A CURA DI

Fiorella Operto

European Union's HORIZON-HLTH-2022-STAYHLTH-02 program under grant agreement no. 101095672

Horizon Europe 2021-2027

HORIZON EUROPE PROJECT

PRAESIIDIUM

Real-Time prediction of prediabetes risk

SPECIAL ISSUE #1

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Special Issue #1

PRAESIIDIUM, a protection against diabetes

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Becoming PRAESIIDIUM

We are a researcher and a consultant, working in different - yet closely related - fields that complement each other significantly in bringing the results of our projects directly to the market and society. From the very beginning, we collaborated on drafting **PRAESIIDIUM** project, focusing on the benefits its outcomes could bring to the quality of life in Europe. Indeed, implementing research findings into everyday medical practice is essential for innovating disease prevention and treatment, as well as for advancing research in areas that contribute to medical innovation. In our case, this includes the use of Artificial Intelligence (AI).

The application of AI in healthcare is improving various aspects of medical care - from prevention to diagnostics to personalized

treatment - with the ultimate goal of optimizing patient care and operational efficiency in clinical settings.

Our area of investigation is the predictive analysis of prediabetes.

The project we are involved in has received European funding. It is part of *Horizon Europe*, and its acronym, **PRAESIIDIUM**, carries a meaning that we will explore later on. The project falls under the European framework of Research and Innovation Actions, started in January 2023 and will end in December 2025. The aim is to identify and describe, concerning type 2 diabetes, the biological, biochemical, and clinical conditions that lead a person from a healthy state to a pre-disease state—in other words, when someone is in a "health to disease" condition that can evolve into illness, a field where the European Commission is increasing its focus.

It is important to remember that diabetes is the second leading cause of death worldwide. Focusing on the analysis of prediabetes - the transitional phase between a healthy state and type 2 diabetes -is essential for all prevention efforts. Prediabetes is a condition in which a person already shows clinical parameters beyond the healthy range, but not yet sufficient to be diagnosed with full-blown diabetes. There are over 500 million adults with glucose levels, one of the key markers of diabetes, outside the healthy range, yet not meeting the criteria for the disease. This represents a major risk factor. Clinical research tells us that this pre-disease condition, when diagnosed early, can be reversible. Appropriate changes in lifestyle, nutrition, and physical activity can return a person to a healthy state, thus preventing the onset of type 2 diabetes, also known by its English acronym, T2DM. On the other hand, once a person has been diagnosed with diabetes, it becomes much harder to return to a healthy state, as tissue and organ damage may already have occurred. In such cases, lifestyle changes alone may no longer be sufficient, and medication might be necessary. This highlights the importance of early—and very early—diagnosis. For this reason, the acronym of the project is inspired by the Latin word Praesidium, meaning "to protect."

Claudia Maltoni specializes in maximizing and enhancing the impact and value of research project results. She brings extensive expertise in market and competitive analysis, impact and cost-benefit assessment, business planning, go-to-market strategies, and project management. With over fifteen years of experience as an exploitation leader, she supports project partners in transforming ideas and prototypes into market-ready solutions. She designs customized business plans and exploitation strategies tailored to the specific needs of the projects, their partners and stakeholders.

Giulia Masetti is a member of the project coordination team at *SPINDOX Labs,* bringing a strong scientific background in bioinformatics and a PhD in Infection & Immunity obtained from the School of Medicine at Cardiff University. Thanks to her experience, she has been able to effectively manage the multidisciplinary nature of the consortium, which directly reflects the complexity and thematic variety of the project.

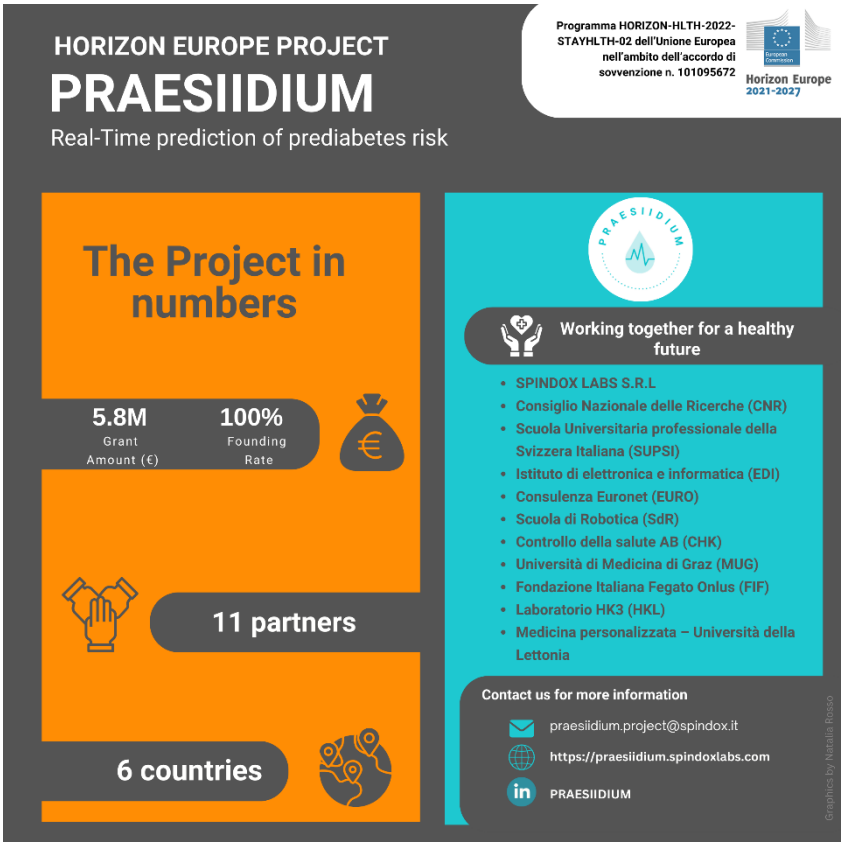
The overall coordination of the project is entrusted to *Leonardo Napoletani* and *Cristiano Carlevaro*, both from SPINDOX Labs, with solid experience in coordinating and managing research projects at both national and international levels. The research and development team at *SPINDOX Labs*, led by Project Technical Lead *Roberto Larcher,* also stands out for its multidisciplinary approach, involving expertise in data science, software development, and physical-mathematical modeling. In the **PRAESIIDIUM** project, the multidisciplinary dimension is further strengthened by the participation of partners with strong expertise in applied mathematics, modeling, and algorithmic development, including: *CNR IEIIT* in Milan, *CNR-IAC* in Rome, the start-up *HK3-Lab,* and the Swiss research institute *SUPSI*. With a consortium of eleven partners and the active involvement of stakeholders, the project is built on a solid and well-structured network of expertise, disciplines, and affiliated entities.

When we started designing the content of **PRAESIIDIUM**, we began by analyzing the competition in the field of type 2 diabetes prevention within both the research and business sectors and immediately identified the need for an activity focused on the valorization and applicability of the results. Additionally, we selected the KPIs (*Key Performance Indicators*) that, in our case, are tools to measure and evaluate the effectiveness of the project in relation to the set objectives. The analysis of the KPIs provided us with a measure of the project's concreteness and depth. In building the partnership, we specifically identified the technicians and experts in models and algorithms, who were also knowledgeable in innovations that could be integrated into prevention projects for a given pathology. Similarly, the clinical partners (*Medical University of Graz*, *Latvia University*, and *Fondazione Italiana Fegato - Italian Lever Foundation Onlus*) were crucial in clarifying the effectiveness of the project proposal when they explained the potential to achieve certain results, the success rate in reaching benefits, the development of therapies, and the associated risks.

In fact, given this complex multidisciplinary structure, we can speak of *projects within the project*, meaning that each group and work package may produce results in autonomous lines. This applies to the studies conducted by the clinical centers; to the development of equations and models; and to the analysis of ethical requirements, entrusted to the partner *School of Robotics* but involving the entire consortium in the accurate production of the project Ethics Self-Assessment, a thorough analysis of ethical requirements that is an ongoing process throughout the project with an authentic methodology.

PRAESIIDIUM innovative elements

The innovative quality of **PRAESIIDIUM** lies in identifying the elements that characterize the prediabetes phase in order to provide people with a series of recommendations to prevent the disease, by modifying their nutrition style and increasing physical activity. We can imagine the effects on the quality of life for hundreds of millions of people who will have avoided diabetes if detected early, even in the absence of disease data; quantify the positive outcomes on national healthcare budgets; and anticipate the effects on clinical research.



Thanks to the market and competitive analysis we conducted beforehand, we found that the solutions available in the field of type 2 diabetes prevention are limited and focus primarily on already diagnosed prediabetic conditions. Furthermore, some of these solutions lack the innovative component, which in **PRAESIIDIUM** is provided by the use of Artificial Intelligence and smart technologies for data collection and processing. In our project, this is

represented by an AI element indicated in the full title: *Physics Informed Machine Learning-based Prediction and Reversion of Impaired Fasting Glucose Management*, where *Physics-informed* (PI) refers to the use of machine learning (ML) trained on real data within a framework dictated by physical equations. This allows for both better model accuracy and ensures transparency and reliability of the algorithm. In **PRAESIIDIUM**, the data on which the ML works are not only synthetic, also real, providing the benefit of greater alignment with the actual development of the disease and, therefore, better solutions. This enables a more precise understanding of what happens in the body, its organs, molecules, and biochemical mechanisms, data that are embedded in an Artificial Intelligence system.

Let us consider now a fundamental aspect in type 2 diabetes, which is the identification of the glucose-insulin dynamics, a data set that has been highly modeled over the years from a mathematical perspective. **PRAESIIDIUM** also relies on physical equations derived from Mission-T2D (*Multiscale Immune System Simulator for the ONset of Type 2 Diabetes integrating genetic, metabolic, and nutritional data*, 2013), a European project coordinated by our partner *CNR IAC*. The objective of this project was to develop and validate an integrated, multi-organ, and personalized model of the patient, aimed at simulating and predicting the metabolic and inflammatory processes involved in the onset and progression of type 2 diabetes. This project created a multiscale model to study the systemic interactions of the biological mechanisms involved: immunological/inflammatory processes, the relationship between energy intake and consumption in response to various nutritional and metabolic stressors. This study of biological mechanisms was innovative because, while large-scale population studies focus on reactions to specific nutrients in terms of quality and quantity, a new area of research has emerged on the gut microbiota, which studies, for example, individual responses to what we eat.

Another advantage of using physical equations is the higher level of transparency of the algorithm that can be achieved, reducing risks and bringing the project in line with European directives on ethical standards. These include that the algorithms and models are trustworthy. A crucial component in achieving transparency in AI systems are three fundamental elements: traceability, explainability and the possibility that these are communicated to users in a manner appropriate to their specific use.

Designing reliable and practically usable models

To enrich the model with real data, two clinical partners take care of analysing real-life scenarios of study participants. The *Medical University of Graz* is conducting a prospective clinical study of healthy, normal-weight people with a normal Body Mass Index (BMI) but a family history of diabetes 2 with close relatives suffering from T2DM. The *University of Latvia*, the Laboratory for Personalised Medicine of the Faculty of Medicine, prospectively follows people who already present metabolic syndrome parameters, such as overweight - but not yet obesity - and/or out-of-normal triglyceride and cholesterol levels. Another partner is the *Fondazione Italiana Fegato*, Italian Liver Foundation Onlus, which has for years been developing research on people with severe obesity - obesity is one of the main risk factors in T2DM. These clinical studies deal with the three scenarios of incidence and progression of T2DM diabetes worldwide, but the project studies the European profile in particular.

The clinical centers in Austria and Latvia carried out the indicated studies, being able to monitor the daily diet and physical activity of the participants through a provided smartwatch, the *Fitbit*, which was chosen based on cost/benefit criteria – however, any commercially available device capable of measuring heart rate and physical activity is suitable. The technology institute in Latvia is, in fact, developing a new sensor that will be tested in the project. Based on the collection of real data and models created using PI-ML, the project is developing a platform (thanks to *CheckHealth* Sweden) for use by clinicians and doctors, capable of collecting and managing input data - diet, physical activity, and other data such as the patient's clinical history - which, based on the algorithm, can generate

predictive analyses. Meanwhile, a mobile app developed by SPINDOX Labs will be available for the patient, allowing them to input data on their diet in terms of macronutrients and physical activity.

Exploiting the results and applications of PRAESIIDIUM

Exploitation, a requirement in most research projects, refers to both the use of results to advance further research and the potential for sustaining those results over time. This includes not only awareness activities such as publications and academic engagement but also identifying outcomes that could evolve into products or services for the market and for adoption by end users. Maximizing a project's impact involves developing a concrete and well-founded business strategy to ensure its sustainability. Turning a research idea into real-world technology that reaches users and is commercially viable is a key aspect of exploitation. This is how research can directly enter the market and benefit society. For example, if **PRAESIIDIUM**'s platform, algorithm, and methodology will be adopted by clinical centres, hospitals, general practitioners for predictive analysis of TD2M, as well as by eHealth technologies such as wearables for health data collection, this would deliver broad societal benefits at the local, national, and European levels.

Currently, exploitation analysis in **PRAESIIDIUM** is on-going. One of the key goals will be to develop an ad-hoc business strategy and plan based on a clear identification of the end-users. Initially, these could be clinicians who would both use the platform and play a central role in its exploitation. In a second phase, the approach may shift toward a broader focus on individual well-being, potentially expanding to a wider market. The exploitation strategy will be tailored to each target group, and regulatory considerations will vary depending on the intended users of the algorithm.

Of course, no new technology is entirely risk-free, especially when it is introduced to the market. Within **PRAESIIDIUM**, we are conducting a risk analysis and developing mitigation plans across different project actions. We include in this context any barrier that could hinder exploitation. These barriers can be commercial, ethical and legal, or related to intellectual property. Some may concern the TRL, or Technology Readiness Level, which is critical for technologies intended for public use.

Conclusions

PRAESIIDIUM represents a concrete example of how multidisciplinary research can generate real innovation, with a direct impact on the quality of life of European citizens. The integration of scientific, technological, clinical, business and ethical expertise has made it possible to build a solid, forward-looking project capable of tackling one of the great health challenges of our time: the prevention of type 2 diabetes. Through the application of artificial intelligence, the use of real data, and the use of transparent and reliable mathematical models, **PRAESIIDIUM** aims not only to better understand the mechanisms underlying prediabetes, but also to provide predictive tools useful to doctors and, in perspective, to individual citizens.

The project's ambition is twofold: on the one hand, to strengthen European research's capacity to generate innovative solutions; on the other hand, to turn these solutions into practical and sustainable tools for prevention and public health. In this vision, every result, every piece of data, every model contributes to building a future in which early and individualized diagnosis becomes the norm, not the exception.

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