



## The LifeTime initiative: Towards cell-based medicine in Europe

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## The LifeTime initiative: Towards cell-based medicine in Europe

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LifeTime aims to understand the onset and progression of complex diseases and their response to therapy at single-cell resolution. This mission will be implemented through the development and integration of single-cell multi-omics and imaging, artificial intelligence and patient-derived experimental disease models during progression from health to disease. Analysis of such large molecular and clinical datasets will discover molecular mechanisms, create predictive computational models of disease progression, reveal new drug targets and therapies. Timely detection and interception of disease embedded in an ethical and patient-centered vision will be achieved through interactions across academia, hospitals, patient-associations, health data management systems and industry.

While advances in medicine have led to spectacular progress in certain disease areas, most chronic disorders still partially or totally escape cure. This is mainly because diseases are detected too late, and/or the selected therapy is inappropriate for the individual concerned. Both can be remedied by a more complete mechanistic understanding of the molecular and cellular events that precede disease onset or that arise during treatment. More accurate cellular and molecular diagnostics will enable disease interception sufficiently early to prevent irreparable damage. To achieve this interceptive medicine (Fig 1), we need to invest in approaches that provide a detailed understanding of the basis of disease heterogeneity in tissues, with sufficient molecular, cellular and temporal resolution. This will enable the detection of disease-promoting events and identify the disease-initiating cells, pathways and target molecules. We must be able to evaluate treatments by quantifying their effects on pathological target cells on a cell-by-cell basis. This strategy has the potential to impact both diagnosis and treatment, improve health and quality of life dramatically and alleviate the societal burden of human diseases such as cancer, cardiovascular and metabolic disorders, chronic inflammation, infectious diseases, and neurological disorders.

The LifeTime Initiative, a pan-European community consisting of over 90 research institutions with the support from 80 companies, several funding agencies and national science academies, proposes a forward-looking Roadmap to transform the detection and treatment of complex diseases. Central to LifeTime's approach is the development and integration of novel technologies, such as single-cell multi-omics and high-content imaging, artificial intelligence (AI) and patient-derived experimental disease models. The development and application of these integrated approaches to both experimental and clinical workflows is expected to directly benefit patients. For example, appropriate single-cell based biomarkers will precociously alert physicians that a cell or tissue is entering a disease trajectory. Understanding disease heterogeneity at the cellular level and knowing the molecular aetiology of a disease will allow the systematic identification of drug targets, resistance mechanisms or define therapeutic approaches, based on a given disease's molecular or cellular vulnerability. This strategy differs significantly from the classical approaches in drug discovery<sup>1</sup>. The stratification of patients based on underlying disease mechanisms, assessed *in situ* within single cells, will help physicians select the most appropriate treatment(s) or employ combination therapies that are tailored to the individual. These will be used first to identify cells that are deviating from the healthy trajectory, to steer them away from disease, and later to reduce the threat of relapse (Fig 1). This transformative single-cell data-driven approach has the potential to increase the success rates of clinical trials and to increase the efficiency of novel therapeutic interventions in clinics over the next decade.

## Single-cell based medicine

Cells develop and differentiate along many different specific lineage trajectories forming functionally distinct cell types and states <sup>2</sup>, which together with their neighbouring cells, underlie normal physiology (Fig 1, blue trajectory). However, even during healthy ageing, cells will accrue many molecular changes that lead to aberrant cellular and tissue states, generating conditions that may progress towards disease. This helps explain why ageing is the largest risk factor for many common diseases <sup>3</sup>. Currently, most diseases are only detected once gross physiological symptoms manifest, provoking a visit to the physician or hospital. However, by this time, tissues and organs have often undergone extensive or irreversible changes, precluding reversion to the original healthy state (Fig 1, red trajectory). At this stage, the choice of interventions is typically quite limited, and treatments often involve invasive or aggressive therapies of modest benefit to the patient.

Why is our ability to detect diseases earlier and intercept them before they progress so limited? For example, medical imaging technologies, developed over the last 20 years, have enabled the earlier detection of certain pathologies, such as metastatic cancer. Yet, the spatial resolution and sensitivity of these approaches is restricted. More recent technology-driven revolutions provide us with the means to probe a patient's physiology at the level of molecules and cells and place them in the context of tissues. Specifically, we are now able to link genetic variation and phenotypic manifestation to understand the molecular basis of disease <sup>4</sup> and create models that recapitulate various aspects of human disease <sup>5,6</sup>. Genetic information helps us elucidate the roles of specific pathways in disease progression <sup>4</sup>. Still, our detection and predictive power is limited, because in most cases our mechanistic understanding of disease is incomplete at the cellular level.

Timely detection and successful treatment of disease will depend crucially on our ability to understand and identify when cells deviate from their normal trajectory (Fig 1). The number of potential cellular states associated with disease is vast (Fig 1) and gaps in our knowledge stem from limitations in the approaches currently used to investigate complex disease landscapes. First, only recently have we been able to resolve cellular heterogeneity across space and time. We have an incomplete picture of cell types, cell states, and cell-cell interactions in the body. We need to understand how cells transition between states as they respond to and generate local microenvironments during tissue formation. We must assess cellular heterogeneity and composition changes within tissues during normal physiology and disease progression, for example, the dynamic immune system responses in chronic inflammation or during infection. To address this, we need to understand the molecular mechanisms that define a cell's state, and control its function, fate and trajectory over time. Second, we have been unable to reconstruct a cell's history or predict its future. This is key to understanding how disease states progress or dynamically respond to therapeutic interventions. Overcoming these limitations requires a systematic and longitudinal profiling of samples from many patients to reconstruct and predict the complex molecular networks that drive cellular trajectories over time. Third, computational frameworks for integrating temporal data as well as patient profiles with large cohorts to identify regulatory changes and to dissect the causes and manifestations of disease remain elusive. Current attempts to model human disease have not succeeded in integrating the thousands of molecular phenotypes that are acquired from patients. Finally, we are limited by our lack of knowledge of the underlying causes of disease. Any given patient's response to a specific therapy may require testing or modifying cells from the patient in an experimental system, a challenge yet to be routinely implemented.

Below, we outline technologies at the heart of LifeTime's approach and present a roadmap for their implementation with the aim of improving the detection and treatment of diseases. Building on related international initiatives that are paving the way by producing reference maps of healthy tissues in the body, such as the Human Cell Atlas (HCA) <sup>7</sup>, the NIH Human Biomolecular Atlas Program (HuBMAP) <sup>8</sup>, and in close collaboration with industry and patients, we foresee the possibility to apply novel technologies to clinical samples, to achieve the necessary molecular and cellular high-resolution view of disease.

## **Technology development and integration**

Single-cell technologies, particularly transcriptomics, are generating the first reference cell atlases of healthy tissues and organs, revealing a previously hidden diversity of cell subtypes and functionally distinct cell states <sup>7</sup>. Application of single-cell approaches to patient's samples are beginning to provide snap-shots of the changes in cell composition, states and pathways associated with diseases including cancer <sup>9-14</sup>, chronic inflammatory diseases <sup>15,16</sup>, Alzheimer's disease <sup>17-19</sup> heart failure <sup>20</sup>, and sepsis <sup>21</sup>. Some studies already provide insight into the basis of early disease detection, by identifying the cells of origin <sup>22</sup>, or by showing how a chronic inflammatory environment can lead to tissue remodeling during the evolution of colorectal cancer <sup>23,24</sup>. Predicting the future course of a cell requires data from patients that are linked to clinical outcomes. Only then can we identify the cellular parameters that are permissive to a therapeutic response, for example during checkpoint blockade immunotherapy <sup>11,25,26</sup>, treatment of multiple myeloma <sup>10</sup>, anti-TNF therapy for Crohn's disease <sup>27</sup>, or the evolution of chemo-resistance during treatment of triple-negative breast cancer <sup>28</sup>. If we can detect rare drug resistant cells that are present prior to <sup>10,28</sup> or that emerge during treatment <sup>29</sup>, we can adapt therapeutic regimens and employ combinatorial treatments to improve outcome.

Since pathophysiological processes within individual cells can occur on different molecular levels, understanding the underlying mechanisms requires integration of current single-cell approaches, such as RNA-seq, (Fig. 2), with methodologies that provide additional information on chromatin accessibility, DNA methylation, histone modifications, 3D genome organization, and genomic mutations <sup>30-32</sup>. Future developments in instrumentation promise to couple these genomics approaches with single-cell proteomes, lipidomes, and metabolomes, adding crucial insight into different cellular states and their roles in health and disease. In addition to specific cell subtypes and the role of cellular heterogeneity, it is crucial to investigate the surrounding tissue context and organ environment. This is becoming possible through the development of new spatial multi-omics approaches, particularly spatial transcriptomics, that include information on the location of diseased cells with respect to each other as an integral part of the data <sup>33-38</sup>. Novel advanced imaging approaches also now enable systematic spatial mapping of molecular components, *in situ*, within cells and cells within tissues <sup>34,39-43</sup>. The cellular context with respect to different immune and stromal cell types, extracellular components and signaling molecules that contribute to disease progression will help identify the roles of specific cell types and interactions in diseases <sup>38,44-46</sup>. The implementation of cell lineage tracing approaches <sup>47</sup>, which link cellular genealogies with phenotypic information of the same cells, may help us understand how populations of cells develop dynamically to form the specific architecture of a healthy or a diseased tissue.

The LifeTime initiative proposes to develop necessary single-cell methodologies and end-to-end pipelines (Fig 2), that will be integrated into robust, standardized multi-omics and imaging approaches, and scaled to be able to profile and map hundreds of thousands of patients' cells.

This will be done in close collaboration with health care providers, to enable an in-depth analysis of longitudinal human samples obtained from patients and cohorts (Fig 3). Handling these large molecular datasets will require sophisticated and distributed computational and bioinformatics infrastructures, (see Implementation and Infrastructure), as well as the development of tools to integrate and ensure interoperability of different data types, including single-cell multi-omics, medical information and electronic health records. This will allow the development of advanced personalized models of disease. To be able to implement routine longitudinal sampling of patients, we will need to develop methods for sampling small biopsies, including liquid biopsies that will detect individual cells or cell-free DNA released from pathological cells before and during therapy <sup>48</sup>. Multi-dimensional descriptors of cell states from patients taken from different stages of disease or therapy will be used to derive new biomarker sets or enhance current panels. Collaboration with ongoing atlas projects, industrial partners and regulatory authorities, will be key for benchmarking and deriving the new standards that will enable us to deploy these new methods in the clinic. This will hopefully achieve earlier disease detection and guide the appropriate selection of drug targets and therapies (Fig 3).

Unlocking the potential of unprecedented amounts of integrated digital information requires AI, in particular machine learning approaches that can identify meaningful molecular patterns in the datasets <sup>49,50</sup>. Although such approaches have proven very useful when applied to medical imaging data and have enabled the identification of subtle disease-associated changes <sup>51</sup>, medical imaging cannot capture the full complexity of human physiology nor the status of the disease at the single-cell level. Machine learning will be key to fully exploiting the high-quality, petabyte scale data generated by LifeTime, by delivering true integration and systems that can "learn" and reason upon biology to identify disease-associated changes and patterns <sup>49,52</sup>. High-content imaging, together with gene expression profiling, chromatin states, protein and metabolic parameters will contribute to the stratification of disease phenotypes. Machine learning and advanced modelling approaches will be used to integrate and analyze the different layers of cellular activity, and generate multi-scale and causal models that will allow us to infer regulatory networks and predict present and future disease phenotypes at the cellular level <sup>49,52,53</sup> (Fig 2).

The deep integration of machine learning technologies with spatial multi-omics and imaging technologies and data has the potential to usher in a new age of digital pathology to aid the decision-making process of physicians (Fig 3). By considering not only anatomical, physiological and morphological aspects, but also multidimensional molecular and cellular data, it will be possible to provide a more granular representation of a patient's disease state to complement the pathologist's slides and bulk measurements in tissues (e.g. mRNA, metabolites). We envision as the final goal the incorporation of new AI-based decision-aiding systems that will integrate and interpret available molecular, cellular, individual disease trajectory and imaging information. Importantly, interpretable and accountable AI systems will also provide the basis for the predictive models and clinical recommendations. Integration of cellular information should lead to a more precise description of a patient's molecular and physiological history, and will guide early detection, allow predictive prognosis, and guide recommendations for therapeutic interventions to deliver more precise and effective treatments (Fig 3).

Understanding the cellular origin and aetiology of disease from a patient-centered perspective requires systems that faithfully recapitulate key aspects of a patient's pathophysiology, and render them experimentally tractable. Organoids are an emerging experimental system that

allow modelling aspects of organ development, regeneration and pathophysiology<sup>5,6,54</sup> (Fig 2). Derived from adult or pluripotent human stem cells, organoids can capture individual features that are unique to each patient and can be interrogated molecularly in space and time. Importantly, by comparing organoid models from diseased and healthy individuals, unique disease features can be extracted even without knowing the specific genetic cause of the disease. Therefore, organoid models offer a unique tool for achieving some of the main goals of LifeTime, especially in cases where repeated access to patient tissues is limited or impossible, for instance for neurological disorders.

Organoids have received great attention, both in the scientific and wider community as a tool for modelling disease<sup>55-57</sup>. Yet they still require significant development to harness their full potential (Fig. 2). While current organoid models contain multiple organ cell types, more complex extracellular matrices and chemical gradients are required to capture the full degree of cellular heterogeneity as well as tissue-specific structural and metabolic conditions<sup>58</sup>. The next generation of models will need to incorporate key physiological aspects, such as immune response, vascularization or innervation. Because complex interactions between multiple tissues and organs are involved in many diseases, it will be necessary to develop novel tissue engineering principles that combine multiple organoids in pathophysiologically relevant crosstalk (organoid-on-a-chip). To harness their full translational potential, LifeTime will engage in standardizing, automating and scaling organoid approaches, allowing for systematic derivation, propagation and banking. Such industrialization is also needed for large scale chemical or genetic perturbations (e.g. CRISPR-Cas screens), and for elucidating the genetic basis for disease variability and drug response at population-relevant scales, in both the preclinical and clinical context (Fig 3). The resulting mechanistic dissection enabled by large-scale perturbations will be used to validate corresponding AI models of disease interception and progression. This approach is enabled by iterative rounds of reinforcement learning that continuously improve these models of human disease.

In addition to organoids, *in vivo* model systems are necessary to translate the science from bench to humans. A complex biological system is required to study the myriad of host-disease and pathogen interactions associated with complex diseases, such as infectious diseases, cancer or Alzheimer's disease. The use of animal models is important for understanding the very complex temporal relationships that occur in disease such as those involving the vasculature and blood brain barrier, the resident microbiota, the immune system and pathogens as well as neuronal networks in the brain. LifeTime will therefore make use of models in which patient-derived tissues can be integrated into *in vivo* models<sup>59-63</sup>. This initiative is identifying opportunities and challenges for improving existing *in vivo* models, as well as the technological developments needed to improve their clinical relevance and render them suitable for studying dynamics of cellular heterogeneity in space and time.

LifeTime, as a community, has the capacity to develop and integrate these technologies, that often require expertise and specialized instrumentation located in distinct laboratories. A coordinated effort will leverage individual expertise and perform the required benchmarking and standardization of technologies, workflows and pipelines. This will also ensure that the data, software and models generated adhere to Findable, Accessible, Interoperable, and Reusable (FAIR) principles<sup>64</sup> (see infrastructure below), are available across national borders, and are in full compliance with international legislations such as the General Data Protection Regulation (GDPR) in the EU. Moreover, LifeTime will ensure that technologies, including AI and organoids, will be developed in an ethically responsible way in collaboration with patients, putting the patients at the centre. (see Ethical and Legal Issues).



## **LifeTime disease Launchpad to identify priorities**

The Launchpad mechanism is an innovative platform that allows LifeTime to identify disease areas where the application of these integrated technologies is expected to have direct impact on patient care. Initially, the focus has been on five disease areas that are a significant burden to society: cancer, cardiovascular and metabolic disorders, chronic inflammatory and other autoimmune diseases, infectious diseases, and neurological disorders. Importantly, other disease areas will be continuously monitored. The LifeTime Launchpad has initiated the identification of clinical challenges in each disease area, and is evaluating specific diseases, groups of diseases or pathomechanisms on which research needs to focus. The criteria used to evaluate the proposed applications include: societal impact (including incidence and prevalence, disease severity, economic impact and the pressing need for new and more efficient clinical treatments and early detection), evidence for cellular heterogeneity that limits current clinical avenues, availability of samples from biobanks, relevant preclinical models, existence of patient cohorts including those enabling longitudinal studies, clinical feasibility and ethical considerations, as well as alignment with national and EU funding priorities. A working group will ensure that sex and gender aspects are fully incorporated during the process.

The LifeTime Launchpad is currently identifying the impact that the initiative can have in each disease area, to determine common and disease-specific challenges in the early detection of disease onset, or in tailoring therapeutic selection for each patient. For example, in neurodevelopmental and neurodegenerative diseases, a major challenge is to understand the molecular and cellular basis for disease onset and progression, as this would enable the stratification of patients based on molecular subtypes, and would enable the redesigning of clinical trials based on disease mechanism subgroups. Great potential exists for developing new preclinical models based on patient-derived cells, to understand disease processes and mechanisms, as well as for testing new drugs and therapies. A similar scenario exists for understanding the cellular and molecular mechanisms that lead to sepsis and heart failure. The role of cellular heterogeneity in the pathology of cancer and chronic inflammatory diseases is only beginning to be revealed<sup>65,66</sup>. There is an urgent need to explore and understand how this relates to the predicted course of disease such as dissemination, response of a patient to one of the numerous available therapies and the development of therapy resistance.

The Launchpad process is also identifying themes that span disease areas and will benefit from coordinated research. For example, inflammation-based mechanisms and the role of metabolism in disease, as well as links between infection/inflammation and cardiovascular diseases, cancer or neurological disorders.

## **Implementation and Infrastructure**

The scale of the data that will be generated and analyzed, the cross-disciplinary and international structure combined with the ambition of LifeTime to pioneer novel analytics using AI, places LifeTime in an excellent position to shape the next generation of European medical and biological data computational infrastructure. This will require close interaction with and evolution of the established European infrastructure (Fig 4), such as the European Open Science Cloud (EOSC) and high-performance computing infrastructures through EuroHPC. LifeTime will also interact with related European Research Infrastructures including

ELIXIR, Euro-Bioimaging, EU-OPENSOURCE, ECRIN, EATRIS and BBMRI and their cluster initiative EOSC-Life to create added value and to avoid duplication of efforts in strategies and tools for sharing and accessing data, development and application of standards. As medicine is inherently decentralized, LifeTime will also contribute to connecting EU medical systems and large centralized European data infrastructures.

To implement LifeTime successfully, fragmentation of research across borders, disciplines and timeframes needs to be overcome. LifeTime data generation and technology development will be harmonized across expert groups and centres, allowing results to be quickly picked up and applied in clinics. This relies on a coordinated approach that integrates the multidisciplinary expertise of single-cell technologies, data science, AI/machine learning, and organoids across Europe. It must also engage clinicians and patients to achieve major medical impact. The LifeTime strategy envisions a multidisciplinary network of LifeTime Centres (Fig 4) with different complementary thematic clusters across Europe, each working in close association with hospitals. These connected, but geographically distributed, flexible innovation nodes will share resources, gather the necessary critical mass for global competitiveness, and be open for collaboration with the entire scientific community. Importantly, LifeTime Centres should deliver a number of key functions:

- Serve as platforms for the development and advancement of breakthrough technologies for single-cell research in omics and imaging, AI/machine learning and experimental/computational disease models.
- Closely and actively collaborate with patients, clinicians, hospitals and healthcare systems, in some cases with a specific disease focus.
- Set standards in data generation, standardization and management implementing FAIR principles.
- Set standards in ELSI programs (ethical, legal and societal issues) by working together in multidisciplinary teams aimed at responsible research and innovation.
- Offer opportunities to collaborate, test and benchmark new methodologies and analysis methods e.g. in adaptive experimental design.
- Offer unique opportunities to industry to translate recent knowledge and novel technologies from the laboratory to the market.
- Provide an early access programme to new technologies developed by companies.
- Function as open, interconnected education hubs, delivering training in the new technologies to researchers, scientific personnel and clinicians, as well as provide engagement activities for patients and citizens.

A federated LifeTime data and computational network building on cloud technologies will provide the necessary capacities to enable federated analytics across the LifeTime centres and will provide a technical and legal framework for integrating core information structures, multi-omics assays, imaging, AI/machine learning technologies and health records (Fig 4). A joint Data Coordination Centre following a multi-level approach will ensure transparent data access control, compatibility and standardization and allow to establish a quality management programme including interlab quality assessments. Within this Framework LifeTime will also coordinate and pioneer open data sharing and reuse and collaboration, including access models prior to publication of data.

To start this cooperative LifeTime Centre network, the initiative can build on first efforts by LifeTime members in a number of European countries, examples are the VIB Single-cell Accelerator Programme in Belgium, Berlin Cell Hospital, the UK's Sanger/EBI/Babraham Single Cell Genomics Centre, or the LifeTime Single-Cell Centre in Poland, to name a few. To avoid duplication and lack of standardisation, the LifeTime Cell Centre network could be coordinated through an entity or framework that optimises coordination and support to achieve the LifeTime vision. Funding for specific research projects that involve one or more LifeTime Centres could come from a portfolio of private and public funding opportunities, both on the national and pan-European level. The network will closely interact with key European efforts and will contribute to EU strategies and programmes.

### **Interaction with industry/innovation framework**

Collaborations with the private sector will be key for the successful translation and delivery of technologies, instrumentation, diagnostics and therapies (Fig 4). Currently 80 companies support LifeTime's vision to revolutionize healthcare. These span multiple sectors as well as industrial associations and networks such as the European Federation of Pharmaceutical Industries (EFPIA), which unites major pharmaceutical enterprises, and the Euro-BioImaging Industry Board (EBIB), which unites major European imaging ventures.

Discussions between academic and industry representatives have identified crucial steps for transforming breakthrough discoveries into solutions that will improve the health of European citizens. This includes creating a unifying framework that fosters and streamlines pre-competitive interactions between academia and industry at the interface of computer science, single-cell biology, -omics, imaging, patient-derived disease modelling and precision medicine. A large-scale collaboration platform across Europe should be developed that includes umbrella agreements, regular physical meetings, dual training of early-career scientists in academia and industry, as well as exchange programs. This will enable joint projects between public and private sectors spanning the entire biomedical innovation cycle from discovery research, technology development and implementation in hospitals and the healthcare industry.

Cross-sectoral collaborations between small, medium-size and large companies with different development timelines and distinct business models is crucial. These long-term networks will be open to academic institutions, hospitals and technology providers and provide flexible new modes of stimulating innovation. To expedite the identification, and investment in the emerging technologies developed in academic and industry laboratories, successful local initiatives such as the tech watch programs and accelerator schemes (e.g. the VIB Single-cell Accelerator) should be scaled and coordinated at the EU level. LifeTime aims to create a networking/match-making platform for individuals, academic and industry organizations that share the goal to develop and integrate breakthrough technologies and apply them in the clinic to benefit patients. Further measures could foster innovation and entrepreneurship within the LifeTime consortium. For example, a pre-seed, pre-incubator funding scheme based on competitive calls to support start-up or tech transfer ideas.

Creating a dedicated European ecosystem is essential since the path to innovation is not linear and includes several feedback loops. To this end, additional key measures such as the development of enabling digital environments, training, promotion of early disease interception with all necessary stakeholders (patients, regulators, payers, etc.) are essential

as described in the LifeTime call for action launched in December 2019 endorsed to date by both individuals and organizations (<https://lifetime-fetflagship.eu/index.php/make-eu-health-research-count/>).

## **Ethical and Legal Issues**

The implementation of LifeTime's vision triggers relevant ethical questions from all societal groups directly impacted by the project (patients, clinicians and scientists), and society in general. LifeTime aims to pioneer a real-time or parallel ELSI (ethical, legal and societal issues) program that will predict, identify, monitor and manage the ethical impact of the biomedical innovations that arise from research and technology development, ensuring that implementation follows ethical guidelines. LifeTime's ELSI program can be used as a testing ground for other international interdisciplinary initiatives (Fig 4). Ethical issues will be identified and managed as early as possible and ensure that ethical and research integrity guidance is implemented throughout the entire research process to stimulate positive effects and mitigate negative ones. Ethics engagement can take different forms, from ad hoc consultation to an embedded ethicist or ethics team that works alongside the research team. LifeTime projects will adopt a prospective ethics mechanism that is more akin to the latter, rather than a retrospective ELSI team in order to be able to steer the development of LifeTime projects in a responsible manner <sup>67</sup>.

LifeTime partners and clinicians have initiated a partnership with specialists in bioethics, public engagement, ethics of technology and lawyers, that resulted in the identification of LifeTime's ethical and societal priority areas. These include questions related to the derivation, storage and use of organoids, the use of AI, data ownership and management, anonymisation of data, equity of access to such revolutionary medical care, the definition of health and illness, and transparent science communication to society. Initiating a relationship of trust with citizens will include novel modes of communication and engagement, for example through art, gaming or citizen science, to promote individual and critical thinking.

With a patient-centred research program as a foundation, compliance with the GDPR is a priority for LifeTime. This is particularly challenging since GDPR implementation, as well as consent form schemes, are not uniform across Europe. LifeTime will therefore establish a team working towards a unified consent procedure to determine: i) who controls the data, ii) who is responsible for the control, and iii) who is liable in case of legal challenge. Moreover, one aspect of LifeTime is its close relationship with industrial partners, which can pose difficulties when obtaining patients' consent to access data and/or samples. These legal matters are being addressed particularly with respect to data generated from human samples, prioritizing ethically-sound data sharing and data management policies that will ensure the protection of personal data. Our goal is to facilitate the exchange of materials and research data (e.g. through establishing expedited uniformized MTAs), while protecting the patient.

## **Education and Training**

To ensure uptake and integration of the LifeTime approaches into common practice, it will require the creation of a LifeTime Academy, which will provide the comprehensive training programs that are necessary to ensure efficient implementation of new technologies and new medical approaches (Fig 4). Importantly, this will be done in an integrative scheme, intersecting the multiple LifeTime disciplines and areas of actions: disruptive technologies

applied to medical challenges, technology transfer and innovation, research integrity, data management and stewardship, ethical, integrity, legal and societal issues. The Academy will have an inclusive philosophy to ensure that it can provide training to the wide community, which includes researchers, clinicians, technical operators, managers and staff of technology platforms, as well as administrators, patients and the lay public.

Training activities will be conceived and organized by dedicated teams involving specialists with a scientific education. LifeTime Academy envisions the formulation of both short and longer courses over several days and weeks, respectively, providing the trainees with new sets of skills. Additionally, the LifeTime Academy will explore the establishment of Masters and PhD programs, as well as the creation of novel training themes such as “artificial intelligence and medicine”. The LifeTime Academy will therefore engage and inform society, and will train a new generation of highly skilled medical scientists and support staff, in order to foster scientific and medical excellence in an ethical, responsible and inclusive framework.

## **Introduction and acceptance of interceptive medicine**

For many medical conditions, early treatment offers the potential to slow or even prevent an individual’s disease from progressing, and is the best situation from which to seek a cure. The concept of interceptive medicine refers to the development of drugs or other medical interventions that work at the earliest time points in the disease process, even before the manifestation of disease symptoms. This requires the availability of appropriate biomarkers. LifeTime aims to introduce interceptive medicine into clinical practice, which will require capacity building in health systems and significant technology deployment in the clinics. The role of a LifeTime Academy for training tomorrow’s physicians, researchers and nurses will be essential, not only in identifying the priorities and needs of the clinical workforce and in educating those involved in technology development, but also developing new professional curricula, for example, in health information counselling.

Our ability for early detection of disease may give rise to new concerns among patients and in the healthy population. Many citizens fear that their privacy, security or safety could be at risk. Thus, involvement of patient advocacy groups, public education and promoting critical thinking amongst citizens will be crucial for acceptance and participation in this new way of delivering medicine.

## **Impact on medicine and healthcare.**

Medicine and healthcare are rapidly expanding pillars of our economy. EU countries collectively spend more than €1,400 billion per year on healthcare for their 500 million citizens. Given the dimensions and spiraling healthcare costs associated with an ageing population, these numbers will continue to increase unless we can mitigate the damaging effects of ageing. We expect that coupling the current health monitoring with early detection and disease interception, will have a major economic impact. In Europe, 20% of the population will soon be over 65, with an age distribution that will continue to change until 12% are over 80 in 2080<sup>1</sup>. Given the prevalence and cost of caring for people with degenerative conditions and the increase in chronic lifestyle-induced diseases, the knowledge and technologies developed by LifeTime will allow us to detect them earlier, and avoid their worst

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<sup>1</sup> People in the EU – population projections. (2015) <http://ec.europa.eu/eurostat/statistics-explained/index.php/>

manifestations. LifeTime would also have an impact in the era of unexpected pandemics such as COVID-19 by rapidly determining the cellular and molecular basis of the disease. This would identify potential therapeutic strategies for patient subgroups as well as starting point for the development of new efficient therapies.

It is within LifeTime's vision to work with companies from multiple sectors and healthcare systems, as well as European and national regulatory bodies and patients associations/platforms, to establish new frameworks for robust science-based health policies. These will integrate the newly developed tools and technologies into standard care, and make innovative early detection tools and novel therapies rapidly accessible to patients. The aim is to provide better value to healthcare payers through pricing schemes that include value-based pricing, based on real world data and healthcare economic comparisons.

One of healthcare's largest outstanding issues is that many patients do not respond to commonly prescribed treatments. Whereas well-controlled randomised clinical trials provide evidence for statistical utility of a given therapy, in actual practice often many patients must be treated before a single patient will show a measurable benefit. Other patients may not benefit at all or even be harmed<sup>68</sup> leading to an economic loss that is estimated to be in the hundreds of billions €/year. The variable therapeutic responses originating from the cellular and genetic heterogeneity that exists in cancer and other complex diseases, contributes not only to the failure of treatments, but also to the rising cost of drug development, which is currently estimated at ~€1-2 billion per drug. *In silico* models for disease trajectories generated by LifeTime will enable the integration of personal genetic and lifestyle information into predictive models of disease course. This will allow physicians to determine and implement optimal therapeutic strategies tailored to the individual (precision medicine) with sophisticated timing of disease interception. The knowledge gained will also contribute to a more appropriate selection of patients for clinical trials.

## Outlook summary

Recent advances in key single-cell technologies, AI and patient-based experimental systems, such as iPS and organoids, have set the stage for their integration and deployment to address important medical challenges. Patients will benefit from cell based medicine through the earlier detection of diseases at a stage where they can be effectively intercepted. The novel, integrated technologies will enable the selection, monitoring and, if necessary, modification of therapeutic strategies for an individual to improve clinical outcomes based on high-resolution cellular information. Within the next decade, the obtained molecular mechanistic information has the potential to revolutionize drug discovery processes, clinical trial design, and eventually be incorporated into clinician's daily decision-making processes. As the LifeTime community continues to grow and the needs of industry and hospital stakeholders are embraced, this platform will provide unprecedented opportunities to implement single-cell and data-driven medicine to address the growing burden of complex and chronic diseases.

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598

599 **Competing Interests**

600 C.B. is an inventor on several patent applications in genome technology and cofounder of  
601 Aelian Biotechnology, a single-cell CRISPR screening company. H.C. is a non-executive board  
602 member of Roche Holding, Basel. A.P. holds European and US patents on “Genome  
603 Architecture Mapping” (EP 3230465 B1, US 10526639 B2). W.R. is a consultant and  
604 shareholder of Cambridge Epigenetix. T.V. is co-inventor on licensed patents  
605 WO/2011/157846 (Methods for haplotyping single cells), WO/2014/053664 (High-throughput  
606 genotyping by sequencing low amounts of genetic material), WO/2015/028576 (Haplotyping  
607 and copy number typing using polymorphic variant allelic frequencies).All other authors  
608 declare no competing interests.

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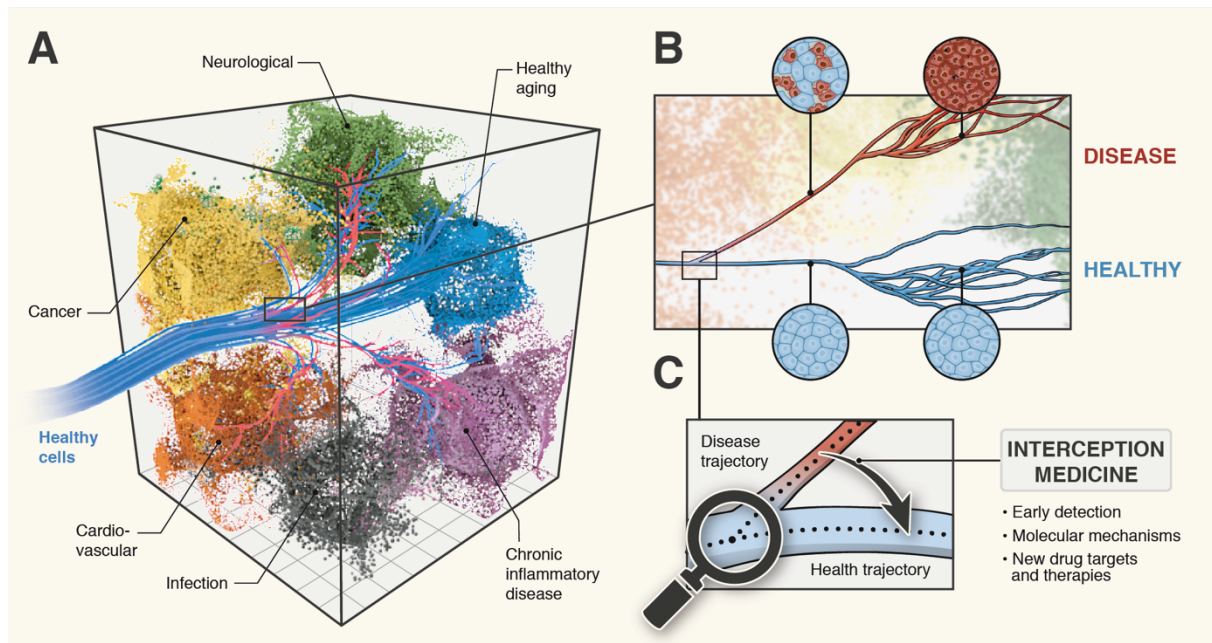
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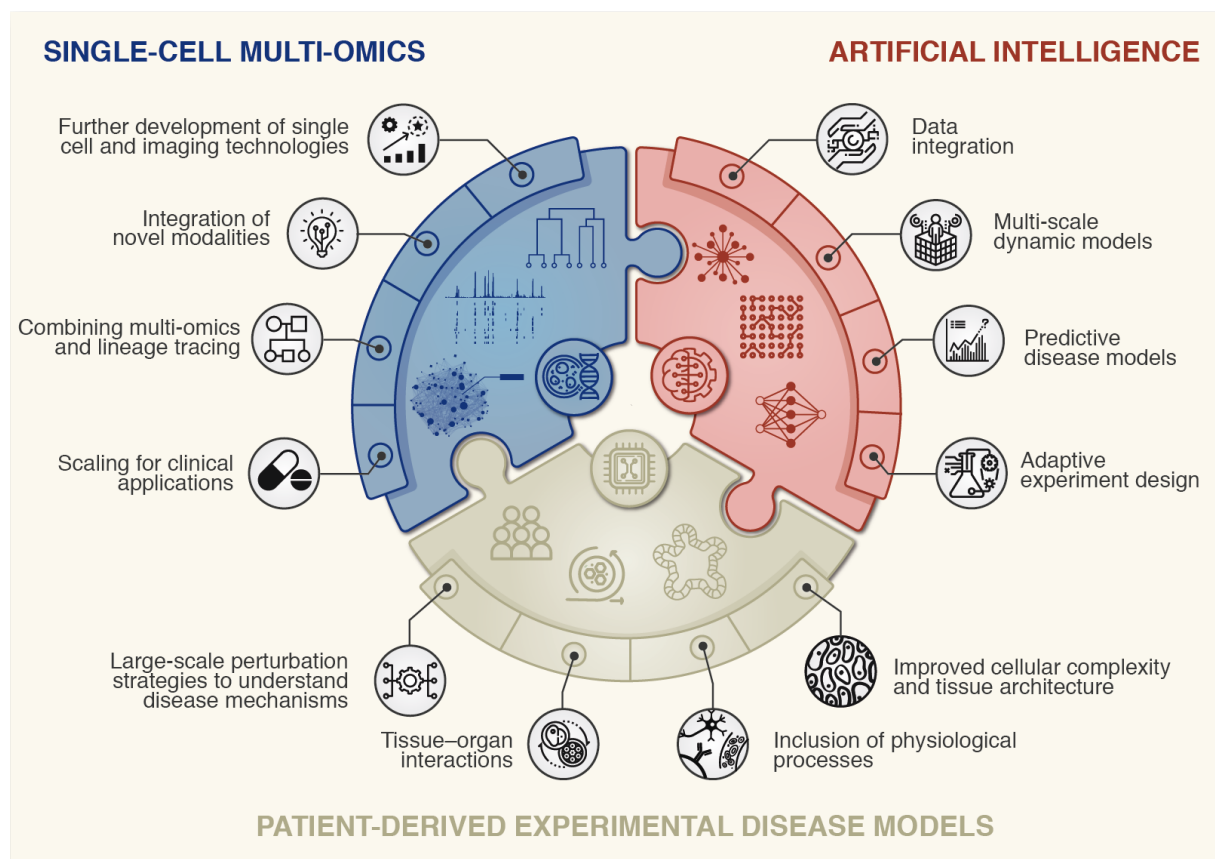


**Figure 1. Early disease detection and interception by understanding and targeting cellular trajectories through time.**

(A) Cells are programmed to develop and differentiate along many different specific lineage trajectories (blue trajectories) to finally reach their functional state. When these normal lineage processes go awry, this can cause a cell to deviate from a healthy state and move towards a complex disease space (coloured manifolds defined by multi-dimensional molecular space – including gene expression, protein modifications, metabolism), as shown by red trajectories.

(B) Many diseases are only detected at a relatively late state with the onset of symptoms (red trajectory) and when pathophysiological changes can be at an advanced stage (red cells). At this point, cells, tissues and organs have undergone extensive and often irreversible molecular and physiological changes since the initial events that caused them to deviate from a healthy state. At this stage the choice of interventions may be limited and often require harsh or invasive procedures.

(C) Understanding the early molecular mechanisms that cause cells to deviate from a healthy to a disease trajectory will provide biomarkers for early detection of disease and new drug targets and innovative therapies to intercept diseases before onset of pathophysiology and manifestation of symptoms.

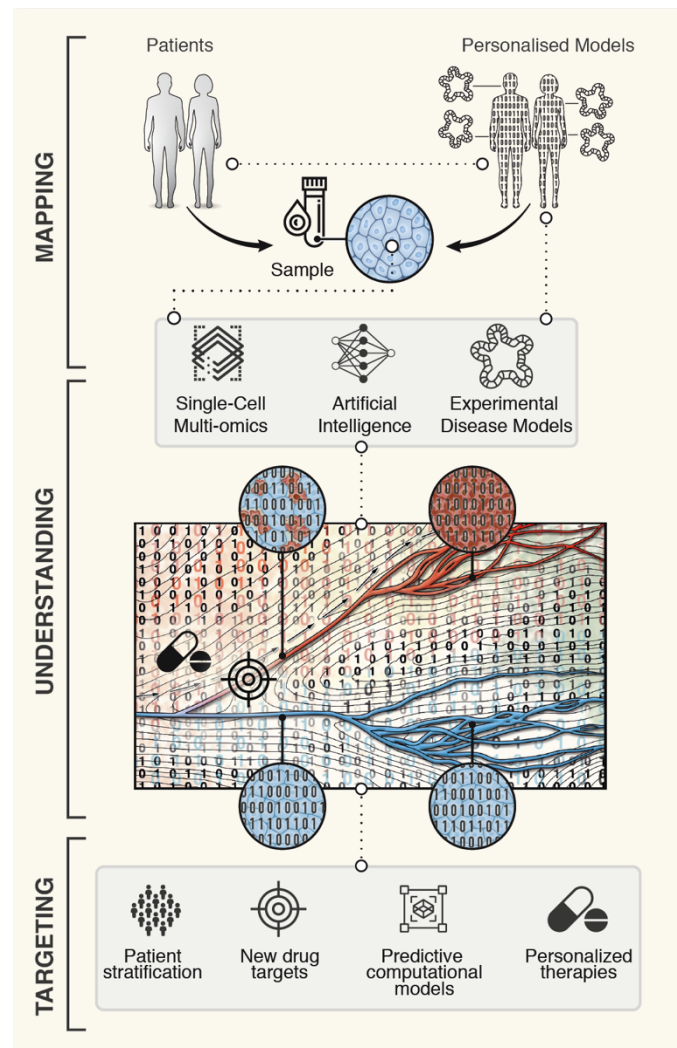


**Figure 2. Hallmarks of the LifeTime approach to disease interception and treatment.**

The scheme represents the development and integration of key technologies for investigating human diseases as envisioned by the LifeTime consortium. Single-cell multi-omics and imaging technologies will be developed for high throughput applications. Different modalities are combined to provide insight into underlying mechanisms based on coordinated changes between different regulatory molecular layers. To obtain insight into cellular genealogies and cellular dynamics requires the integration of lineage tracing tools. Technologies will also need to be scaled for deployment in the clinics.

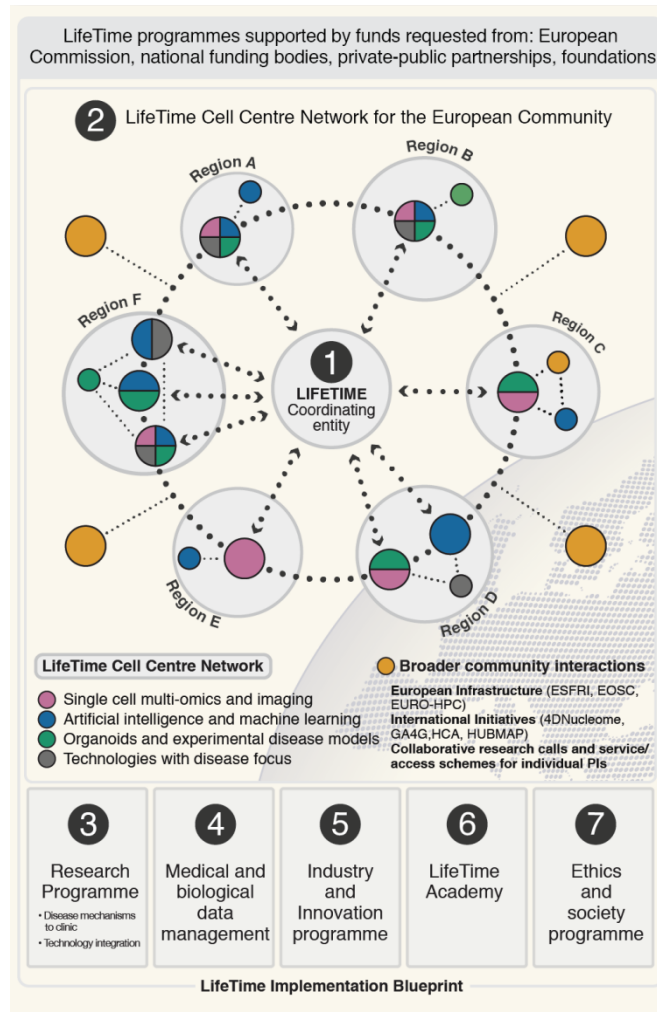
Integration and analysis of large, longitudinal multi-omics and imaging datasets will require the development of new pipelines and machine learning tools. These include development of causal inference and interpretative machine learning approaches to create molecular networks for predictive and multiscale disease models.

Patient-derived disease models such as organoids will be further developed to improve tissue architecture, incorporation of physiological processes, such as vasculature, nerve innervation and immune system to provide models that more faithfully recapitulate disease processes. Improved knowledge of disease mechanisms requires application of large scale perturbation tools to organoids. Tissue-tissue and organ-organ interactions will be recreated using microfluidics and organ-on-a-chip technologies to study key systemic interactions in diseases.



**Figure 3. Exploiting the LifeTime dimension to empower disease targeting.**

Multi-omics analysis of patient derived samples (blood or tissue) or personalised disease models (e.g. organoids, experimental disease models) will be profiled longitudinally to cover the different disease stages. Large-scale multidimensional datasets will be analysed using AI/machine learning to arrive at predictive models for disease trajectories providing single cell resolution and molecular mechanisms of disease onset and progression. Models will be validated using large-scale perturbation analysis and targeted functional studies in disease models, which will be used in an iterative process to improve both computational and disease models.



**Figure 4. Blueprint of the LifeTime Initiative.**

LifeTime proposes a large-scale research initiative to coordinate national efforts, as well as foster collaboration and knowledge exchange between the public and private sector. LifeTime recommends the implementation of several programs. (1) Community Coordination structure to avoid duplication of efforts and increase effectiveness requires funding instruments for a central coordination body (2) Network of Cell Centres to support European Community. A network of interdisciplinary centres would complement each other's strengths and expertise in the three LifeTime technology areas and operate in tight association with hospitals, and integrate technology development with clinical practice. The connected but geographically distributed nodes would serve both as innovation hubs with strong links to industry as well as open education and training centres. (3) LifeTime Research and technology integration program. (4) Medical and biological data management platform. (5) Programmes fostering industry and Innovation. (6) LifeTime Academy. (7) Societal engagement.