PUBLISHABLE SUMMARY

Summary of the context and overall objectives of the project (For the final period, include the conclusions of the action)

DIGIPREDICT aims to develop a digital twin platform accurately mapping the individual (patho)physiology of patients and predicting the course of viral infectious diseases. The main objective is to identify, monitor, and screen high-risk patients, and provide them with personalised supportive therapy based on individual referral decisions. The project contributes to the understanding of the complex relationship between viral infection, host response, (hyper)inflammation, and cardiovascular injury in COVID-19, and allows predictions of which patients will experience mild symptoms and which will rapidly develop multi-organ failure. This could be extended to non-COVID sepsis patients.

DIGIPREDICT aims to create a groundbreaking digital twin model, designed, developed, and calibrated using patient measurements of various digital biomarkers and their interactions, to address the needs identified during the global pandemic.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far (For the final period please include an overview of the results and their exploitation and dissemination)

Great progress was achieved and major scientific milestones were reached including (i) organisation of the internal workshop "Digital Twins in Healthcare"; (ii) progress on technical aspects including the fabrication of the nanoscale sensors for the priority biomarkers, the development of the GISMO interface chip capable of providing both voltametric and amperometric readouts and the flexible membrane multielectrode array chip (FMMC), and the delivery of a small batch of fully functional PhysioPatch wearables for monitoring patient physiological data; (iii) ethical and regulatory aspects e.g. the preparation of ethics documents and a study protocol for the in-vivo deployment of the DIGIPREDICT Physio demonstrator, the preparation of protocols for the operation of a blood vessel-on-chip model and the implementation of regulatory preparatory activities for microneedle chip; (iv) and dissemination activities, including the establishment of a website, a social media presence for the consortium and its involvement in five international online and seven conference and journal papers.

In the second period, significant progress was achieved based on the amendments adopted for this period. The consortium continued the regulatory activities previously started, preparing clinical trial plans and completing the regulatory dossiers for submission to the EU for two clinical trials with the DIGIPREDICT-Physio and DIGIPREDICT-Bio demonstrators. Ethical approval has been obtained for the DIGIPREDICT-Physio investigation, and the other investigation is in an advanced stage of preparation. The PhysioPatch devices used in the DIGIPREDICT-Physio clinical investigation were successfully manufactured. An interoperable workflow and data integration architecture including data from the PhysioPatch, routine hospital data, and data from study visits was also developed. An extraction system for in vivo ISF collection using silicon microneedle arrays was designed and manufactured in time to support the bio clinical investigation. Great progress has been made in the detection of inflammatory biomarkers and in the development of measuring devices: the fabricated biosensors for continuous real-time pH, C-reactive protein monitoring based on silicon nanowires FETs and the lactate biosensors are compatible with ISF microneedle technology in terms of size and the small amounts of ISF required for detection. Innovative carbon nanotube-based MEMS devices have been designed and fabricated. Significant results have been achieved in the development of a powerful and interpretable machine learning algorithm for the analysis of irregularly sampled time series in electronic health records (EHRs). A custom breath rate estimation algorithm and a data acquisition reduction technique called Polygonal Approximation Sampler (PAS) for impedance respiratory signals captured by our PhysioPatch were developed. This PAS allows a significant reduction of the data acquisition without sacrificing performance, and the algorithm for estimating respiratory rate shows promising results. The achievements were demonstrated in the preparation of the early prototype of the in vitro demonstrator for the detection of prioritised biomarkers. Joint in vitro experiments demonstrating the compatibility of the selected biosensors with the previously developed GISMO interface chip were conducted. A 3D vessel on a chip with endothelial cells from human induced pluripotent stem cells was also developed. The effects of cytokines on the function of human stem cell-derived heart tissue were analysed using the next-generation heart-on-chip platform. A translational organ-on-chip (TOP) platform with a multi-electrode array (MEA) chip was fabricated and used for the successful cultivation of human stem cells. Progress was also made in integrating the scientific and industrial community in the field of digital twins in healthcare.

We have collaborated with two other FET initiatives to produce the Virtual Human Twin (VDT) manifesto initiated by the EC and to work on the roadmap for VDT. With MedTech Europe, DIGIPREDICT organised a special session at the 2023 Annual Congress and is preparing the "First International Symposium on Digital Twins in Healthcare" to be held in Larnaca, Cyprus, in May 2024. We published five papers in conference proceedings, updated the exploitation plan, created a dedicated community building section on the website and co-organised the first inter-project event. Overall, DIGIPREDICT has achieved important milestones in the areas of clinical investigations, data integration, biomarker discovery, MEMS device design, algorithm development and dissemination, advancing the use of Digital Twins in health technology.

Progress beyond the state of the art, expected results until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far)

DIGIPREDICT aims to propose innovative solutions in multiple domains, that surpass current standards. The wearable systems developed under the project, such as the Physio Patch and the Biomarker Patch, include features and components that go beyond the state of the art. Their use in clinical settings is expected to improve the state of the art in understanding biomarker dynamics in selected patient categories.

The development of new models accurately representing patient-specific (patho)physiology to enable early detection and predicting infectious viral diseases and their cardiovascular effects is considered progress beyond the state of the art. Examples include the machine learning algorithm for analysing irregularly sampled time series in electronic medical records, a custom algorithm for estimating respiratory rate, and a technique for reducing data collection called Polygonal Approximation Sampler (PAS).

DIGIPREDICT develops unique multimodal data generator wearable technologies to support the construction and acquisition of digital twin models validated by both in vitro and in vivo methods.

Examples of advances beyond the state of the art include the highly miniaturised wireless Physio Patch, the first validations of lactate and CRP sensors in ISF, and regulatory advances with the ISF Extractor.

DIGIPREDICT aims to advance physical vascular organ-on-chip (OoC) technologies beyond their current design to facilitate the realisation of the aforementioned goals. In the project so far, significant progress was made in all three areas and their interactions. Examples are the development of the Translational Organ-on-Chip (TOP) platform with a multi-electrode array (MEA) chip and a 3D vessel-on-chip with endothelial cells derived from human induced pluripotent stem cells.