DIGIPREDICT FINAL PUBLISHABLE SUMMARY

May 2025

DIGIPREDICT aims to develop a Digital Twin (DT) platform that accurately captures individual (patho) physiology and predicts the progression of inflammatory and cardiovascular (CV) diseases.

With the help of multimodal data technologies and federated learning, a DT platform with key elements for clinical use was successfully realised, which encompasses digital biomarkers and physiological signals. Key outcomes are: (i) real-time wearable biosensors for lactate and pH monitoring in interstitial fluid (ISF) via silicon microneedles, (ii) platforms combining biomarker and vital sign sensing, (iii) first clinical deployment correlating ISF and blood-based CV and inflammation markers, (iv) predictive AI models using statistical correlation and federated learning, and (v) Vasculature-on-Chip and Heart-on-Chip systems modelling cytokine-induced dysfunction and electrophysiological responses. These DIGIPREDICT achievements lay the foundation for clinically deployable, data-driven DTs.

During the first period, DIGIPREDICT achieved several key milestones:

- A workshop 'Digital twins in healthcare' for internal cooperation
- Fabrication of nanoscale sensors for priority biomarkers; the GISMO interface chip for readouts; a Flexible Membrane Multielectrode Array Chip (FMMC); and an initial batch of functional PhysioPatch wearables
- The ethical and regulatory documentation as well as study protocols for in vivo use of the DIGIPREDICT physio-demonstrator, protocols for a blood vessel-on-chip model and the legal basis for microneedle sampling
- The DIGIPREDICT website, social media presence, and contributions to scientific conferences

In the second period, we focussed on the challenges of clinical use:

- Regulatory dossiers for two clinical studies were prepared. Ethical approval was obtained for DIGIPREDICT-Physio and DIGIPREDICT-Bio studies.
- The PhysioPatch devices for clinical use were successfully produced.
- An interoperable data integration architecture was developed.
- A silicon microneedle-based system for in vivo ISF collection was designed and fabricated.
- Biosensors were developed, including i) silicon nanowire field-effect transistors (SiNW-FETs) for real-time pH and C-reactive protein (CRP) detection and ii) lactate biosensors for low ISF volumes.
- Novel MEMS devices based on carbon nanotubes were designed and fabricated.
- Machine learning innovations include a robust algorithm for irregular time-series analysis in electronic health records (EHRs) and a custom Polygonal Approximation Sampler (PAS) for efficient respiratory signal acquisition via PhysioPatch, reducing data load.
- Biosensors were integrated and validated with the GISMO interface chip in vitro.
- Progress was made on organ-on-chip (OoC) systems through i) a 3D vessel-on-chip with induced pluripotent stem cell (iPSC)-derived endothelial cells, and ii) a next-generation heart-on-chip to study cytokine effects on cardiac tissue using microelectrode array (MEA) platforms.

In the final period, we focussed on in vitro and in vivo demonstrators, clinical deployment and data collection, successfully completing the most challenging phase of DIGIPREDICT. We also made strategic contributions to the DT ecosystem:

- We co-authored the Virtual Human Twin (VHT) Manifesto and roadmap.
- We partnered with MedTech Europe for a special session at the Annual Congress 2023.
- We hosted the 'First International Symposium on Digital Twins in Healthcare' (May 2024, Larnaca, Cyprus)
- We contributed high-impact publications, including the EDITH roadmap on VHTs.
- SME partner Ascilion and EPFL's startup XSENSIO exploited DIGIPREDICT results
- We used DIGIPREDICT results for a follow-up project on real-time point-of-care technologies for cancer and CV applications (RealCare).

DIGIPREDICT delivered critical advances in multi-modal sensing for inflammatory biomarkers (CRP, lactate, pH, troponin) across in vivo and in vitro platforms, demonstrated ISF-blood biomarker correlations, developed novel MEMS devices and interpretable AI algorithms, and strengthened the translational path of DTs, accelerating their time-to-clinic and time-to-market.

The following achievements reflect the DIGIPREDICT progress beyond state of the art:

1. Real-World validation of multi-modal multiplexed wearable biosensors in ISF: DIGIPREDICT enabled the first successful in vivo validation of miniaturized biosensors for lactate and pH, embedded in a wearable format (EPFL, IMEC-NL), using real ISF samples collected through a microneedle system (Ascilion). This small amount of 2 µL of ISF sets a new benchmark for low-volume continuous biochemical monitoring. We demonstrated simultaneous detection of multiple biomarkers (e.g., lactate and pH) with excellent sensitivity in ISF. This represents a major step towards multiplexed wearable diagnostics.

2. Clinical integration of wearable PhysioPatch for ICU/IMC monitoring: The PhysioPatch was clinically deployed at two major university hospitals, successfully collecting continuous electrocardiogram (ECG), respiration, and vital sign data from ICU/IMC patients, alongside blood samples. The structured dataset generated is suited for AI-driven DT development and patient stratification.

3. Advanced microneedle ISF extraction platform (PELSA) surpassing clinical requirements: Ascilion's microneedle platform achieved >40 µL/system ISF collection volumes, exceeding initial targets. It has been successfully revised to meet clinical safety standards and used in cardiac stress tests.

4. FL algorithm for ECG in clinical settings: A privacy-preserving FL framework for ECG signal analysis was developed and validated, showing the feasibility of distributed AI applications in sensitive clinical environments. This supports scalable and secure DT across hospital networks.

5. Heart-on-chip and vasculature-on-chip with electrophysiological readouts: We created functional OoC platforms (Heart-on-Chip and Vasculature-on-Chip 2.0) simulating cytokine-induced inflammation using human iPSC-derived cells, combined with high-density MEA-based electrophysiological sensing. These platforms model patient-relevant CV responses and provide a testbed for drug screening.

6. High-sensitivity troponin I optical sensor using nanoparticle conjugates: Partner EPOS developed a lanthanide-functionalised gold nanoparticle-based sensor for cardiac Troponin I, achieving an LoD <0.4 pg/mL, comparable to commercial systems. The system has potential for point of care implementation.

7. Synthetic EHR generator using generative adversarial network (GAN) for privacy-preserving training: EPFL created a GAN-based synthetic EHR generator, which outperforms prior work in data realism, privacy preservation, and utility for AI model training, providing a powerful tool for scaling DT training datasets without compromising patient confidentiality.

8. First integrated demonstration of DT from sensors to OoC: We completed an end-to-end integration from wearable biochemical and physiological sensing, to real-time clinical data collection, to in vitro biological emulation in OoC systems, validating a full DT cycle.

9. Thought leadership and ecosystem building for DT: DIGIPREDICT played a central role in co-developing the EC's Virtual Human Twin (VHT) roadmap and co-organizing the '1st International Symposium on Digital Twins in Healthcare', setting the strategic direction for DTs in Europe.