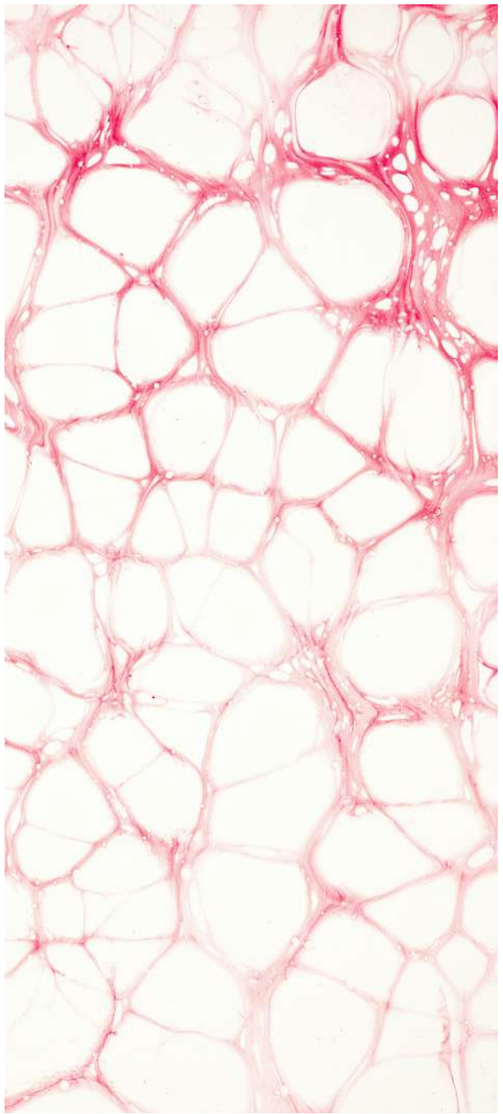
ALTAI is a self-assessment tool on the reliability of AI systems used in European projects. It is grounded in the protection of people's fundamental rights, according to the EU Treaties, the Charter of Fundamental Rights (the Charter) and international human rights law. (8,9).

Compared to other AI Trustworthiness assessment methods such as ISO/IEC standards, especially ISO/IEC 42001 (10) designed for AI e management systems; the IEEE methodology presented in the Ethically Aligned Design: A Vision for Prioritizing Human Well-being with Autonomous and Intelligent Systems (A/IS) created by committees of The IEEE Global Initiative on Ethics of Autonomous and Intelligent Systems (11), and procedures for industry risk assessment such as the Safety of the intended functionality, SOTIF (12), ALTAI seeks to bring together in a comprehensive self-assessment method the main ethics issues that may arise from the use of AI and ML, suitable for healthcare applications, research and industry.

ALTAI identifies the ethics issues assessing the application of AI with the protection of human rights defined in the EU Treaties, the Charter of Fundamental Rights (the Charter) and international human rights law (8,9) and suggests an articulated procedure of self-assessment, mitigation measures, and the early-involvement of all consortium partners - using **participatory meetings and survey techniques to produce a shared Ethics Self-Assessment for each year** during the project lifetime - to ensure human rights in clinical practice, an homogenisation of procedures and to avoid issues that multi-disciplinary projects may encounter. Through the adoption of the Assessment List for Trustworthy AI (ALTAI) for the Ethical Self-Assessment procedure, **Ethics by Design principles are translated into accessible and dynamic checklists to grow them into practice**, ensuring the project benefits from AI without unnecessary risks. (4,5). The partner responsible for the Ethics Self-Assessment (ESA), the Italian School of Robotics, and the Data Protection Officer collaborated with the consortium to produce the preparatory documentation for the ESA in the various versions corresponding to the project years, one per year. All partners collaborated not only on the specific ethical issues arising from their activities, as they all contributed to the discussion even on areas not directly concerned with their work.

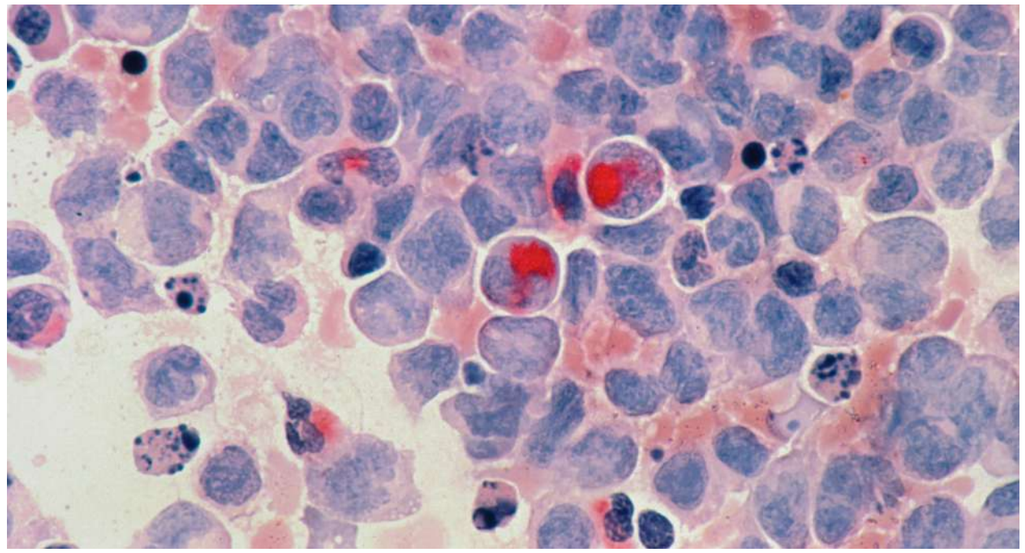
In PRAESIIDIUM, issues related to respecting and protecting the privacy of participants the clinical trials of the Medical Centers in Latvia and Austria, were evaluated by the respective Ethics Committees, so that the selection of volunteers was free from any bias or stigmatization of particular social groups,

respected the gender balance and the privacy of participants was assured. Similarly, it was ensured that the data represented diverse cultures and different dietary habits and lifestyles. Ethical issues related to the use of AI models, model validation, and the relationship between clinicians and digital and AI tools were also evaluated using the ALTAI tool.



The project is producing datasets obtained from wearable sensors, retrospective and prospective clinical data, and AI algorithms and mathematical models are trained on these datasets to define individualized recommendations for risk reduction, e.g., through diet or physical activity. The risk characterization and reduction algorithm will be implemented through a web-based platform, into which both patients and physicians will be able to input data from a variety of sources in order to estimate risk in real time and enable risk reduction through individualized interventions.

For the analysis of Ethical, Legal, and Societal Issues, the two fields involved are clinical medical and AI applied to health. Because of this, the ethical assessment presents a relative complexity compared to other health projects or AI research projects since it involves **two fields that were relatively distant until some decades ago:** ethical issues in medical research and innovation and ethical issues in the development and AI and digital health devices for human applications. The consortium sought to minimize differences in approaches between clinicians and AI experts by involving the former in model research and the latter in the complex relationships between clinicians, physicians, and patients with respect to diagnosis and treatment and the relationship that health care professionals have with digital technology and AI.



The first step was to establish in Ethics Board of the project in which all Consortium Partners participated and create an Ethics Roadmap that identified, based on the Ethics by Design methodology, GDPR and European guidelines on the ethical use of AI, the main issues related to the use of real, retrospective and prospective data; the guidelines to achieve a Trustworthy ML AI; the privacy, well-being and usability issues of wearable devices and sensors for data collection.

In drafting the Ethics Roadmap, the following requirements outlined in the DoA of PRAESIIDIUM were considered:

M1) How to ensure reproducibility of a data-driven prediction system?

M2) How to enhance the interpretability and trustworthiness of machine learning (ML) solutions?

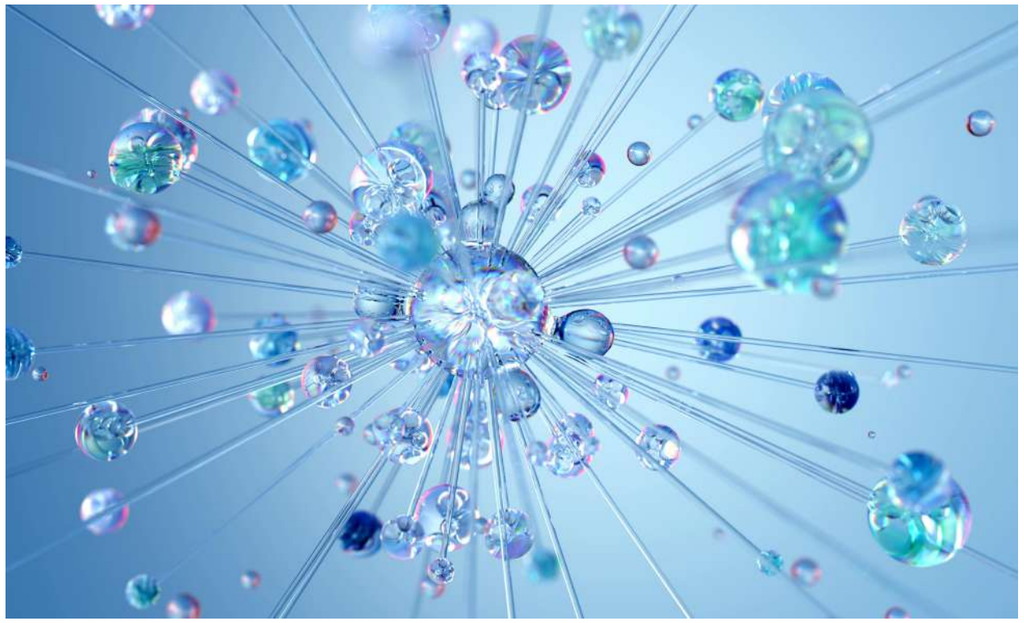
M3) How to improve a risk prediction accuracy while reducing the computation time?

M4) How to integrate data attributes, such as completeness, fairness, quality requirements into a computer aided diagnosis (CAD)?

M5) How to ensure that the general design of the project is compliant with ethical requirements from the outset?

M6) How to ensure that clinical investigations are designed to be compliant with all ethical and societal requirements?

Each of these requirements expresses different ELS issues that may be explicit or implicit and were derived from studying the consequences of the answers to these questions. For example, the type of answer developed by the Project to the question/requirement,



only on the surface a technical issue, *"How to improve a risk prediction accuracy while reducing the computation time?"* entails important ethical effects: a difference in the parameters of sustainability, well-being, risk assessment, incidence of false positives/negatives, accuracy of predictive medicine, and complex physician-patient relationships.

In PRAESIIDIUM's Ethics Roadmap, the stated requirements have been translated into the 'ethical analysis of the **seven macro categories of ALTAI,** which correspond to the **people's fundamental Rights to be respected and protected** and the requirements necessary to **achieve and employ, a Trustworthy AI.**

These categories are:

- human agency and oversight
- technical robustness and safety
- privacy and data governance
- transparency
- diversity, non-discrimination and fairness
- environmental and societal well-being and
- accountability.

If we consider the categories and the requirements of ALTA with respect to the ethical requirements of the project, the question, for example, *"How to improve a risk prediction accuracy while reducing the computation time?"* corresponds to the technical robustness and safety and environmental and societal well-being requirements.

The human agency and oversight category involves ethical analyses on several levels, including the hierarchy of control of

AI by human operators and patients in order to ensure that the **human** is always placed in an **on-the-loop** position; that the ultimate **responsibility for the effects of AI is always attributable to a human**; and that the transparency and Xplanability of AI is ensured in a way that guarantees human agency, i.e., control and ultimate decision-making over the use of AI systems:

AI systems should support human agency and human decision-making, as prescribed by the principle of respect for human autonomy. This requires that AI systems should both: act as enablers for a democratic, flourishing and equitable society by supporting the user's agency; and uphold fundamental rights, which should be underpinned by human oversight. In this section AI systems are assessed in terms of their respect for human agency and autonomy as well as human oversight. (ALTAI, cit., p.7, 13).

Based on the Ethics Roadmap, a series of questions /Ethics Survey) aimed at eliciting both general and specific reflections regarding the ethics requirement informing all project activities were proposed to the consortium. SdR held remote and in-person meetings with individual partners to clarify the scope and direction of the questions and to accurately apply the ALTAI methodology. A very important category for the project is Trustworthiness of models and ML with respect to problems that may arise and that may open ethical questions.

SdR analyzed and collated the partners' responses to the Survey into a document expressing the consortium's Consensus Statement on Ethics.

The project has completed its second year of actions and the process of producing the second Consensus Statement on Ethics is underway. At the conclusion of the third year, it will produce a Final Consensus on Ethics suggesting to the European Commission, as good practice, the articulated and comprehensive procedure adopted by PRAESIIDIUM for the evaluation of ethical issues.

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AI that Understands the Laws of Nature

SUPSI-IDSIA

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SUPSI-IDSIA is a Swiss research institute - one of the most prominent European research institutes in AI - with pioneering expertise in mathematical modelling and optimization, machine learning, advanced statistics, distributed systems, control of swarm intelligence and Bayesian methods. optimization, and machine learning.

The AI Problem No One Talks About

AI is transforming fields, from finance to healthcare, powering everything from self-driving cars to medical diagnostics. But there's a problem: AI is hungry for data and in many critical fields, data isn't always easy to get. Especially in medicine, patient data is scarce, sensitive, and often incomplete, making large-scale AI training difficult. Unlike data-rich fields, which can collect vast amounts of data, medical AI is constrained by privacy laws, ethical concerns, and the simple reality that gathering real-world clinical data is slow and expensive. How can AI make reliable predictions when data is limited?

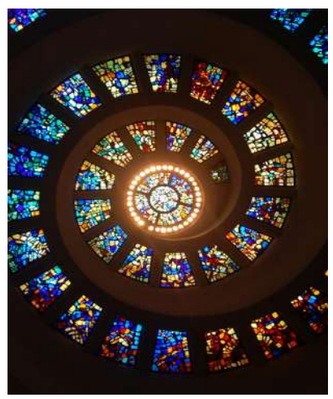
The answer lies in leveraging what we already know - the laws of nature – to guide AI learning. Instead of relying purely on data, Physics-Informed Machine Learning (PI-ML) embeds fundamental laws of physics or biology directly into AI models. This allows AI to move beyond pattern recognition and make predictions

that remain meaningful, even in data-scarce environments.

Unlike traditional AI, which relies purely on past examples, PI-ML ensures that predictions follow biological or physical constraints. This allows AI to:

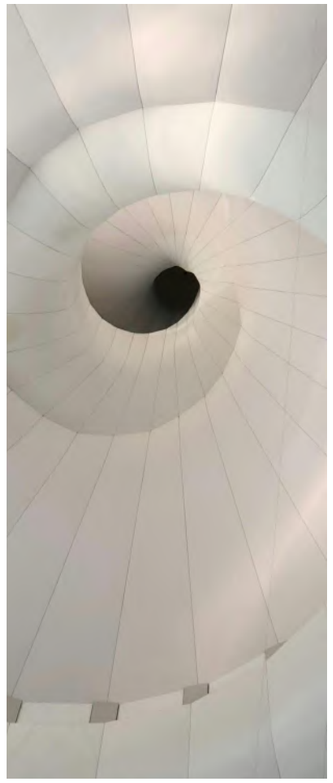
- Work with less data - since it doesn't need to "discover" physical laws from scratch.
- Make more reliable predictions, because it is constrained by fundamental principles rather than just past examples.

For example, consider blood flow prediction: A traditional AI model learns from past cases but might struggle with a new patient who has unique vascular conditions. A PI-ML model, however, incorporates principles of fluid dynamics, allowing it to make accurate and physiologically valid predictions, even in cases it has never seen before. Hence, PI-ML is bridging the gap between data-driven AI and real-world constraints, making it a powerful tool in fields where accuracy is critical and data is limited.



How PI-ML Embeds Scientific Knowledge into AI

AI models are trained by adjusting their predictions until they match real-world data as closely as possible. However, traditional AI only optimizes for accuracy on past examples, without any understanding of whether its predictions make sense in a biological or medical context. PI-ML changes this by modifying the loss function, the mathematical formula that guides AI training. Instead of only penalizing incorrect predictions, PI-ML also incorporates constraints based on established medical principles. This means the



AI isn't just learning patterns, it is actively penalized from making implausible predictions.

For example, a PI-ML model predicting glucose metabolism is not just trained on patient data. It is also constrained by known metabolic processes, ensuring that its outputs follow realistic physiological trends. Similarly, a model predicting blood flow is not only optimized for accuracy but also penalized if it violates fundamental principles of fluid dynamics.

This fundamental change in the learning process means that PI-ML does not rely entirely on large datasets to make accurate predictions. Instead of needing to see every possible scenario, these models can generalize more effectively by combining data with established scientific knowledge. A useful analogy is to think of traditional AI as a student who memorizes answers to past exam questions. This approach works well when the new questions are similar to those seen before. However, when faced with a completely new problem, this student may struggle. PI-ML, on the other hand, is like a student who understands the underlying concepts and can apply them to unfamiliar situations, solving problems even when data is limited.

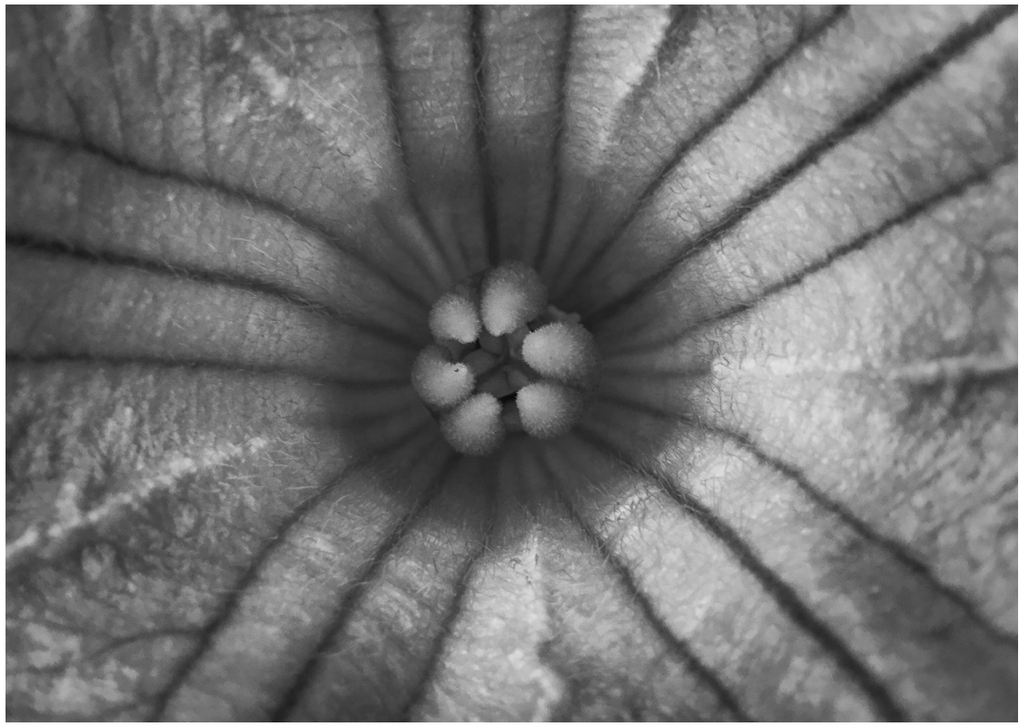
This approach has important consequences. First, it reduces the dependence on large amounts of training data, making AI more practical in fields where collecting new data is costly or difficult. Second, it improves trust in AI predictions, since the results are not only based on patterns in the data but also constrained by fundamental scientific principles.

How PI-ML is Transforming Medical Predictions

One key application is metabolic modeling, where PI-ML enhances predictions of glucose regulation and insulin response. Traditional AI models trained only on patient data often struggle to generalize across diverse populations. By embedding established metabolic principles, PI-ML ensures that predictions remain grounded in known physiological mechanisms, improving their reliability for clinical decision-making.

This approach is central to the PRAESIIDIUM project, where PI-ML is used to better understand and predict prediabetes progression. Clinical datasets on prediabetes are often small, making it difficult for standard AI to provide personalized risk assessments. PI-ML addresses this challenge by combining patient data with fundamental knowledge of metabolic regulation, allowing for more precise and individualized predictions.

By accounting for how glucose dynamics interact with insulin resistance over time, PRAESIIDIUM's models can estimate how lifestyle changes or medical interventions might alter disease progression. This provides clinicians and patients with actionable insights.



The Future: Smarter AI with Built-in Prior Knowledge

AI is moving beyond pattern recognition toward models that incorporate fundamental physical or biological prior knowledge. PI-ML represents a shift in machine learning, allowing AI to make predictions even when data is scarce, expensive, or incomplete.

As research advances, PI-ML is poised to drive breakthroughs in personalized medicine, disease modeling, and predictive healthcare. By integrating biological and physiological principles into AI, future models could improve early diagnosis, optimize treatment strategies, and support clinical decision-making with greater confidence. For PRAESIIDIUM, this approach opens the door to more accurate and explainable models for understanding prediabetes progression, potentially helping to identify risks before symptoms appear.

The next generation of AI won't just be data-driven, it will be guided by established knowledge. And in medicine, where trust and accuracy are critical, that distinction will make all the difference.

How math models and explainable AI help detect diabetes risk early

Consiglio Nazionale delle Ricerche

Consiglio Nazionale delle Ricerche

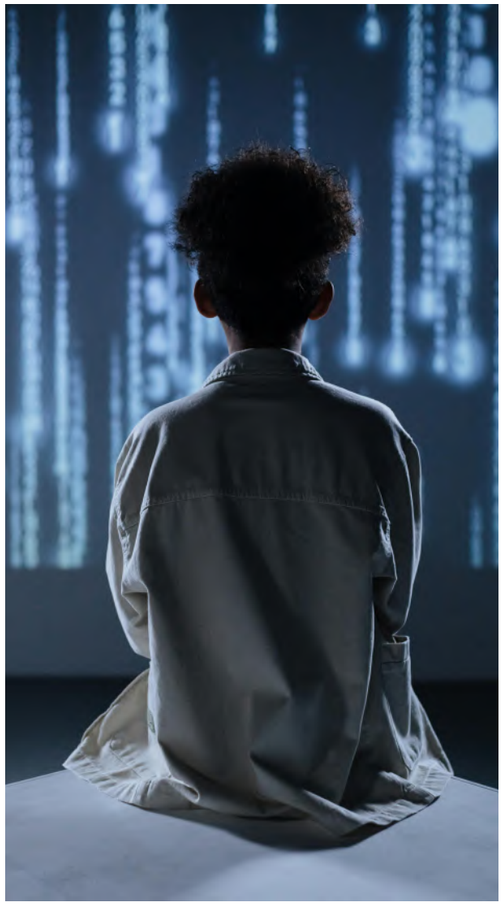
The National Research Council of Italy (CNR) is a public organization; its duty is to carry out, promote, spread, transfer and improve research activities in the main sectors of knowledge growth and of its applications for the scientific, technological, economic and social development of the country.

How math models and explainable AI help detect diabetes risk early

Developing prevention strategies to reduce the risk of type 2 diabetes is essential to help prevent the disease in the early stages. While 'one size fits all approaches' may fail in helping patients reach their prevention targets, individualized recommendations can help support patient motivation and therefore help implement lifestyle interventions for diabetes prevention.

To support personalized prevention in patients at risk of diabetes, math-based and data-driven approaches can be helpful to support patient awareness and engagement. For example, these approaches can be used to monitor the individual risk in real time, thus helping the patient understand how the risk decreases when preventive strategies are implemented (e.g., changes in diet, physical activity, inflammatory status, stress management, drug prescriptions).

Within the framework of PRAESIIDIUM, the CNR team is working on the development of a combination of methods, encompassing mathematical and data-driven models, to lay the groundwork for



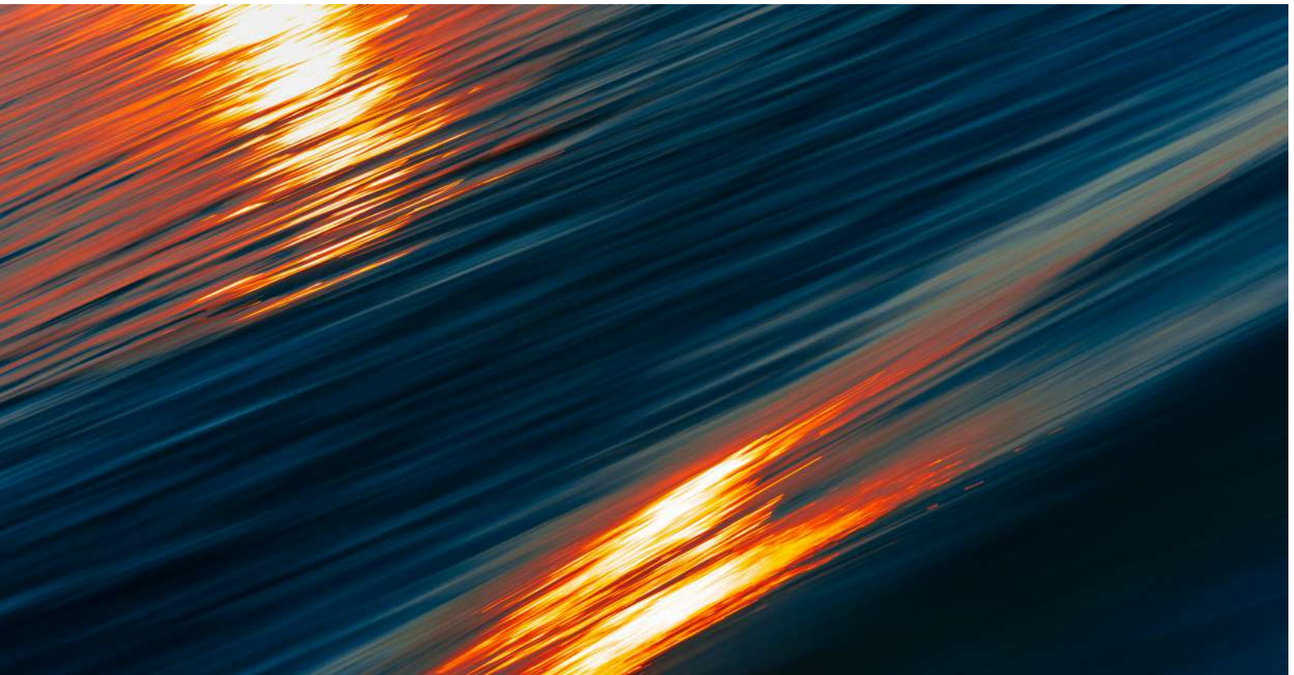
future digital twins. These will help assess the individual risk of developing diabetes and identify personalized countermeasures to reduce the risk as early as possible.

Multiscale mathematical models to simulate the metabolism of real individuals

Multiscale mathematical modeling is an approach used to describe complex systems that operate on multiple levels or scales—such as time, space, or organization. These models are particularly useful in fields like biology, physics, and engineering, where different processes interact across vastly different scales (Cappuccio et al., 2016).

To enhance the understanding of metabolic regulation of our body and its impact on diabetes risk, multiscale mathematical models have been developed and validated to simulate the whole-body fuel homeostasis under various physiological conditions. The MT2D is one of such models and has been originally developed at CNR on the basis of the immune system simulator C-ImmSim under the previous EU FP7 project "Mission-T2D". It integrates a glucagon-insulin model to describe the metabolic and hormonal responses to exercise and nutrition, allowing for a personalized assessment of glucose regulation and energy balance, thus providing a holistic view of metabolic and immune regulation. Such integrated model takes into account, and allows to tailor to individual, the immune system responses (such as inflammation) and the metabolism, following what the experts now call "meta-flammation": indeed, both aspects are critical in the onset and the progression of diabetes.

More specifically, the MT2D model builds upon existing frameworks (Kim et al., 2007) and integrates a dynamic representation of metabolic activity throughout the entire body and, also, multiple tissue compartments, including the heart, skeletal muscle, liver, gastrointestinal tract, adipose tissue, and brain. By considering factors such as age, gender, anthropometric characteristics, and fitness status of the subject, the model achieves greater adaptability and user-specific customization.



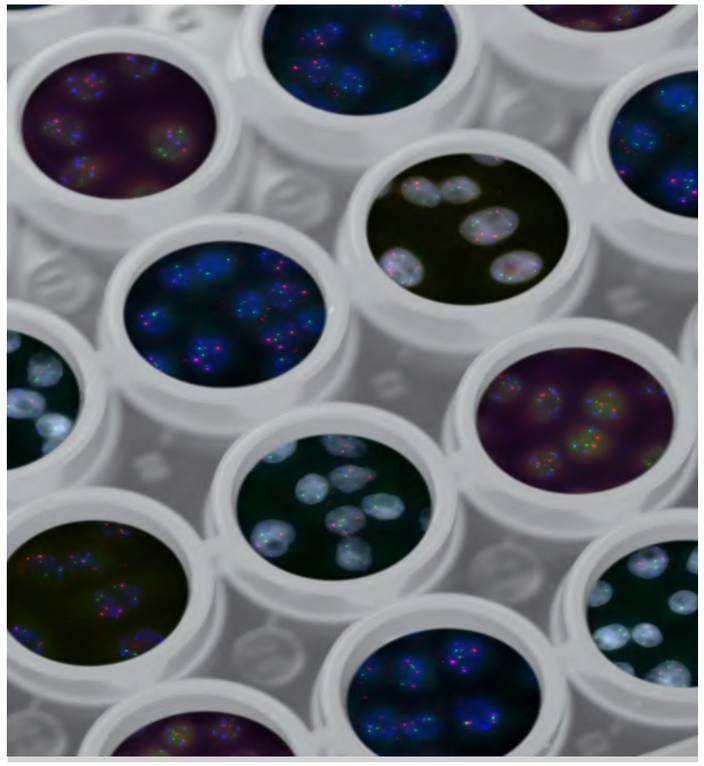
Why a multiscale model for the human body metabolism?

A deeper understanding of the effects of physical exercise in body metabolism and in particular its influence on the control of glucose homeostasis is of primary importance to manage and delay the onset of type 2 diabetes. To this aim, the MT2D model describes the metabolic responses to a session of physical exercise, a challenging task from the modeling point of view since the effects vary depending on its intensity, duration, modality and on the subjects' physical characteristics (e.g. age, sex, body weight, fitness status), thus providing a good level of personalization (Palumbo et al., 2018). Moreover, the beneficial effects of exercise seem to be exerted trough the modulation of the cytokine Interleukin-6 (IL-6), an immune controller which triggers a cascade of inflammatory cytokines. Leveraging the model's immunological component, IL-6 dynamics during and after exercise is incorporated to provide a comprehensive view of physical activity's impact on the subject's metabolic and inflammatory status (Morettini et al., 2017). All these features are packed inside the MT2D model.

Another key advancement in this approach that will be fully exploited in the PRAESIIDIUM project is the inclusion in the model of two compartments, one related to food intake, and another related to the gut microbiota. Modeling stomach emptying, absorption of macronutrients during and after the ingestion of a mixed meal that includes proteins, carbohydrates, and fats will enable a more comprehensive representation of real-life metabolic fluctuations and lifestyle influences on glucose homeostasis (Palumbo et al., 2023).

In summary, the MT2D multiscale computational model is used in PRAESIIDIUM to design and simulate virtual cohorts of subjects differing in sex, age, height, weight, and fitness status, for specialized in silico challenge studies aimed at designing exercise and nutrition schemes to support health. The hormonal and metabolic predictions can span over a large amount of time, even years, due to a good numerical stability of the model. These simulations show in very fine detail the trajectories over time of a large number of biometric, metabolic, and immunological parameters but they require significant computational resources due to their complexity. Thus, once a substantial amount of synthetic data has been obtained through this powerful but complex approach, it will be leveraged to develop and fine-tune physics-informed machine

learning (ML) surrogate models, which can much more efficiently approximate complex metabolic processes, enabling faster and more scalable predictive tools for personalized healthcare applications.



Modeling the benefits of Physical Activity: how does physical activity influence diabetes progression?

Regular physical activity affects blood sugar regulation over the long term. While state-of-the-art models address only short-term effects (such as how a single workout influences glucose levels), an additional model developed within PRAESIIDIUM (De Paola et al., 2023; De Paola et al., 2024) incorporates the role of IL-6, a protein released during exercise, to address both short- and long-term outcomes. Sustained release of IL-6 due to regular physical activity helps protect pancreatic beta cells, promoting insulin production and reducing inflammation in the long term, ultimately reducing the risk of developing diabetes. The model can predict the benefits of physical activity of varying workout intensities and durations, and it precisely mimics real-world exercise recommendations (such as those from the World Health Organization) to simulated patient outcomes. The results confirm that moderate-to-vigorous exercise significantly delays diabetes progression in individuals at high risk to diabetes. Moreover, the models also predict what happens when people stop exercising: while some benefits persist for a while, discontinuing physical activity eventually negates its protective effects in the long term. This highlights the importance of maintaining an active lifestyle rather than viewing exercise as a temporary fix. Based on this mathematical model, we have developed a control-theoretical approach optimizing physical activity for glucose control (De Paola et al., 2025). Instead

of generalized recommendations, this model uses real-time data and predictive algorithms to suggest personalized exercise regimens based on an individual's health status. This framework, known as model predictive control (MPC), could be incorporated into future digital health tools, allowing users to receive real-time feedback on how much and what type of exercise they should engage in to manage their glucose levels effectively. Future research in this area will focus on refining these models to make them more personalized and adaptive, providing patients with more precise guidance on their physical activity needs.

Data-driven dynamical models: how do multiple health factors interact in diabetes progression?

Within the framework of PRAESIIDIUM, novel data-driven dynamical models have been developed to analyze how different biomarkers interact over time in individuals with varying risk for diabetes (Simeone et al., 2023). These models adopt a "multi-input, multi-output" approach, examining how various health indicators, measured in a given individual in different medical encounters, influence each other and concur to determine the individual trajectory in the future. For example, these models consider how cholesterol levels, blood pressure, and body mass index together affect glucose metabolism and therefore diabetes risk. By incorporating real-world data from primary care electronic medical records, the models developed can predict biomarker trajectories in time and predict if an individual is likely to develop diabetes in the future, up to 8 years after a medical encounter. These findings demonstrate that tracking multiple biomarkers simultaneously can predict the onset and timing of diabetes, which is crucial for early intervention strategies. Expanding these models to include lifestyle and behavioral data could further improve their accuracy. Additionally, incorporating AI-driven real-time monitoring could allow for early warnings and preventive lifestyle adjustments, reducing the incidence of prediabetes and diabetes in the general population.

Explainable AI: How Can AI Predict Diabetes Risk More Accurately?

Within PRAESIIDIUM, we used explainable AI in the form of "counterfactual explanations" to generate personalized recommendations for diabetes prevention. This approach identifies the smallest possible changes in biomarkers—such as blood sugar, cholesterol, and blood pressure—that could significantly reduce a patient's risk of developing diabetes. By analyzing primary care electronic medical records from thousands of patients, we provide a more targeted approach to lifestyle modifications, offering actionable insights for both patients and healthcare providers. For example, in a recent study we found minimum viable recommendations, e.g. for fasting blood sugars, wei-

ght loss, or systolic blood pressure, able to shift high-risk patients into a lower-risk category, therefore enabling diabetes prevention (Lenatti et al., 2022). Interestingly, the approach revealed that hypertensive patients required more drastic biomarker changes compared to non-hypertensive individuals to achieve the same level of risk reduction. These findings emphasize the need for tailored interventions rather than one-size-fits-all recommendations.

Another study performed within the framework of PRAESIIDIUM focused on using counterfactual explanations to estimate personalized recommendations able to prevent the progression from prediabetes to full-blown diabetes (Console et al., 2024). Using data from primary care electronic medical records, the AI-based models achieved high accuracy in forecasting whether a patient with prediabetes would develop diabetes. Importantly, these explainable AI models not only make predictions but also provide insights into which factors are most influential in leading to these predictions. This approach may support doctors create personalized prevention plans, potentially reversing prediabetes before it transitions to a lifelong

diabetes. Future research could focus on integrating lifestyle data, such as diet and activity levels, to refine the AI-driven predictions. Developing user-friendly apps that provide real-time feedback and health recommendations based on AI predictions could make these tools more accessible and impactful. Moreover, integrating counterfactual explanations into AI-driven clinical decision support systems could help tailor prevention strategies more effectively.

What Do These Studies Mean for Diabetes Prevention?

Together, the mathematical and data-driven models developed within the Project PRAESIIDIUM paint a multifaceted picture of how diabetes develops and how we can intervene. These studies emphasize the importance of regular physical activity and healthy diet, show how AI can enhance early detection, and introduce new modeling approaches to understand disease progression. Future applications of these models could include digital health tools that track personal health data, alerting individuals when they are at risk and suggesting tailored lifestyle interventions. With continued research, these insights could lead to more effective strategies for preventing and managing diabetes, ultimately improving millions of lives worldwide.

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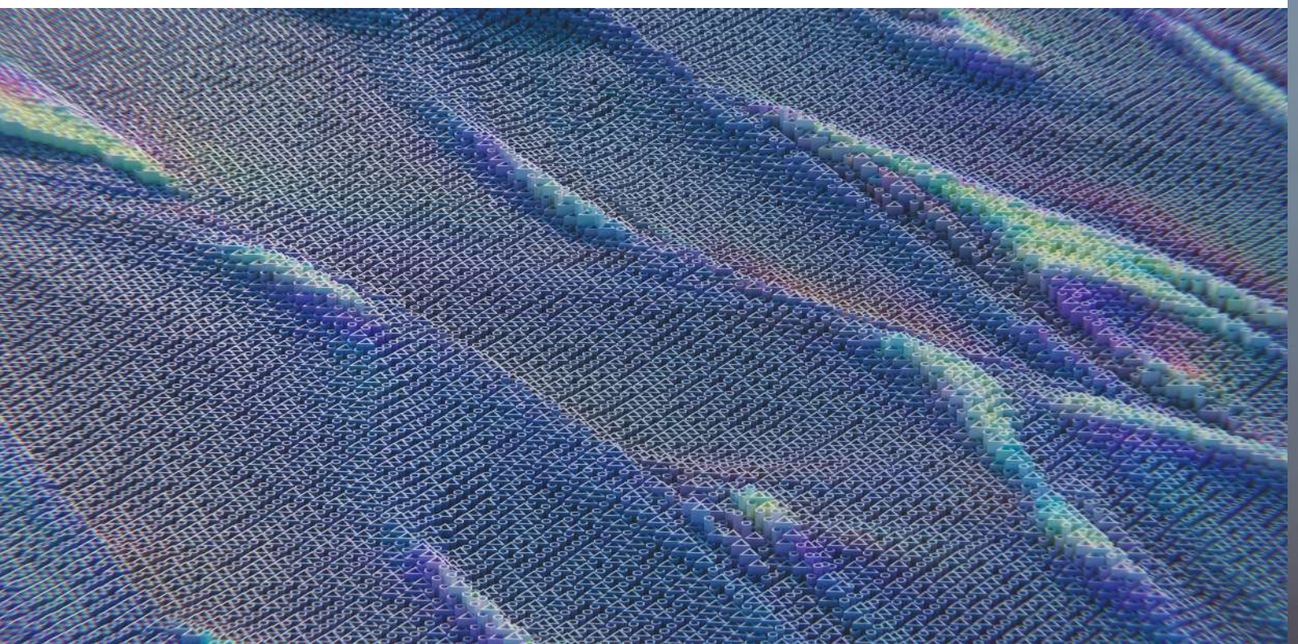


Combining generative AI, speech technology and telephony to collect health metrics

Check Health Sweden

CheckHealth (CHK) is an innovative medtech company developing and marketing solutions to help care organisations implement customised remote patient monitoring programmes.

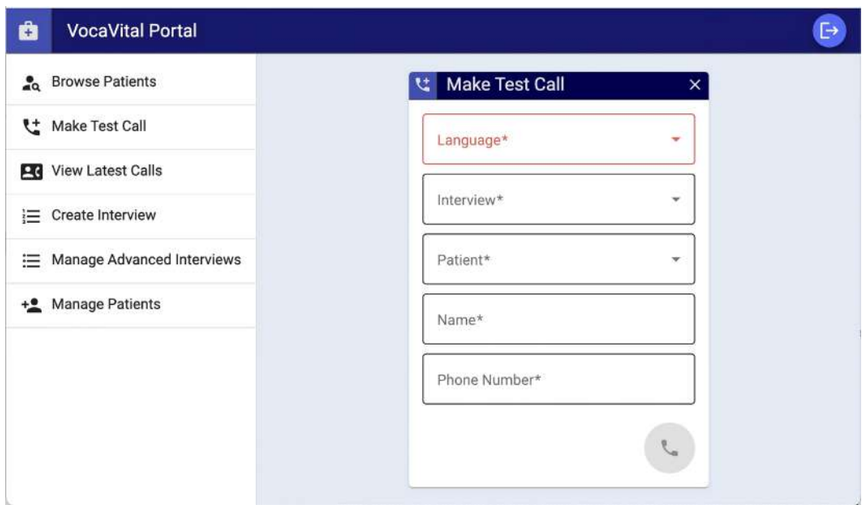
By combining the latest generative AI, speech technology and telephony, Checkhealth has created a **digital health application with the most natural and intuitive user interface possible: human conversational speech over the phone.** No apps, no downloads, no language restrictions and no technical knowledge is required. If patients can answer the phone, they can interact with the application Vocavital.ai - that is perceived as an friendly AI health assistant.

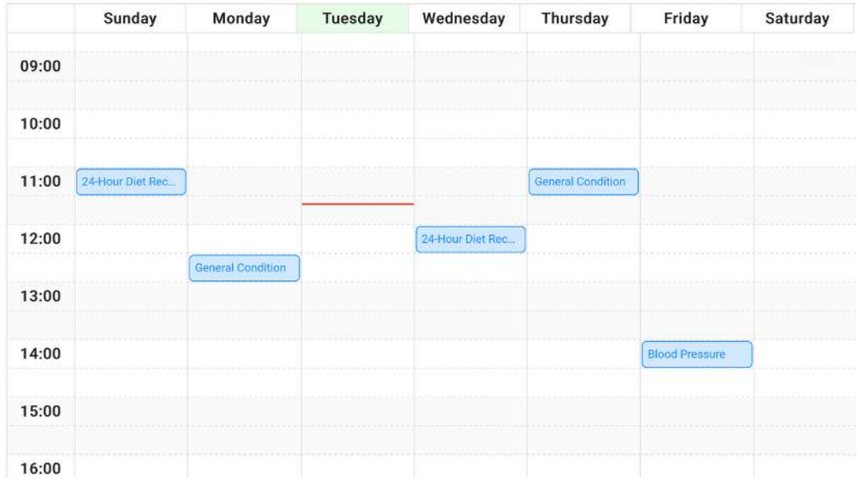
VocaVital.ai demonstrates how AI-powered phone interviews can be used to support patients and monitor their health in a highly efficient manner. The AI health assistant has been developed for use in a cli-

nical study on diabetes and dietary habits as part of the EU project PRAESIIDIUM.

The Vocavital application consists of a portal intended for care teams to use to design and schedule patient interviews. No technical knowledge is needed. The AI assistant then conducts regular phone interviews for each patient according to the specified schedule. All Interviews are automatically transcribed, analyzed, and insights are delivered to the care teams.

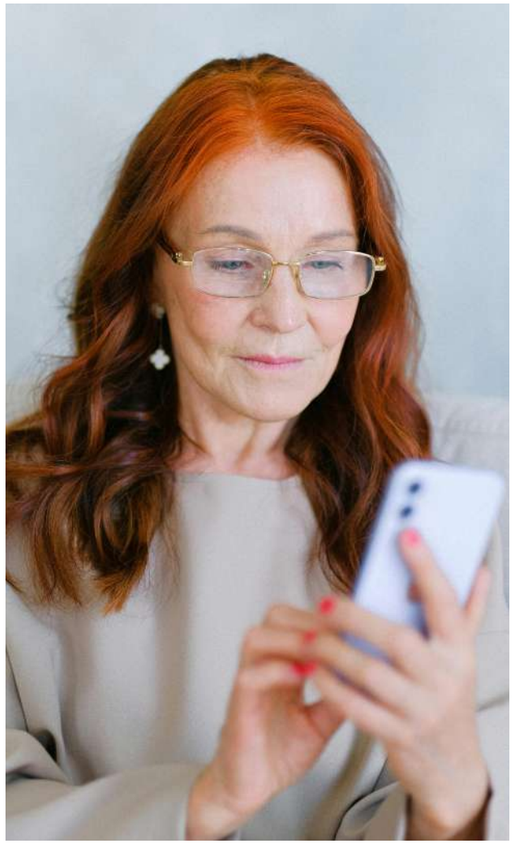
The technology behind Vocavital.ai is improving rapidly. Today we are combining the best components we can find to balance response time and quality. For instance we are currently using different suppliers for Speech-to-text (STT) and Text-to-speech (TTS) due to the fact that telephony in general needs special model training because of the volatility in audio quality in telephony applications. Moreover, a human conversation requires fast response times. Therefore we are using one fast LLM for the interaction with the patient and another a little bit slower but more intelligent, for the analysis of the resulting interview. In the future general multimodal models like OpenAI Realtime may be able to replace all other components in the technical architecture.



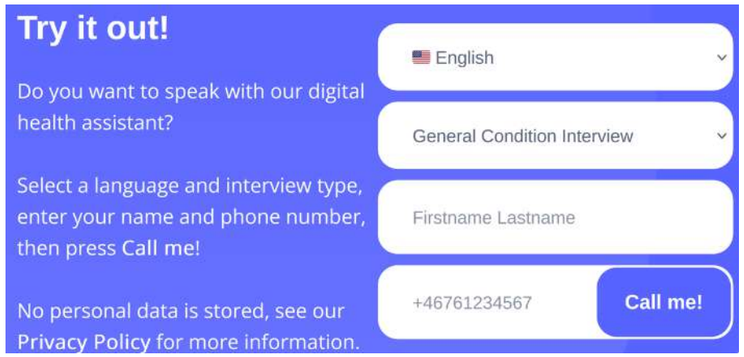


- *Imagine having the resources to call every patient and answer every patient call. The technology is improving very rapidly. Therefore we believe that the AI Health Assistant will be able to perform any phone call a human can, says Mattias Hällström, Business Developer at Checkhealth.*
- *Moreover the AI Health Assistant will be able to analyse and efficiently extract important health information from the patient that can be transferred to existing care systems.*

The AI Health Assistant currently supports 11 languages, but the language support in the speech-to-text and text-to-speech components used is constantly improving. **An open demo of the AI Health Assistant is available on https://vocavital.ai.**



The purpose of the demo is to showcase the commercial potential of the technology developed by CheckHealth AB. We are currently looking for a partner interested in bringing AI-powered phone interviews closer to the European healthcare market.



Wearable Bioimpedance Sensor for Heart Rate and Activity Detection

The Institute of electronics and computer science

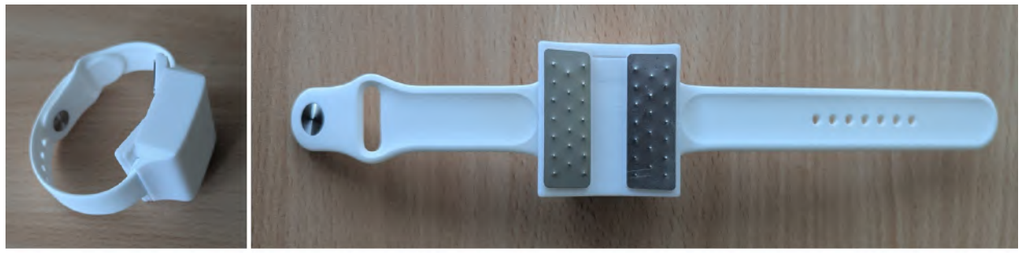
ELEKTRONIKAS UN DATORZINĀTNU INSTITŪTS
INSTITUTE OF ELECTRONICS AND COMPUTER SCIENCE

The Institute of electronics and computer science (EDI) is a Latvian public state research institute conducting fundamental and applied research in the broad area of Smart Embedded Cooperative Systems.

Introduction

In recent years, wearable technology has revolutionized health monitoring, offering devices that can track vital signs such as heart rate and physical activity through non-invasive means. Our team has developed an innovative wearable bio-impedance sensor designed to complement these advancements by providing accurate measurements of heart rate and physical activity levels.

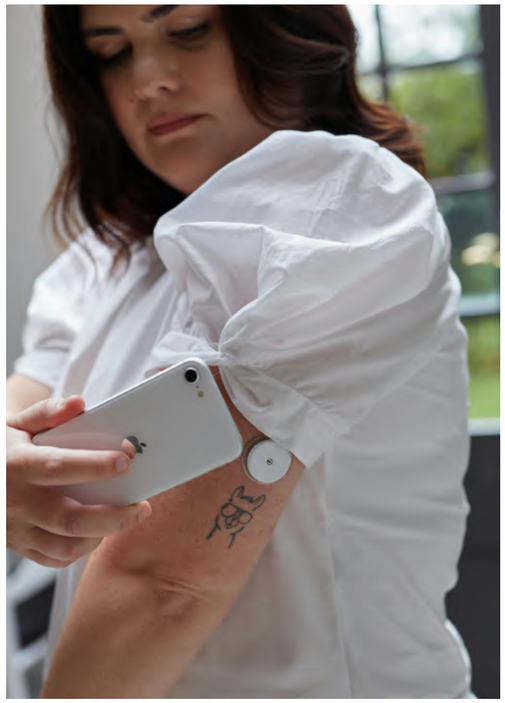
This sensor represents a step forward in health monitoring, particularly for individuals with chronic conditions like diabetes, where tracking heart rate and physical activity can be crucial even in the absence of direct glucose readings. For example, the sensor may aid in performing physical activity exercises by monitoring the activity intensity and heart rate that should stay in appropriate zone for the activity to be efficient and effective. By providing valuable insights into cardio-



vascular and physical activity metrics, the bio-impedance sensor aims to empower individuals with essential health information, fostering better lifestyle choices and overall well-being.

Sensor Design and Functionality

The developed system includes a wearable device with a bio-impedance sensor MAX30001 and accelerometer ICM-20948, a smartphone application for device management, and a backend solution for data processing on a server. The wearable, as seen in the figure below, is worn over the wrist of a person with two electrodes measuring the tissue resistance there. The resistance changes with the flow of the blood and therefore may be used for determining the heart rate. One of the challenges is to remove the noise that is added to the signal due to the movement of the arm, and can be done partially on the device and during the postprocessing. The device has a processing and radio module NORAB10600B that is able to transmit the data over a Bluetooth channel to a smartphone application, that in turn forwards the data to the server. All of the communication is encrypted providing the security and privacy.

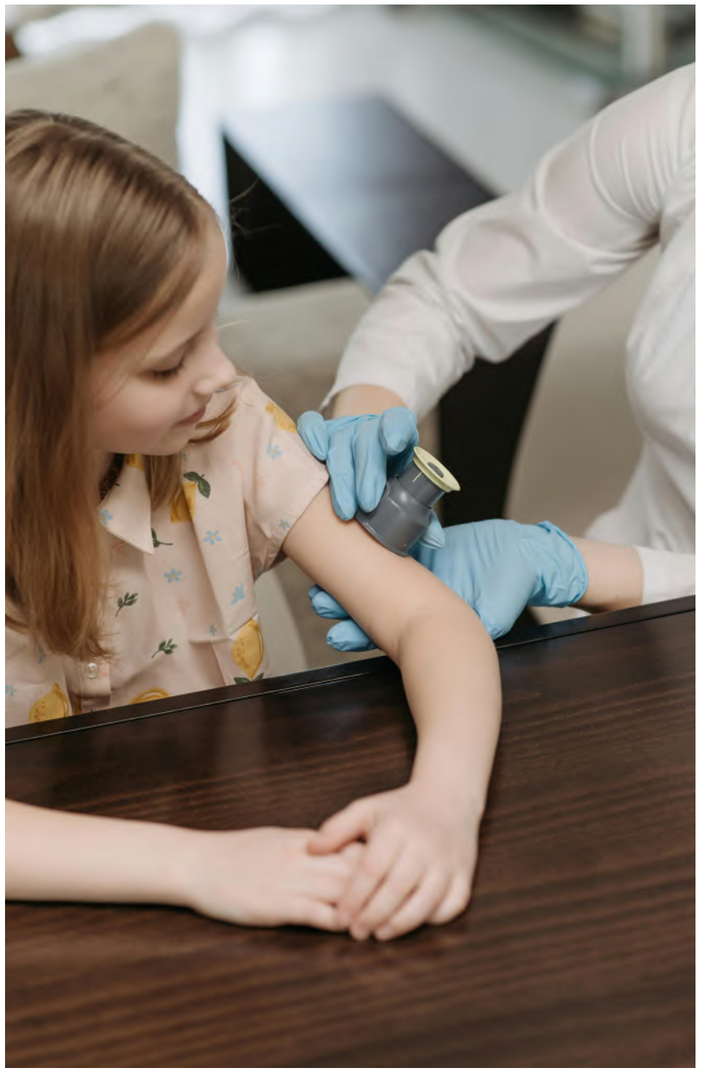


Estimating Heart Rate from Wrist-Measured Bioimpedance

The algorithm processes bioimpedance signals to estimate heart rate using a wearable device worn on the wrist. Bioimpedance involves measuring small changes

in the body's electrical resistance caused by blood flow during each heartbeat. The wrist device uses a bipolar electrode configuration - two electrodes placed close together - to capture these signals continuously over a few days, including during sleep in some cases. The goal is to provide a non-invasive way to monitor heart rate over extended periods, which could be valuable for health tracking.

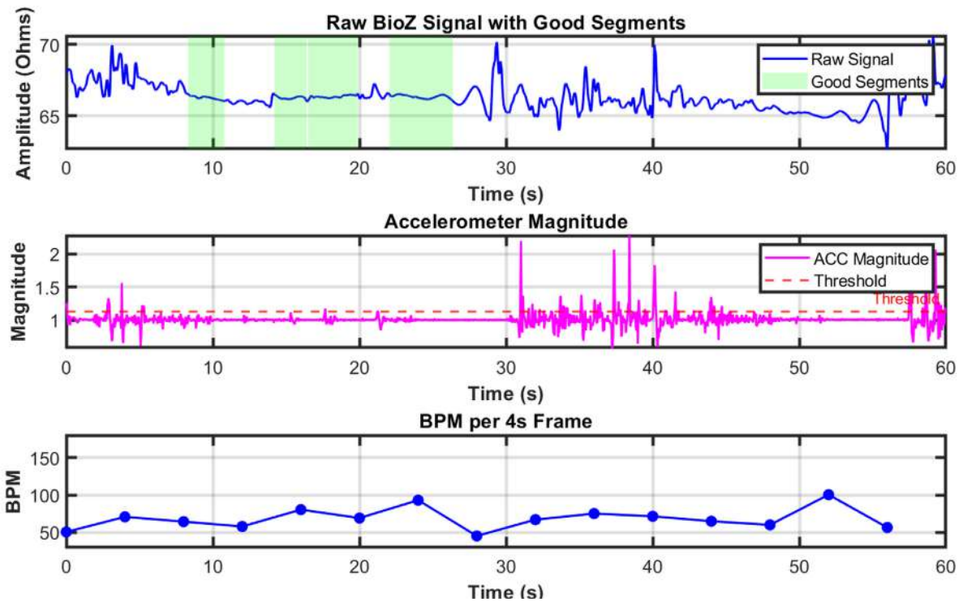
The raw bioimpedance signal is collected at a sampling rate of 64Hz and divided into 4-second segments, each containing 256 data points. The 4-second window is chosen because it is long enough to capture several heartbeats but short enough to track changes in heart rate over time. The algorithm then analyzes each segment in two main steps: first, it estimates the heart rate using cross-correlation, and second, it refines this estimate by de-



tecting peaks in the signal that correspond to heartbeats. Additionally, an accelerometer in the device helps filter out noisy data caused by movement. The following figure illustrates each step of this process.

Activity Recognition

We developed a mobile application enabling seamless data collection from a wearable device. The application is designed for Android devices with a minimum SDK level of

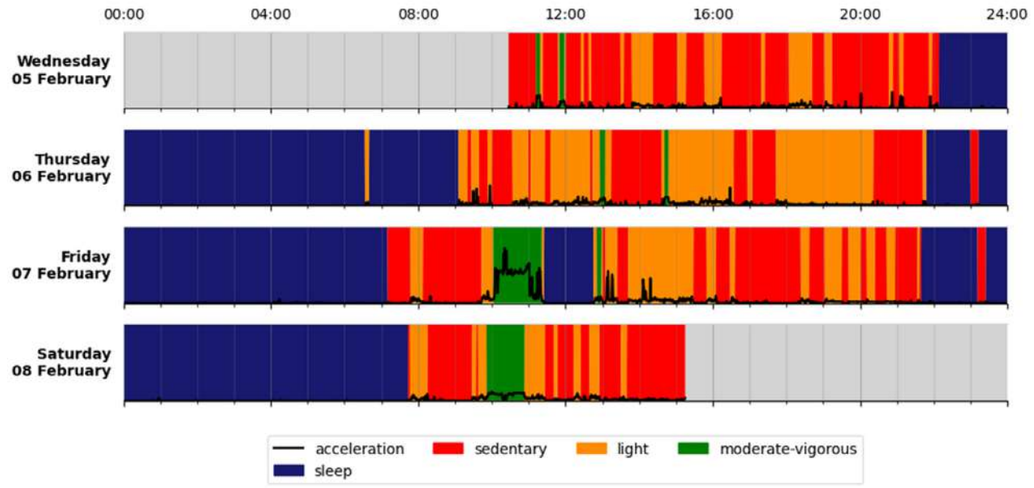


29, ensuring broad compatibility with a wide range of study participants' devices. It follows Material UI design principles to provide a user-friendly interface and smooth navigation.

The application operates in two key stages: the setup stage and the operational stage. During setup, users pair their wearable device and establish a secure communication channel with the backend server, utilizing Bluetooth connectivity and a one-time password for authentication. The operational stage allows real-time monitoring of the wearable device's status, secure data exchange with the backend, and continuous tracking of study-related metrics.

Built using the Android Jetpack library suite, the app follows the Model-View-ViewModel (MVVM) architecture to ensure efficient data handling and separation of UI logic. It integrates components such as Hilt for dependency injection, Room for local database storage, and Datastore for shared preferences. Secure communication is enforced through Mutual Transport Layer Security (MTLS), guaranteeing encrypted data transmission between the mobile device and backend server. A persistent foreground service ensures continuous data transfer, even when the app runs in the background, supporting reliable and uninterrupted study operations.

The collected raw data was processed using activity detection algorithm producing a time-series of



activities. An example of this can be seen in the following figure, where data from four days has been processed and categorised in four activity levels: sedentary, light activity, moderate-vigorous, and sleep. The line represents the raw acceleration data.

Challenges and Future Directions

There were several challenges identified during the tests of the device that leads to possible future directions for the research in the area. Perhaps, the most important challenge is related to the noise in the data due to movement artifacts. The signal processing and sensor fusion algorithms should be improved for better ability to detect the heart rate in a noisy signal, or the signal should be marked as too noisy for reliable data. Another challenge is the battery life. Currently the wearable can be used for four days non stop. After this the battery needs to be recharged. However, at the moment the signal has been measured all the time, with no duty cycling. Alternatively, by introducing duty cycling and combining that with the signal quality analysis the battery life can be improved many-fold. Another venue for improvement may be the selection of alterntive materials for the skin contacts that would improve the signal quality. Ultimately, the device could be improved by doing at least some of the analysis on-board and providing other medical insights about the human body.

Conclusion

The development of the wearable bio-impedance sensor represents a significant advancement in health monitoring technology. This innovative device of-

fers non-invasive methods for tracking heart rate and physical activity, complementing existing sensors that monitor glucose levels. Its dual utility makes it invaluable for individuals with chronic conditions such as diabetes, providing essential cardiovascular insights alongside glucose data.

Beyond medical applications, the sensor empowers general populations to maintain optimal health through consistent activity monitoring, promoting fitness and lifestyle improvements. For athletes and older adults, it enhances performance and physical well-being by enabling real-time monitoring of physical activity intensity and heart rate zones.

Technologically, the wearable system integrates bio-impedance sensors and accelerometers for accurate measurements, supported by a smartphone app for user management and a backend server for secure data processing. Addressing challenges like arm movement noise and ensuring data security through encryption, this system offers a comprehensive solution for personalized health monitoring.

Exploiting the results of the PRAESIIDIUM Project:

From Research to Market Impact

ALPHA Consult

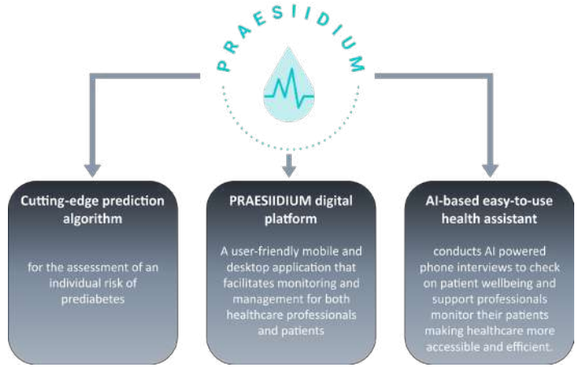
ALPHA Consult is a European consultancy delivering tailor-made solutions supported by senior staff with significant strategic development, market assessment and business modelling experience.

The project

The PRAESIIDIUM project is transforming how we approach prediabetes prevention and management. Leveraging advanced artificial intelligence (AI) and physics-informed machine learning, the project has developed an innovative tool that predicts an individual's risk of developing prediabetes while also offering continuous monitoring. The objective is clear: detect and address prediabetes early to prevent the onset of type 2 diabetes in order to increase overall health of general population and improve the quality of life. To achieve this, several conditions must be fulfilled – along the research and development of models and innovative solution, it is also crucial to "get it out" towards the final users. This is the goal of the exploitation activities that are fundamental to all similar projects.

The Key Exploitable Results

The project's success depends on defining key exploitable results (KERs) early and developing a tailored exploitation strategy. These high-TRL outcomes shall be market-ready after the project ends, unlike other more scientific results requiring further development. Through structured assessment, the consortium identified three key exploitable results:



These innovations stand out in the market by offering a proactive rather than reactive approach to diabetes prevention.

The market and competition

The European digital and mHealth markets present significant opportunities for PRAESIIDIUM, with the digital health sector projected to grow from USD 81.86 bil-

lion in 2024 to USD 188.20 billion by 2029, and the mHealth market from USD 27.61 billion to USD 85.72 billion in the same period. Government investments in digital healthcare and the increasing use of mobile health apps drive this growth, making Europe a promising market for PRAESIIDIUM. The rising adoption of wearable health devices and AI-driven healthcare solutions further support the demand for cost-effective, accessible preventive care. With European healthcare expenditures expected to grow from USD 2,750 billion in 2023 to USD 3,900 billion by 2029, there is increasing pressure to reduce costs as about 80% of healthcare spending comes from public sources. This will make cost-saving solutions like PRAESIIDIUM, which emphasize early detection and management of chronic diseases, highly attractive for integration with primary healthcare. With approximately 475,000 general practitioners and 24,000 hospitals in Europe, the potential market is substantial. Strategic partnerships with pharmaceutical companies and medical sales representatives will be key to driving adoption and commercialization, ensuring the solution effectively through the highly fragmented market.

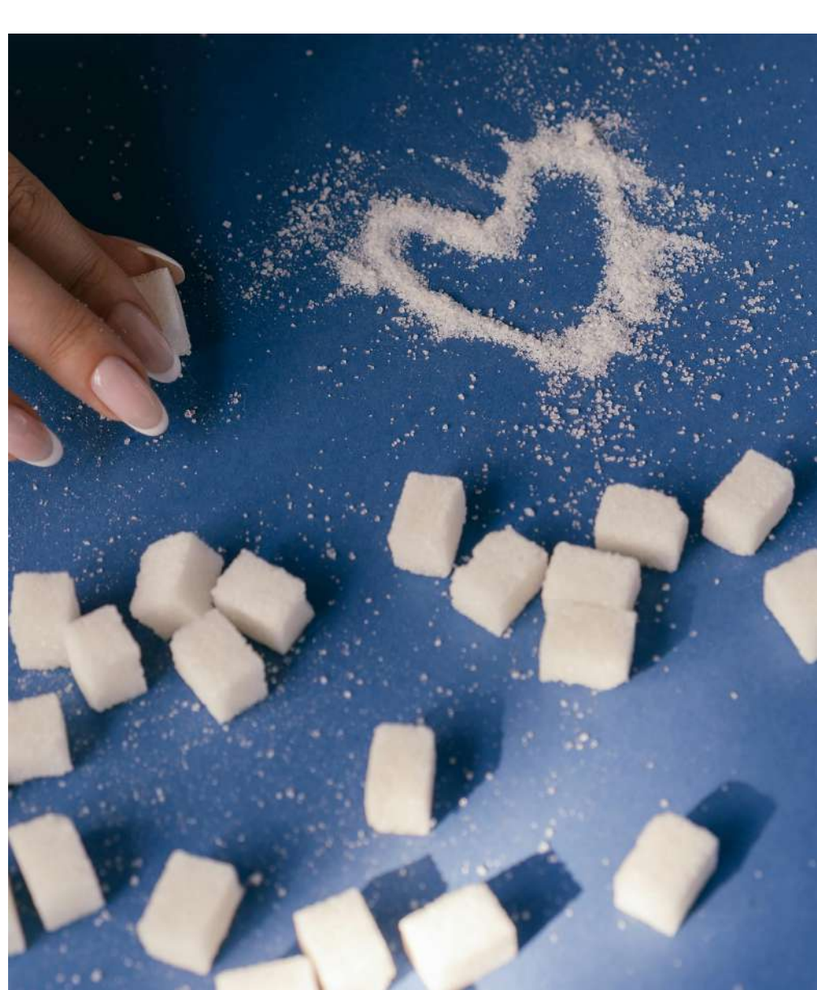
The first commercialization phase will focus on PRAESIIDIUM's AI-enhanced platform through a Business-to-Business (B2B) model. The go-to-market strategy includes a subscription-based SaaS pricing model for healthcare providers, collaborations with medical institutions and digital health companies, and seamless integration with existing healthcare platforms. Market adoption will be supported by consortium members leveraging their expertise, international presence, and established connections with user communities.

PRAESIIDIUM, a unique solution for prediabetes prediction

The analysis of competition highlights PRAESIIDIUM's unique approach, integrating AI with multi-scale, multi-organ modelling for real-time prediabetes risk prediction. Unlike competitors that primarily focus on managing existing diabetes, PRAESIIDIUM offers a proactive approach by identifying individuals at risk before the onset of diabetes, facilitating early intervention. This motivates to focus on general practitioners rather than specialists. PRAESIIDIUM is an innovative digital health platform that leverages AI. **By integrating a refined MT2D model with extensive data,** it offers an advanced prediction algorithm supporting healthcare professionals and at-risk individuals. Available as a mobile and desktop application, it enables **continuous patient monitoring,** providing doctors with data-driven insights and personalized health guidance for users. Using Explainable AI (XAI), PRAESIIDIUM ensures **transparency in its predictions,** essential for user' trust and regulatory approval. By providing a comprehensive platform with risk assessment, real-time monitoring of physical activity and blood sugar levels, user notifications, and dietary data input, PRAESIIDIUM supports a **holistic approach to health management.** Its early detection capabilities enhance preventive healthcare, reducing the burden of type 2 diabetes on individuals and public health systems. By facilitating timely intervention, PRAESIIDIUM lowers healthcare costs and **improves quality of life,** positioning itself as a leading solution in the growing digital health market.

About Alpha Consult

ALPHA Consult is a European consultancy delivering tailor-made solutions supported by senior staff with significant strategic development, market as-



sessment and business modelling experience. Alpha's key competences lie in: 1) Exploitation: business plans, impact assessments, market / competition assessments, go-to-market strategy, IPR; 2) Communication & Dissemination: on-site promotion (events, workshops), on-line promotion (websites, social media); 3) Support to Project Management: quality assurance plans, risk management, ethics.

Alpha Consult plays a pivotal role in the project, defining the business plan and exploitation strategy, driving the PRAESIIDIUM's impact, and ensuring its innovations transition from research to market.

For more information on Alpha Consult, please visit https://alphacons.eu/.

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Research Project

A magazine on research and development topics of interest to the Spindox Group.

More information about the research project

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