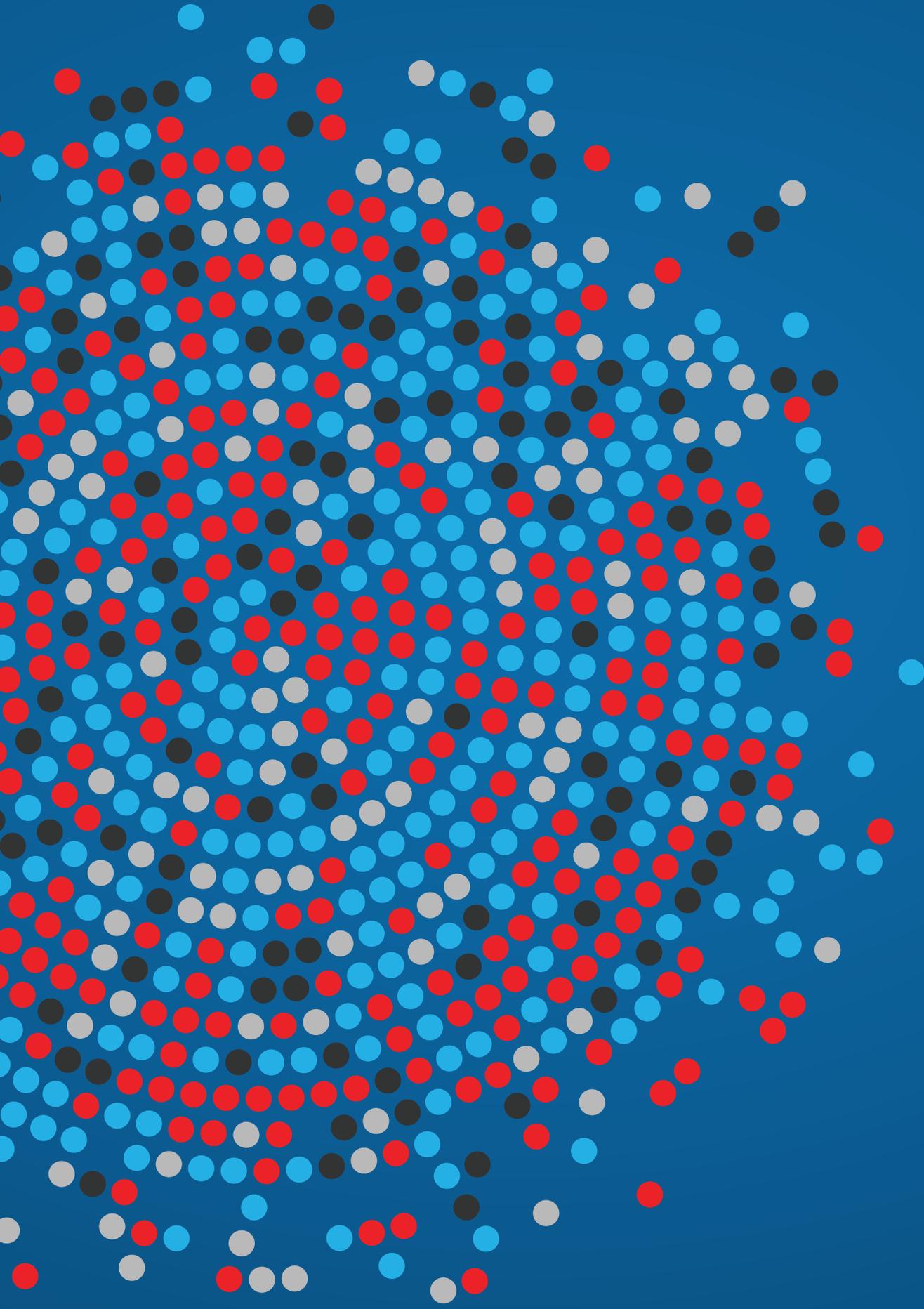




Strategic Research Agenda



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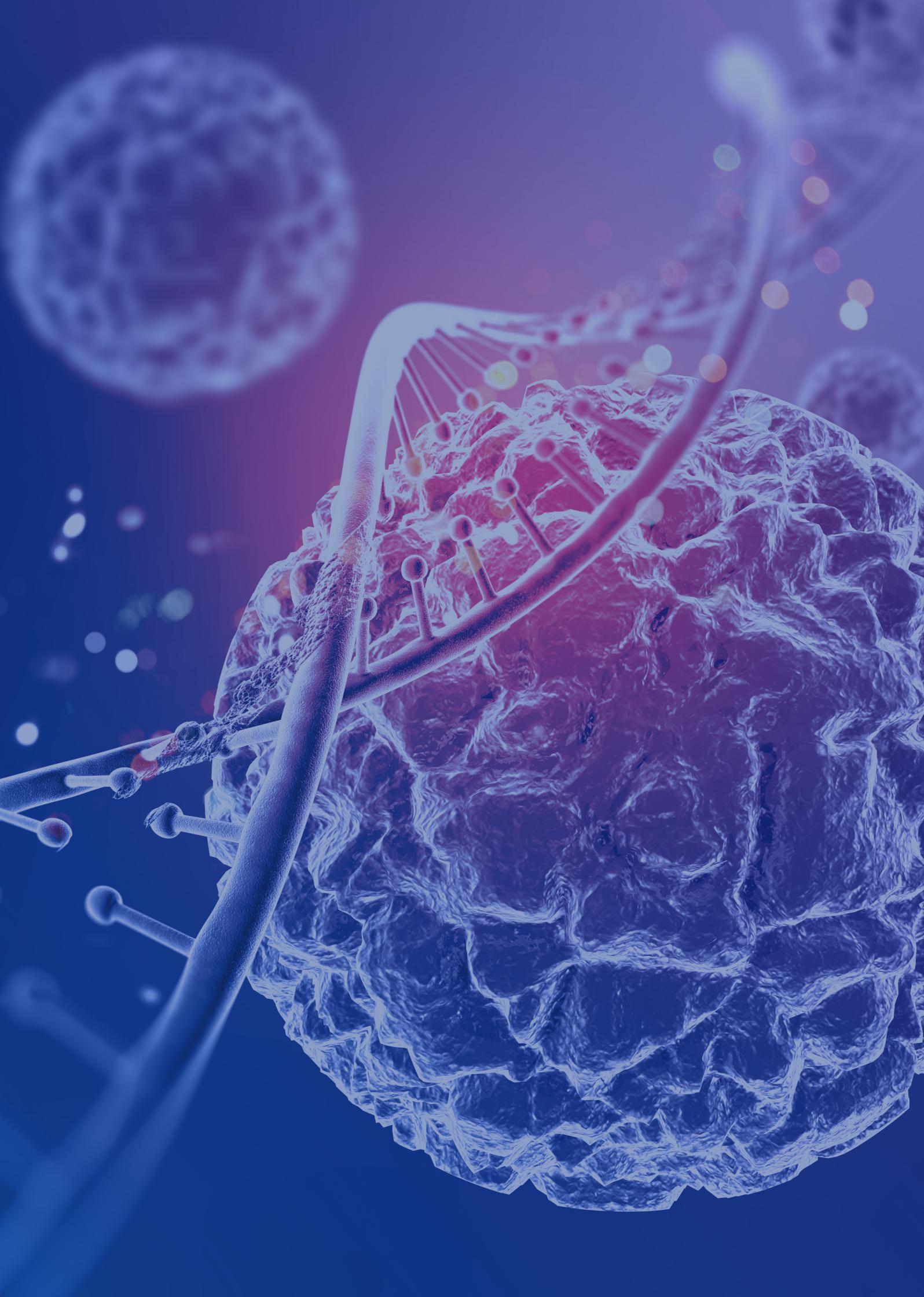
TABLE OF CONTENTS

	Executive Summary	7
01	Introduction	13
	1.1 Why This Strategic Research Agenda?	13
	1.2 Why LifeTime?	14
	1.3 Vision for Cell-Based Interceptive Medicine	17
	1.4 Covering the Whole Innovation Chain	22
	1.5 What This Will Mean for Europe?	22
02	Creating Sustainable Impact for Europe	25
	2.1 LifeTime Unique Value	26
	2.2 EU Leadership in Breakthrough Research Directed at Patient Needs	28
	2.3 Transforming European Healthcare Through Cell-based Medicine	30
	2.4 Increasing European Competitiveness Through a Flourishing Innovative Industry	31
	2.5 Strengthening Citizen Engagement and Ethical Responsibility	38
	2.6 Benefits for All European Member States	39
03	LifeTime Science and Technology Roadmap: Towards Cell-based Medicine in Europe	41
	3.1 Developing Technologies for Cell-based Medicine	43
	3.1.1 Single-cell Multi-omics and Imaging	43
	3.1.2 Data Science, Artificial Intelligence and Machine Learning	51
	3.1.3 Patient-derived Experimental Disease Models	64
	3.2 Solving Medical Challenges - Disease Roadmaps	72
	3.2.1 Cancer	72
	3.2.2 Neurological and Neuropsychiatric Diseases	80
	3.2.3 Infectious Diseases	90
	3.2.4 Chronic Inflammatory Diseases	100
	3.2.5 Cardiovascular and Metabolic Diseases	110
04	A Multisector Strategy for Industry and Innovation	121
	4.1 Accelerating Technology Adoption and Development	124
	4.2 Fostering Successful Transition from Lab to Market	126
	4.3 Enabling Exchange between Industry and Academia and Across Different Industry Sectors	129
	4.4 Stimulating the Creation of Successful and Sustainable Spin-offs	131
	4.5 Reciprocal Expert Advising	132
	4.6 Creating a Globally Competitive Innovation Framework for Companies in Europe	133

05	Implementing an Ethically Responsible Strategic Research Agenda	135
	5.1 A LifeTime Ethics Mechanism	136
	5.2 Mitigating Ethical and Societal Risks	137
	5.2.1 Research on Patients' Material and Sharing of Data and Samples	137
	5.2.2 Innovative Technologies in Research and Healthcare	139
	5.2.3 Emerging Issues in Healthcare	138
	5.3 Engaging Citizens	140
06	Preparing Europe for Cell-based Medicine	143
	6.1 Promoting Interdisciplinary University Education	144
	6.2 Encouraging Lifelong Workforce Training	145
	6.3 Empowering Citizens and Disseminating Knowledge	146
	6.4 Harmonising the LifeTime Education and Training Programme	147
07	Implementing the LifeTime Strategic Research Agenda	149
	7.1 The LifeTime Cell Centre Network	151
	7.2 Medical and Biological Data Management Platform	155
	7.3 Community Coordination and Governance	158
	7.4 Research and Technology Integration and Training	159
	7.5 Ethics and Society Programme	160
	7.6 A dedicated Innovation Framework to Implement the LifeTime Industry Strategy	161
	7.7 European and International Context and Collaboration	163
	Appendix	166
	LifeTime Working Groups	166
	Glossary	168



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Executive Summary

European citizens are living longer, gaining years, which they should spend with the highest quality of life. To ensure that people remain healthy throughout their lifetime, Europe needs a new approach to medicine. Not only do we have to change the way diseases are detected and treated, we also need to think ahead and prepare for emerging health challenges. Digital and biomedical technologies have the capacity to potentiate other breakthroughs and transform medicine. They can impact every stage of medical care from early disease detection, correct diagnosis, selection of the most effective treatment and protect recovering patients from the threat of therapy resistance and relapse. Their integration promises to provide high-quality healthcare, strengthen Europe's research and health industry, innovation capacity and global leadership.

Creating a new generation of digital health and biomedical technologies will offer solutions for medical and societal challenges. Disruptive research and breakthrough innovation enabled by these technologies will provide the necessary new approaches to prevent suffering from diseases through new modes of detection and diagnosis. By understanding the underlying causes of a disease, the right therapy can be selected for a patient and new drugs and therapies can be developed based on this knowledge. Not only will this lead to healthier lives and ageing for Europe's citizens but also relieve the growing unsustainable burden on its healthcare systems over the next decade.

LifeTime, as a large-scale long-term research initiative proposes to generate the technologies required to drive a new digital age in medicine. Instead of diagnosing diseases once symptoms arise, LifeTime aims to detect them much earlier to increase the opportunities for intercepting disease before irreparable damage occurs and curing patients by treating disease causes instead of their symptoms. Driving this transformative change in medicine requires more knowledge of the molecular basis initiating disease at the level of individual cells, the fundamental building blocks of our bodies. Understanding and predicting the future course of a disease and its response to treatment requires knowledge of the hundreds of thousands of different molecules in a single cell and how these differ between millions of cells in tissues and across many thousands of individuals in a population. Detecting and therapeutically targeting the specific cells that cause diseases is key to intercepting and curing them. Digital health solutions will provide ways to create and unlock the potential of biomedical 'big data' and implement cell-based interceptive medicine in Europe.

LifeTime aims to:

- Understand diseases and therapies at cellular resolution and use this information to intercept diseases by creating and integrating new digital and biomedical technologies**
- Establish approaches that enable the large-scale sharing and use of medical data across national borders to provide personalised health solutions for European citizens**
- Enable long-term European leadership in cell-based interceptive medicine through developing new technologies and driving innovation at the interface of multiple sectors**
- Develop a dialogue with citizens and stakeholders, ensuring an ethically-sound implementation and making citizens active contributors to European research and health strategic decisions**

The LifeTime Strategic Research Agenda (SRA) lays out the priorities for developing and integrating the next generation of digital and biomedical technologies - single-cell multi-omics and imaging, artificial intelligence and machine learning and patient-derived experimental disease models - and their introduction into medical practice in the next decade. It details ten-year roadmaps for co-developing these technologies during multidisciplinary research programmes and applying them in the clinics to address urgent medical challenges. These roadmaps are supported by key programmes covering industry and innovation, ethics, legal, societal issues and education and training to introduce cell-based interceptive medicine.

Developing Technologies for Cell-based Medicine

Sequencing of the human genome launched the vision of precision medicine, whereby the right therapeutic strategy is tailored for an individual at the right time. Until now we have lacked the required approaches to understand how an individual's genetic information influences the molecular status of individual cells and use this knowledge to drive precision medicine. Integrating different breakthrough technologies will make it possible to discover the cellular basis of health and disease at a resolution that has previously been impossible. Creating new single-cell multi-omics and imaging technologies will provide information on the different types of molecules in cells, their position in tissues, interactions with other cells and their origin to quantify their status in health and disease. This will generate the essential 'big' high-quality data to unlock the potential of artificial intelligence in medicine. Machine learning approaches will integrate and extract meaningful information on a patient's health or disease. These computational models will discover molecular mechanisms, predict the future course for a particular patient and the most effective therapeutic options, which will be tested in cell and tissue models derived from patients to ensure that the most effective therapy is provided. Use of this data across Europe will require investment in computational infrastructure for storing, accessing and querying data across national borders. This is a golden opportunity for Europe to drive the establishment of standardised technologies, data formats to ensure interoperability and secure access. In parallel, the process will promote health-data exchange and research on preventative strategies, therapies and outcomes. Currently, the US, China and Europe are investing heavily in precision medicine. However, only the US and China are also investing in large-scale single-cell technology-driven initiatives such as the Human BioMolecular Atlas Program (HuBMAP), Human Tumor Atlas Network (HTAN), 10 Million Single-Cell

Transcriptome Project (scT10M) to better understand human biology and disease. Europe needs to step up and build on its precision medicine investments to ensure that it establishes itself as a leader in cell-based interceptive medicine.

Solving Disease Challenges Through Cell-based Interceptive Medicine

Detecting and correctly diagnosing diseases sufficiently early, selecting a therapy to which a patient will respond and developing disease-modifying therapies are current barriers in medicine. To rapidly translate the development of new technologies to benefit patients, LifeTime has identified key medical challenges where single-cell analysis, artificial intelligence and patient-derived cell and tissue models can make the greatest impact for patients. This SRA details current medical challenges and provides five ten-year roadmaps, where investment in research is required at the interface of biology, artificial intelligence, mathematics, engineering and medicine. Multidisciplinary research programmes will create next-generation technologies and apply them to large-scale patient populations to move beyond the currently limited one-size-fits-all approach to medicine. These address the current barriers to effectively treating and curing cancer, neurological and neuropsychiatric diseases, infectious diseases, chronic inflammatory diseases as well as cardiovascular and metabolic diseases. Newly created artificial intelligence-based approaches will alert and guide a physician's decision-making process to select the best therapy strategy for an individual as well as identify new validated drug targets for the pharmaceutical industry. Within a decade, the next-generation biomarkers discovered through biomedical 'big' data driven solutions will enable the implementation of precision medicine based on the early detection and targeting of specific cell populations.

Creating an Interactive Community to Drive European Innovation and Competitiveness

An undertaking as far-reaching as realising cell-based interceptive medicine across Europe cannot be achieved by cutting-edge academic research alone. New cost-effective enabling technologies and instrumentation need to be co-developed, standardised and commercialised to make sure they become widespread in both research and clinical use. Products need to be brought to market readiness, adhere to regulatory guidelines and provide information that can be immediately used by physicians in the clinic. This task is the responsibility of the biotechnology, pharmaceutical and IT sectors, who need to rapidly pick up discoveries from research and translate them into medical solutions. An integrative dynamic ecosystem is necessary to stimulate innovation and facilitate interactions between relevant players. Together with industry, LifeTime proposes five synergistic engagement platforms in this SRA: i) technology adoption and development, ii) strategic partnerships, iii) networking brokerage, iv) entrepreneurship and v) expert advising. They address important bottlenecks that currently hinder cross-sectoral exchange. If implemented, they will drive solution-oriented breakthrough discovery, foster transition from lab to market, stimulate the creation of spin-offs and contribute to new research and innovation policies. A competitive innovation framework for innovative ways of interacting and sharing risk between stakeholders, supporting public/private partnerships, and business creation will generate a highly dynamic and attractive market space

for accessing early-stage innovations. The suggested measures will require significant investments such as those introduced by other global leaders. But more than just committing funds, it is necessary that all stakeholders, in particular, industry and academia come closer together, find unifying goals and join forces behind a common vision. This will strengthen European competitiveness and ensure leadership in a future medicine that has single-cell based innovation at its core.

Implementing an Ethically Responsible Strategic Research Agenda

An integral part of developing and implementing LifeTime's SRA involves addressing the ethical questions, relevant to both medical and research communities, and also to citizens, including patients. To prioritise individual interests and foster trust between researchers, clinicians and the public, we propose creating a LifeTime Ethics Mechanism that will co-produce the ethical, legal and societal impact of LifeTime's biomedical innovations. It will identify risk areas and steer research and healthcare innovations into ethically-sound directions and ensure the protection of patients' privacy through regulated data access within Europe. It will also evaluate the societal implications of innovative technologies in research and healthcare and address emerging issues that impact people's life choices. Through awareness and engagement strategies based on transparency and trust, the LifeTime Ethics Mechanism will promote critical thinking and empower citizens to actively engage in decision-making processes and have a voice in strategic decisions.

Preparing Europe for Cell-based Interceptive Medicine

Combining and applying knowledge and innovation from various scientific and technological fields and sectors will require professionals with an interdisciplinary, open and creative mindset. Due to limited training opportunities and scarcity of experts in LifeTime's core technology areas, most higher-education European institutions are currently unprepared to face this challenge. A European interdisciplinary Education and Training Programme, based on a culture of lifelong learning and high adaptability to the constantly evolving medical challenges and technology development, will sustainably respond to these needs. LifeTime will develop a programme where scientists, clinicians, managers of technology platforms, research and clinical technical staff or administrators can acquire new skills in technological intersections, cross-sectoral collaborations or communication and bioethics. Committing to a general dissemination of knowledge and to prepare citizens to embrace a new kind of medicine, LifeTime will create a science outreach programme that will contribute to public openness and trust in science. Through education, training and outreach, LifeTime will sustainably prepare its future professionals, will contribute to European scientific and clinical excellence and will support a more knowledgeable and engaged society confident in research, healthcare and innovation.

Realising LifeTime in Europe

LifeTime aims to create the knowledge and necessary conditions to ultimately put cell-based personalised medicine into practice for millions of European citizens. To answer this challenge, we propose to establish a long-term, large-scale research initiative that not only spans across multiple disciplines but also many countries. Sustaining an open and interactive European community, the LifeTime implementation plan is designed to provide flexibility to respond to rapidly developing technology areas while building an active and cooperative research and innovation ecosystem. It builds on existing programmes and recommends the creation of connected infrastructure hubs, the multidisciplinary LifeTime Cell Centres, to generate critical mass, new opportunities for innovative research and clusters of innovation, collaboration and partnership. Closely associated with hospitals, the open network of these centres with synergistic and complementary specialisations will connect the expertise that is necessary to foster the progress of LifeTime technology development.

Everywhere in Europe the Cell Centre network will support interoperability and complementarity and provide cost-effective access of researchers and innovators to the LifeTime technologies. The framework includes a shared biomedical data management programme, a medico-scientific research and technology integration programme, programmes for training and bioethics as well as an open innovation scheme accelerating the translation of knowledge into clinical use. A central coordination body will guarantee cohesion, coherence and collaboration. Complementing and strongly cooperating with projects of the ESFRI Roadmap and other existing national, European and international efforts, LifeTime's consolidated pan-European action plan offers the potential of propelling European science and medicine into a position of global leadership.

LifeTime is the large-scale collaborative multidisciplinary research initiative necessary to shape future European healthcare and approach to medicine. Through sustained synergies created with coordinated investments in research and infrastructure by private and public fund injections, we aim to have a transformative impact on the industrial economy, healthcare, and innovation to establish Europe as a leader in cell-based interceptive medicine. Research at the interface of several technologies and medical areas will ensure that Europe attracts the best young talent and established researchers to develop research projects in world-class laboratories, medical centres and innovation clusters. Most importantly, over the next decade LifeTime will enable European patients and the whole of society to benefit from truly personalised, cell-based and effective healthcare interventions.



01

Introduction

1.1 Why This Strategic Research Agenda?

This Strategic Research Agenda (SRA) provides a roadmap for implementing cell-based medicine in Europe within the next decade. It is the combined vision of more than 100 institutions and medical centres, 80 companies and is supported by patient organisations as well as prestigious European scientific societies and research funding organisations. The SRA recommends significant investment in research and infrastructure programmes to address key clinical challenges and drive the transition to cell-based and patient-centred European healthcare. Implementing the proposed [Science and Technology Roadmap](#) will enable earlier detection and effective therapeutic treatment of diseases to improve the quality of life of European citizens, stimulate the European economy and ensure Europe as a leader in the cell-based interceptive medicine of the future.

The LifeTime Initiative began as a consortium with a vision to transform European healthcare over the next decade as a Future and Emerging Technologies (FET) Flagship. The European Commission awarded the Initiative a Coordination and Support Action to develop its vision and an SRA. Between March 2019 and June 2020, the initiative organised multiple meetings and workshops, stakeholder interviews, an impact study and several community surveys. These have brought together leading European scientists, experts and multiple stakeholders to identify the challenges, priorities and solutions to implement a new research, technology and healthcare vision. The recommendations from this work are detailed in this document.

The SRA describes the priorities for developing and integrating the next-generation of digital and biomedical technologies that have originated largely independently in different fields. It details 10-year roadmaps for co-developing these technologies during multidisciplinary research programmes and applying them in the clinics to address urgent medical challenges. These roadmaps are supported by key programmes covering industry and innovation, ethics, legal, societal issues and education and training. Recommendations for implementation are open and flexible to be incorporated within national and European programmes to ensure efficient use of funding and building on previous investments. Together, this will drive cell-based interceptive medicine to revolutionise European healthcare.

This SRA is not a static, fixed plan but will continue to incorporate new technology developments, medical challenges and research programmes as the LifeTime initiative grows over time.

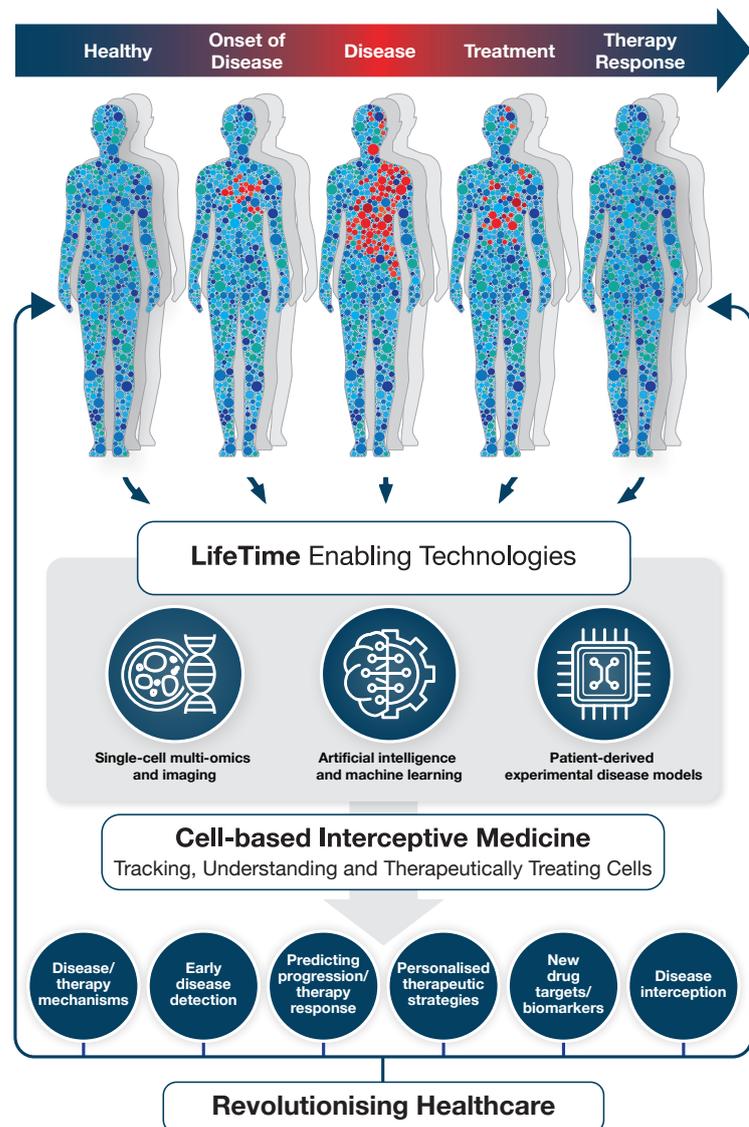
1.2 Why LifeTime?

Early Disease Detection and Interception

Europe has a growing ageing population with the number of people above the age of 65 predicted to double by 2050. It is critical that its citizens live their lives with the highest possible quality throughout their lifetime. Achieving this requires new innovative cost-effective solutions to prevent suffering from chronic and complex diseases.

Advances in medicine have led to spectacular progress in certain disease areas. Nevertheless, most diseases today are only detected relatively late once symptoms appear, provoking a visit to the physician or hospital. By this time, tissues and organs have often undergone extensive or irreversible changes, with the choices in therapy being typically quite limited. Interventions often attempt to treat the symptoms and not cure the disease or involve invasive or aggressive therapies of variable benefit to the patient.

LifeTime's vision is to fundamentally change the way diseases are detected and treated. By providing new knowledge and integrated digital and biomedical technological solutions, diseases will be detected much earlier than is currently possible and intercepted using the most effective therapeutic strategy. Importantly, the choice of treatment will be based on the underlying molecular and cellular causes of the disease in a particular patient. Understanding the early events or response to treatment is key to intercepting diseases before irreparable damage occurs. This new cell-based interceptive medicine will alleviate the suffering, the increasing costs and the societal consequences of living with these diseases.



The LifeTime vision

Making cell-based interceptive medicine a reality depends on creating, integrating and applying breakthrough digital and biomedical technologies. Single-cell and imaging technologies, artificial intelligence - in particular machine learning to leverage the enormity and complexity of biomedical data - and patient-derived disease models are currently being predominantly developed in separate research fields.

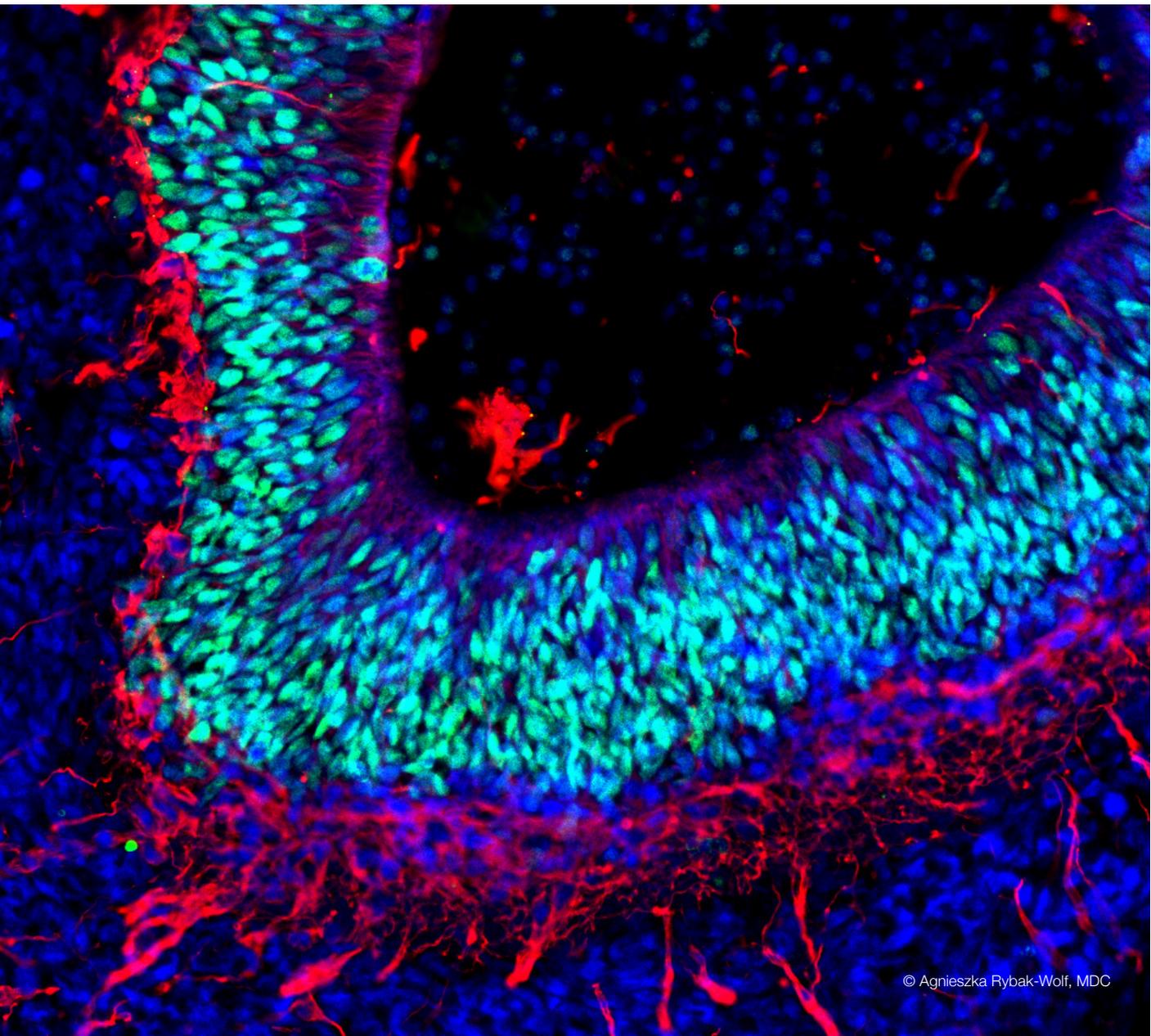
Applying them to human diseases will provide an unprecedented single-cell view of disease mechanisms and processes, predict their future course and study the underlying causes in a human setting. The resulting knowledge and technology applications will provide new diagnostic strategies, new therapies and an increased portfolio of validated drug targets based on the cause of the disease. Together, they will make it possible to overcome the biomedical barriers to implementing precision medicine in Europe.

This SRA capitalises on previous European investments in precision medicine as well as computational and biomedical infrastructures and programmes such as the 1+ Million Genomes' Initiative. To achieve the envisaged impact and change the way diseases are detected and treated, requires large-scale European level coordination across multiple stakeholders to:

- // Develop and apply breakthrough technologies, including computational approaches, to increase understanding of key diseases at the level of individual cells, the most basic building blocks of tissues**
- // Create and use knowledge for the development of non-invasive approaches to detect disease signs before symptoms manifest and new ways for preventing them**
- // Generate and use large-scale datasets and machine learning approaches to predict disease progression based on the current health status of a patient and identify the most effective therapeutic strategy for an individual**
- // Transform research and healthcare infrastructure to enable close collaboration and facilitate molecular and medical data generation, storage and analysis across national borders**
- // Develop personalised patient-derived disease models to understand the disease, identify and validate personalised drug targets and accelerate the creation of new therapies**
- // Implement programmes to enhance translation of scientific discoveries into clinical solutions for the benefit of patients**
- // Provide new single-cell based biomarkers for patient stratification, newly designed clinical trials and therapeutic response monitoring**
- // Increase public-private cooperation by creating an innovative ecosystem in Europe involving start-ups as well as small, medium and large enterprises**
- // Promote sustainable European leadership in cell-based interceptive medicine through a dedicated training programme for the new generation of clinicians and researchers**

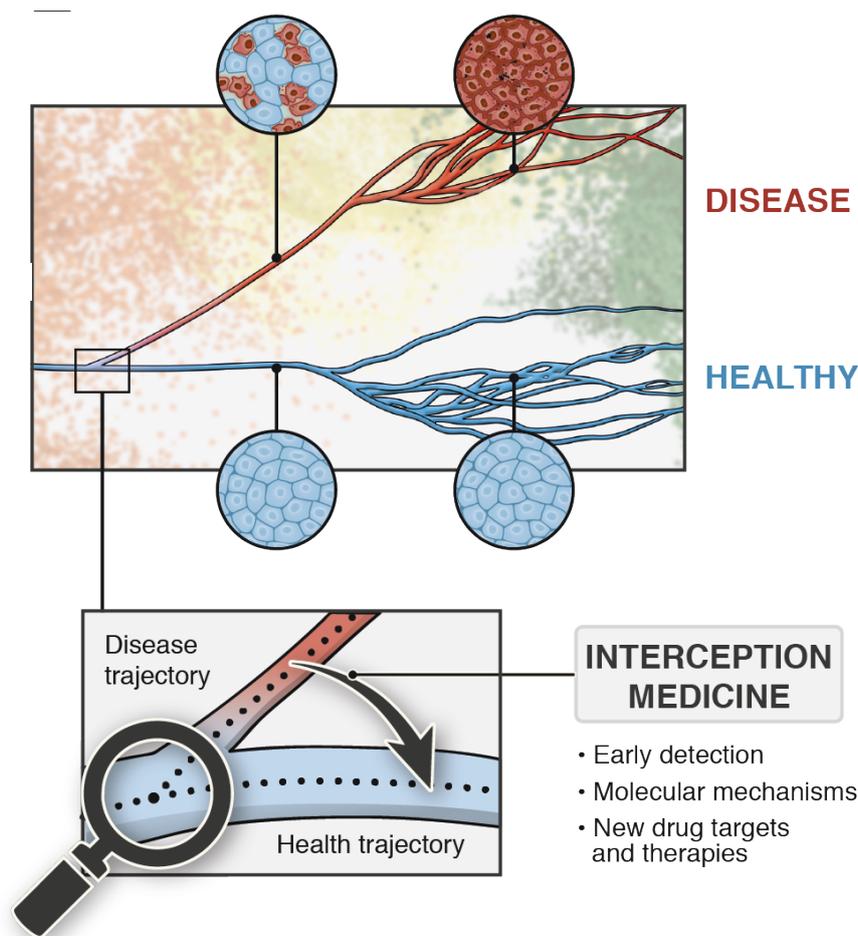
By implementing its vision and precision medicine in Europe, LifeTime will overcome the following fundamental barriers to early disease detection and interception:

- // **Incomplete knowledge of the cellular and molecular causes of diseases and an inability to detect the initiating or rare early events in disease onset, progression or therapy response**
- // **A lack of understanding of the underlying differences or heterogeneity in the causes of disease between patients**
- // **Inability to predict the future course of a disease as well as the most effective therapy for a particular patient or take preventative actions against therapy resistance and relapse**
- // **Therapeutic strategies that treat symptoms without curing the disease**
- // **Inefficient translation of new therapies into the clinics largely due to scarcity of validated drug targets identified based on an understanding of disease mechanisms and adequate pre-clinical disease models**



1.3 Vision for Cell-based Interceptive Medicine

Cells are programmed to follow particular developmental paths during which they acquire specific identities and functions. When they deviate from their healthy path they progressively accumulate changes that lead to disease. Implementing a more precise, personalised and effective medicine for European citizens requires a deeper understanding of the types of cells and molecular changes responsible for driving the onset and progression of diseases or emergence of therapy resistance in each patient. The ability to resolve diseases at the level of individual cells is only now becoming possible due to the development of powerful single-cell approaches. Knowledge of the early events that cause cells to shift towards disease will enable us to detect them earlier and rationally design therapeutic strategies to intercept the disease, with the goal of reverting cells back towards a healthy state. This approach will enable earlier disease detection, discover disease mechanisms and systematically identify new drug targets, creating new opportunities to develop cures.



Cell-based interceptive medicine concept

Cells develop along specific molecular paths to reach states in which they can perform their roles in tissues (blue path/trajectory). During their normal paths, molecular changes can cause cells to take another path towards disease (red path/trajectory). Detecting diseases earlier and intercepting them requires understanding of the molecular events that cause a cell to switch from a healthy path to a disease path. Such knowledge will help discover therapies to revert a cell to a healthy state.

LifeTime has identified key current challenges in five disease areas in which the initiative's approach can directly impact patient care and outcomes. The five areas are: i) cancer, ii) neurological and neuropsychiatric diseases, iii) infectious diseases iv), chronic inflammatory diseases, v) cardiovascular and metabolic diseases. Importantly, the modular technologies and LifeTime's approach are not limited to a specific medical challenge but equally applicable to other disease areas as well as processes that are common to several disease areas, e.g. fibrosis, inflammation.

Successfully generating knowledge and translating it into clinical applications requires technological solutions that enable us to:

- Monitor human cells and tissues to measure cellular, molecular and organisational changes over time, a LifeTime**
- Predict the future course of a disease and its response to therapy based on a patient's current molecular, cellular and clinical state using computational models**
- Resolve disease heterogeneity by simultaneously measuring all different types of molecules in many individual cells from cohorts of patients across a large population**
- Understand and incorporate the role of tissue environment in disease progression and therapy response by monitoring signalling between cells and cell-cell interactions**
- Discover disease mechanisms and validate drug targets by manipulating cellular models of human tissues**

LifeTime has identified an opportunity to combine strategically and co-develop technologies that can address all the above needs:

- Single-cell and advanced imaging technologies** allow us to analyse tissue and cellular features at an unprecedented level of detail. They form the basis for ongoing global research initiatives that are providing reference maps of all cell types present in healthy human tissues. LifeTime will use these reference maps and develop multi-omics methods that describe all the molecular layers in a cell to reveal molecular mechanisms, tissue composition and function in healthy and disease states ([section 3.1.1](#)).
- Data science, artificial intelligence (AI)** and machine learning will allow the integration of datasets from the various technologies together with clinical data and health records, to extract meaningful information and facilitate the early detection of disease. This will be crucial for creating predictive disease models for a patient and establishing causal relationships to guide the design of personalised therapeutic strategies ([section 3.1.2](#)).
- Patient-derived disease models** recapitulate key aspects of a patient's disease and will allow efficient manipulation of their cells to decipher molecular mechanisms as well as introduce personalised drug testing ([section 3.1.3](#)).

The successful application of cutting-edge computational approaches depends critically upon the availability of consistently-curated and large volumes of data. LifeTime will implement **pan-European strategies to enable controlled data access, sharing and analysis of large amounts of medical data** across national borders, in full compliance with international legislations such as the European General Data Protection Regulation (GDPR).

Technologies will be co-developed through multidisciplinary research programmes that will bring together single-cell technology and computational experts, mathematicians, engineers, disease modellers and clinicians. LifeTime recommends this to be done in the context of 10-year disease roadmaps addressing specific medical challenges ([section 3.2](#)) as a strategy to implement cell-based medicine in the next decade.



Towards Cell-based Medicine in 2030



Profiling cohorts to understand the heterogeneity of disease and generate big datasets required to create predictive models:

Single-cell technologies will provide a high-resolution picture of an individual's health status. To understand disease onset, progression and response to therapy, these multi-dimensional measurements of different molecular layers will be collected for millions of cells from large cohorts of individuals. These molecular data will be linked to clinical outcomes by integration with electronic health records, medical imaging and clinical data to obtain information on the cellular and molecular changes associated with disease onset and progression. Applying machine learning will create models of individual disease trajectories for patients and together provide an overview of the disease landscape in a population.

Analysis of these population-scale big data using machine learning will provide multi-dimensional biomarkers for early disease detection, reveal the causal underlying mechanisms and begin to predict the future course of a disease in an individual and, based on the mechanism, select which therapies would be most effective for disease interception. They will also identify candidate cell types, molecular pathways and drug targets, and hence the most vulnerable hubs of the diseased tissue or organ.



Single-cell based profiling of non-invasive liquid biopsies for early detection, AI-based digital molecular pathology:

The establishment of cell-based medicine will enable a new level of screening for the early detection of diseases. For example, routinely taken blood samples will be profiled using single-cell based molecular assays adapted for clinical use. Multi-dimensional biomarkers for disease onset can inform a physician and suggest the need for further tests. In relevant cases a follow up small tissue biopsy will be taken and analysed by single-cell multi-omics and imaging, complementing a pathologist's slide analysis under the microscope with artificial intelligence and multi-scale computational disease models. Advanced data visualisation and analytics tools will guide potential therapeutic strategies based on the cell population present in the tissue microenvironment, heterogeneity, potential plasticity, and specify numerous potential genes and genomic loci as drug targets that can be used to make precision treatment decisions.



Using patient specific predictive computational models to select personalised combinatorial therapies and test them on organoid avatars:

For certain diseases, the pathophysiological tissue will be sampled, morphologically characterised and processed through single-cell analyses while the patient's organoid "avatar" is expanded in the laboratory. Disease-specific vulnerabilities to existing drugs or drug combinations will be inferred by data-driven integration of multi-dimensional molecular parameters, relative spatial locations of cells, cell shapes and patterns of structural niches in histological slices captured through single-cell multi-omics and advanced imaging technologies. Predicted optimal drug combinations will be first tested in the patient's organoids and subsequently in n-of-1 clinical trials closely monitored by single-cell based technologies.



Systematic identification of high confidence drug targets for disease modifying therapies:

To drive new efficient processes of drug discovery, multiple patient samples from a disease of interest will be analysed using single-cell multi-omics as well as highly sensitive imaging approaches to create a comprehensive computational model. Such models will describe the relevant cell types and their precise molecular status and identify critical nodes that may represent novel drug targets. Compounds and repurposed drugs will be tested in newly developed experimental disease model systems that adequately represent the biology of the disease. This may also involve targeted *in silico* as well as experimental screening efforts for new therapies that will be driven by readouts discovered through single-cell profiling. The most successful integrated experimental/computational models will form the basis for a complete drug discovery and validation process facilitated by a mechanistic understanding of cellular function and regulation.

1.4 Covering the Whole Innovation Chain

At the beginning of the multi-stage research and development process leading to an effective impact on citizens' health lies research investigating the foundations of life. 80% of the most transformative drugs approved by the U.S. Food and Drug Administration (FDA) between 1985 and 2009 originated in basic discoveries made by scientists seeking to understand a biological mechanism or disease, with an average time span of 31 years from first basic discovery to FDA approval¹. Diagnostic and therapeutic interventions that enable us to tackle the health challenges Europe is facing today require to extend our knowledge base of how diseases start and evolve. We severely limit our potential to make a real difference to people's lives if we base new diagnostic and therapeutic concepts on the understanding of disease mechanisms gained a decade ago. More knowledge equals more opportunities. Investment in low Technology Readiness Levels (TLRs) delivered through European and international research collaborations is imperative, or we risk losing future impact ([section 2](#)). LifeTime's research programme follows a complimentary route to the ERC's blue sky approach, it is founded on fundamental science with a clear purpose in mind, directed towards creating the necessary understanding for solutions that will change people's lives and the way we do medicine. The genomic/ bulk sequencing (i.e. Human-Genome-like) approach has by now been largely exploited and most clinically relevant discoveries have been developed and brought to the market or are on their way. Basing new applications exclusively on these technologies will curb our progress in the fight against diseases to very small advances. To make big leaps forwards we need innovative approaches and ways to look at diseases. We require new, integrative concepts engaging and connecting all stages of the innovation process to shorten the time span between fundamental discovery and market introduction ([section 4.2](#)). LifeTime proposes a comprehensive concept that builds on creating synergistic connections between the different elements of the innovation chain, on taking down the barriers between fields, disciplines and communities, between academic and industrial research and promises to efficiently catalyse and accelerate the translation of ideas from bench to bedside ([section 7](#)).

1.5 What This Will Mean for Europe

Boosting European Competitiveness and Leadership

A large-scale, coherent funding of LifeTime activities will generate synergies, increase speed of discovery, and achieve a long-lasting impact, as demonstrated by previous initiatives such as the Human Genome Project ([section 2](#)). Europe needs to uniquely position itself with regards to next-generation precision medicine and the big data revolution. Owing to conditions favourable to the commercialisation of knowledge, its conducive regulatory environment and the well-established financial/investors landscape, the US is well placed to lead innovation. China has the capacity to generate and process data on a very large scale and speed, giving it a considerable competitive edge. Europe's main strengths are high efficacy through coordinated, transparent and open research programmes and the focus on disease area applications. Its unique advantage will be to take an ethical approach rooted in its humanistic cultural heritage. It will support the translation of

¹ Spector, Jonathan M., Rosemary S. Harrison, and Mark C. Fishman. "Fundamental science behind today's important medicines." *Science translational medicine* 10.438 (2018): eaaq1787.

knowledge to clinical practice and address key challenges relating to data protection and/or “data as public good” to protect innovation and maintain a patient-centric approach in the future medicine. Importantly, LifeTime will commit considerable resources to look specifically at the potential ethical, legal and societal issues raised by the development of LifeTime technologies and research on selected diseases ([section 5](#)).

In a context where Europe is not hosting any of the technology giant companies that dominate the global landscape, an interesting role will be carved out for SMEs and generally new entrants and players in healthcare. Investing in collaboration models particularly inclusive of them will bring innovation and next-generation medicines to low- and middle-income countries, with a resulting positive global footprint.

LifeTime will reshape today’s varied healthcare delivery practices by fostering harmonisation of healthcare systems and healthcare delivery across Europe, considering that next-generation drugs increasingly require close collaboration between laboratories, clinics and manufacturing. Industry, from large to small companies, and across sectors, has already started to build capacities in the field of single-cell multi-omics research, thereby indicating their recognition of the relevance of LifeTime’s core technologies.

Currently large, long-term investments in digital and biomedical technologies such as single-cell multi-omics and imaging research are taking place primarily in the US and China. Without comprehensive funding of this type of research, Europe risks losing the most promising talents. Leading private funders, such as Wellcome Trust and the Chan Zuckerberg Foundation are already extensively funding single-cell multi-omics (e.g. Human Cell Atlas), which is an indicator of the strength and appeal of large-scale research initiatives. It is to be expected that single-cell analysis will reshape healthcare delivery in 2030+; in order to take a lead in and favour the uptake of the future technologies, Europe needs to invest now in suitable infrastructures, including computational and data, where different competencies can come together to generate knowledge and technological advancements. Such investments are unlikely to come from the commercial sector, which tends to look to public sources in this respect.

Building on European Programmes and Priorities

This Strategic Research Agenda ties in with European digital and health priorities on many levels. The proposed deep integration and sharing of medical, genomics and omics data across domains will require investments in AI technologies and high-performance computing, which are both mainstays of the Digital Europe strategy. The recommended core data infrastructure for LifeTime ([section 7.2](#)) will closely link to the European Open Science Cloud (EOSC) and European data programmes such as European Genome-phenome Archive (EGA) and the European ‘1+ Million Genomes’ initiative. LifeTime will play a key role in connecting currently separate biodata infrastructures through common protocols for data sharing and standards. The proposed research and development programme ([section 3](#)) has the potential to substantially impact initiatives such as Europe’s Beating Cancer Plan and the Horizon Europe Mission on Cancer ([section 3.2.1](#)) or contribute to a joint European response to the COVID-19 pandemic ([section 3.2.3](#)). The International Consortium for Personalised Medicine (ICPerMed) will be an important contact point and discussion partner regarding the implementation of personalised interceptive medicine, especially in areas such as data integration and data sharing.



02

Creating Sustainable Impact for Europe

By generating a wealth of new tools and technologies to measure, analyse and predict cellular and molecular mechanisms during disease onset and progression, LifeTime will profoundly expand our basic understanding of genome function within cells and tissues, having a fundamental impact on basic science across multiple fields. It will lead to a redefinition of the role of artificial intelligence (AI) in precision medicine, which will be based on cellular biology. The synthesis of 21st century biology and data sciences will impact medical practice and improve human health, while reducing suffering of European citizens.

New developments in the health sector will provide benefits in terms of business volume, jobs, and personal income for European households. The pharmaceutical industry in Europe will be strengthened by the general acceptance of targeted medicines. The use of innovative technologies in toxicology studies and improved patient stratification in clinical trials will lead to substantial savings in the cost of drug development. The high-tech industry and emerging AI sector will be boosted by innovations far beyond the state-of-the-art in linking molecular analysis at single-cell resolution to early detection and interception of diseases, thus making Europe a leader in this key driver of future economic growth. European SMEs developing a variety of applications will spin off and flourish. Improved early disease detection and interception will enable healthier aging, leading to substantial savings in healthcare expenses.

Ethics engagement will ensure that the European citizens will benefit from a Science and Technology Roadmap founded on principles of societal responsibility. Open and transparent communication, and citizen empowerment strategies will contribute to a more knowledgeable society and will facilitate public dialogue and uptake of citizens' assessments in strategic decisions.

LifeTime will have a long-lasting structural effect on the European Research Area by streamlining key European efforts. It will create a coordinated anchor point in Europe for international cooperation, and it will generate and nurture talent by training a new generation of researchers. Together this will ensure a leading position for Europe. Access to and training in the LifeTime technologies will help reduce differences between Europe's regions, thereby raising scientific excellence across the board and stimulating investment in new innovative infrastructure.

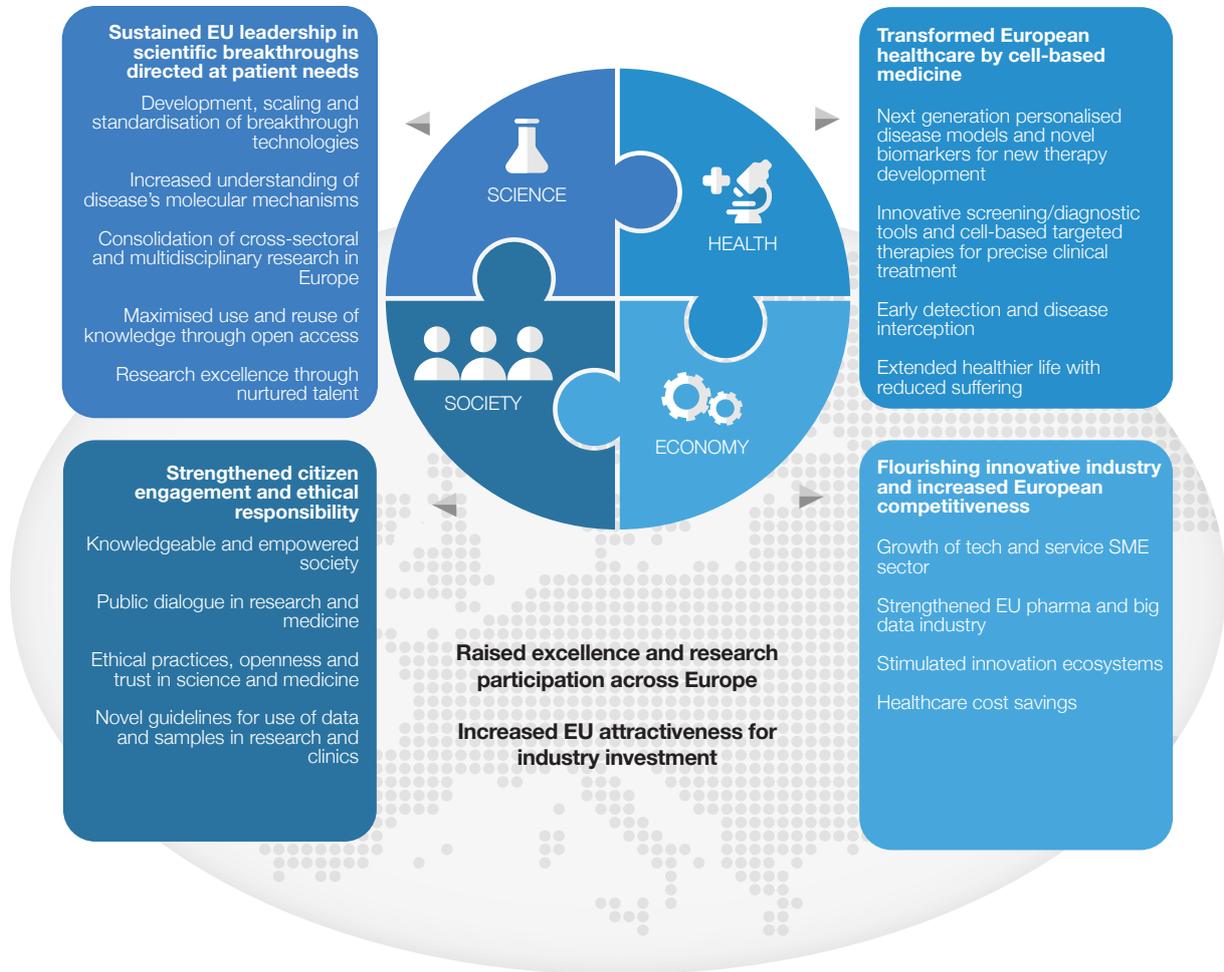
2.1 LifeTime Unique Value

LifeTime is characterised by a unique approach that has immense potential to introduce early disease detection and interception. The initiative brings together a unique constellation of basic and translational researchers, computational scientists, engineers, clinicians, large corporate organisations and SMEs in a process that will foster valuable discoveries and technological advances. Collaboratively developed, they will lead to the final overarching goal of intercepting diseases in patients. The reaction to the COVID-19 pandemic has demonstrated the crucial nature of basic research, and how input from the science at the bench is needed by healthcare professionals and policy makers. Unlike existing consortia, LifeTime's unique value resides at the intersection of disciplines. Promoting a model of exchange among all relevant actors in healthcare, LifeTime collaboration does not happen only across disciplines, but also increases collaboration within disciplines. Importantly, LifeTime brings together scientists working in basic and applied research, clinicians working on different diseases, with a focus on bringing the patient perspective into single-cell multi-omics research.

Creating the tremendous impact envisaged by LifeTime's vision for Europe requires large, long-term investment and resources available for infrastructure building, and long-term planning, exchange and coordination across all workstreams (research and innovation, ethics, public engagement, education). This would be driven by multiple factors such as:

- // Disease area scientists and clinicians' ability to leverage discoveries, technologies and models from other laboratories/ research streams leading to coordinated faster innovation**
- // Attraction of substantial and focused industry investments, far more impactful than sparse support of current small pilots**
- // Education of the next generation of scientists able to embrace breakthrough technologies, driving sustainable innovation in the long term, which will be crucial for the new generation of precise medicines that will reach the market in 10 to 20 years**
- // Construction of long-lasting infrastructures, generating critical mass and clusters of innovation, collaboration and partnership**
- // Definition of a "value chain" and processes to support scientific collaboration and exchange particularly between basic and applied research**
- // Creation of an integrated European system of advanced labs and data platforms that will rapidly and successfully address public health goals (e.g. testing, screening, predictive modelling, etc.) during health emergencies such as the COVID-19 crisis**
- // Think-tank on Europe-wide relevant frameworks concerning e.g. patient centricity, data protection and usage, global impact of LifeTime research, innovation models**
- // An advocacy role for LifeTime, as a strong actor influencing healthcare transformation, also by shaping national and international research agendas**

A long-term collaborative approach will ensure that Europe will benefit from all synergies mentioned above. They will increase the speed of discovery and achieve long-lasting impact. Large scale initiatives such as the Human Genome Project have historically demonstrated the success of this model.



LifeTime impact for Europe

2.2 EU Leadership in Breakthrough Research Directed at Patient Needs

LifeTime will create scientific and technological breakthroughs with an expected long-lasting impact on the European scientific landscape. Globally, LifeTime's impact in science will encompass the generation of knowledge of immediate relevance and impact to the European citizens, through the development and application of breakthrough technologies. With an output-orientated mindset in combination with the creation of a multidisciplinary collaborative cross-sectoral European research programme, LifeTime will provide the solutions for implementing precision medicine in Europe ([section 3](#)).

The routine application of LifeTime's technologies to patients' samples over time will contribute to an unprecedented detailed knowledge of the molecular and cellular events involved in healthy and diseased tissues. Several LifeTime technologies have been described at the technology readiness level of proof of concept, or validated in the laboratory, such as single-cell multi-omics, spatial transcriptomics, genomics, proteomics and metabolomics, high-throughput imaging and single-cell computational models ([section 3.1.1](#) and [section 3.1.2](#)) Together with other stakeholders these technologies will be developed, validated and commercialised for clinical applications, which will require and lead to method standardisation across Europe and scaling for their systematic use in thousands of clinical samples. Likewise, LifeTime will develop further personalised disease models, including advanced patient-derived organoid cultures and more complex cellular 3D co-culture systems, and importantly contribute to improved genetic and drug perturbation protocols and tools using these complex cellular systems ([section 3.1.3](#)). Combined use of these technologies will bring a more directive dimension to fundamental research performed for the patient, leading to clinical breakthroughs ([section 3.2](#)).

The scientific challenges LifeTime aims to solve can only be addressed by international and collaborative cross-disciplinary research ([section 3.2](#)). The implementation of LifeTime's recommended infrastructure connecting academic research laboratories, hospitals and industry will decompartmentalise research and contribute to the consolidation of collaborative research programmes in Europe. This will enable the rapid societal



uptake of scientific breakthroughs. Moreover, LifeTime can create a coordinated anchor point in Europe for international cooperation and benefit broader scientific community building contributing to European research leadership.

Application of LifeTime's technologies to patient samples on a European scale will result in the generation of single-cell repositories of patient data and samples during different stages of disease progression ([section 3.1.2](#)). In full compliance with the General Data Protection Regulation (GDPR), and when applicable, LifeTime data will be released on open access platforms. Such data repositories will be free to use and will be established following the principles of Findability, Accessibility, Interoperability and Reusability (FAIR), contributing to a more sustainable, effective and ethically-responsible research culture. LifeTime will also ensure open access to all peer-reviewed scientific publications of data generated by the initiative, and participate in the Open Research Data Pilot to improve and maximise access to and re-use of research data, making the generated knowledge accessible and available to benefit society.

The LifeTime framework and infrastructure will lead to an expansion of the European scientific job market, due to the requirement of a highly trained scientific workforce as well as the need for professionals dedicated to research implementation and research infrastructure. Through its Education and Training Programme ([section 6](#)), LifeTime will prepare a new generation of cross-disciplinary scientists to sustainably contribute to achieve LifeTime's scientific goals. These highly trained professionals will be highly employable by other research and innovation organisations, contributing to overall scientific excellence in Europe.



2.3 Transforming European Healthcare Through Cell-based Medicine

With the European patient at the heart of LifeTime's ambition to revolutionise healthcare, the LifeTime Strategic Research Agenda puts forward research programmes for five key disease areas: cancer, neurological and neuropsychiatric diseases, infectious diseases, chronic inflammatory diseases and cardiovascular and metabolic diseases, leading to innovative solutions across all disease groups ([section 3.2](#)). LifeTime has the potential to create truly personalised interventions for those in need, with evident consequences on populations' health. LifeTime research output will lead to innovative ways to deliver care, such as:

- Implement screening and diagnostics using novel biomarkers that enable early diagnosis and prediction of disease trajectories based on disease mechanisms – which will require the uptake of single-cell based analytical techniques in clinical settings, and/or the creation of hybrid clinics/laboratory structures, where healthcare professionals will be able to run individualised assays**
- Prescribe patients the best suited treatment, by e.g. running organoid-based *in vitro* tests specific for an individual patient, or using novel stratification biomarkers combined with predictive AI/machine learning algorithms – which will require advanced laboratory capabilities and skilled professionals not only to run, but also to interpret tests and imaging outputs**
- Design new cell-based targeted therapies for precise clinical treatment – which may require innovative and flexible manufacturing solutions for the most innovative applications**

These medical advances will substantially improve outcomes for patients and will make important contributions to more efficient health systems ([section 2.4](#)), thereby profoundly impacting society at large.

LifeTime will involve the rapid medical uptake of science-driven applications through technology development in close proximity to the clinics. Conducting research, innovation and the practice of medicine together will transform our current medical systems and how society perceives healthcare. The ability to detect, diagnose and treat diseases more accurately and at earlier stages will contribute to an extended and healthier life, with reduced suffering for patients and their families. Tackling diseases earlier will not only increase therapeutic effectiveness but can also result in milder treatments with less harmful consequences. This will have a tremendous impact on patients' quality of life and will allow patients to pursue more actively their roles in society and in their families.

Encouragement of more regular and routine medical consultations will further facilitate earlier disease interception and influence citizens' behaviours regarding their own health. People will be empowered to more actively consult their physicians and to maintain up-to-date information regarding certain health parameters. This new proactive attitude and the more systematic use of machines to process information will contribute to a change in the relationship between patients and clinicians. Clinicians will have the opportunity to dedicate more of their time to communicate with their patients, including through new tools such as online consultations.

2.4 Increasing European Competitiveness Through a Flourishing Innovative Industry

LifeTime research and innovation output will positively affect the European economy, mostly in terms of industrial growth and potential healthcare cost savings.

Innovation and Industrial Growth

Biomedical research typically yields high returns on investment and significantly contributes to economic growth. A pivotal initiative such as the Human Genome Project, which described human genes and paved the way to today's genomic industry, has been shown to have generated USD 141 in tax revenues for each dollar spent by the US government over the years¹. Notably, single-cell research will explain human gene behaviour, bringing disruptive knowledge and innovation, in the wake of what the Human Genome Project achieved. Therefore, considerable economic drive can reasonably be expected in relation to LifeTime research and innovation output. New LifeTime technologies will instantly stimulate start-ups and spin-offs across Europe, which in turn will feed the pipeline of larger pharma and technology companies in Europe. Despite intrinsic uncertainty related to a 10+ year time horizon, key impact areas and dynamic trends in the industrial economy LifeTime will shape have been identified.

¹ Tripp & Grueber (2011), Economic Impact of the Human Genome Project, Battelle Memorial Institute



During the next decades, the industrial field developing around single-cell multi-omics research and precision medicine will be characterised by the creation of innovative business models and strategies, as many key industrial players will have the opportunity to re-define their product/service portfolio and focus to position themselves in the new healthcare landscape. For example, today's life science technology providers might expand in the direction of in-vitro diagnostic products to be used in combination with their instruments. By partnering with technology developers, LifeTime will drive new instrumentation design, testing and adoption ([section 4.1](#)). Companies could also develop sequencing services for institutional clients (e.g. hospitals). Similarly, SMEs today focused on discovery services will need to choose business models oriented around a product- or service-based approach. SMEs focusing on imaging will develop technologies to monitor individual cells and organoids in three dimensions over time and to integrate advanced imaging into digital pathology. Companies deploying AI algorithms that can analyse large datasets from clinical trials, health records, and genetic profiles will streamline the drug discovery process. In addition, new software and infrastructure will be developed to support enterprise analytics and storage solutions for use in biomarker discovery, drug development and clinical implementation. Also, for the pharmaceutical industry, individualised therapeutic solutions might require new supply chain and manufacturing solutions, as is the case today for advanced cell-based therapies.

In addition, the evolution of today's regulatory framework around data protection and usage will unlock new opportunities and requirements, for example if steps will be taken in the direction of Business-to-Government (B2G) data sharing and the "re-usage of data for the common good"². Industry players and academia will need to define new business models, data generation strategy, and monetisation options to obtain the most impact from their work.

² European Commission (High-Level Expert Group on Business-to-Government Data Sharing), Towards a European strategy on business-to-government data sharing for the public interest. Luxembourg: Publications Office of the European Union, 2020



These transformations will be accompanied by an overall growth of the single-cell multi-omic global market which, at least for laboratory equipment and consumables, will reach already USD 5.32 billion size in 2025³ – and will likely grow well beyond that to face increased demand from academia, industry, and hospitals/clinics.

LifeTime technologies will feed the future needs of the European pharmaceutical industries (a sector worth €220 billion in 2018 and directly employing almost 800,000 people⁴) as they position themselves to embrace personalised or precision medicine as the new standard of care. The interest from pharmaceutical companies around single-cell multi-omics research is ever growing, as shown by the recent nomination of a leading scientist in single cell analysis (the co-chair of the Human Cell Atlas) as head of R&D at Genentech.

Pivotal initiatives such as LifeTime have an enormous impact on the entire industrial ecosystem. Single-cell multi-omics research stems from the historical Human Genome Project, which applied a bulk sequencing approach to characterise the human genome. The impact of the project is lasting till today, and has reached beyond the pure medical applications and transformed biomedical research and clinical practice. Besides the important genomics industry that was born from the project success, a further important consequence was the development and commercialisation of new technologies driven by leading companies. This has drastically reduced today's sequencing costs enabling large scale initiatives to sequence huge numbers of samples.

Today, liquid biopsy applications have tremendous potential for early disease detection where considerable investment has been made, including from among others Bill Gates, Jeff Bezos and Illumina, to develop affordable technologies. In the cancer detection space, hundreds of companies distributed across the US, Europe and China are using new technologies (omics, immunotherapies, antibody conjugates, etc.) to develop cancer diagnostics. The global *in vitro* diagnostics market is currently valued at USD 60.8 billion, and it is projected to grow at a 4.4% annual rate until 2028⁵.

LifeTime will rely on a network of multidisciplinary Cell Centers in Europe ([section 7](#)) to foster exchange across sectors and create an environment conducive to innovation. Combining several scientific disciplines with medical science and clinical research it will provide the best creative and open environment to develop public-private partnerships, promoting very favourable conditions for the uptake of innovation, and translation into commercial products and services that can reach patients.

3 BIS Research (2019). [Global Single Cell Multi-Omics Market. Focus on Global Single Cell Multi-Omics Market by Product, Type, Workflow, End-User 15 Countries Mapping, and Competitive Landscape - Analysis and Forecast, 2019-2025](#)

4 EFPIA member associations (official figures) EFPIA estimate; Eurostat (EU-28 trade data 2018)

5 <https://www.grandviewresearch.com/industry-analysis/in-vitro-diagnostics-ivd-market#:~:text=The%20global%20in%20vitro%20diagnostics,diagnosis%20is%20expected%20to%20fuel>

Expected economic impact of LifeTime research and innovation in Europe in the focus disease areas - savings in 2030 (selected components)

Therapeutic area	Cancer	Neurological diseases
(Example) disease	All cancers (and breast cancer)	Alzheimer's disease
Today's situation	<ul style="list-style-type: none"> Overall cancer cure rate is 60% (breast cancer, 10-year survival rate 84%) Mis-diagnosis rate estimated to be between 1 and 5% in most advanced healthcare systems 	<ul style="list-style-type: none"> Symptoms typically manifest late in life but heavy social and financial burden is associated with the disease Increasing disease prevalence in <65-year-old patients
Current standard of care	<ul style="list-style-type: none"> Limited tools to target therapies, not able to treat metastases Patients suffer long-term disability after cancer therapies 	<ul style="list-style-type: none"> Diagnosis occurs when disease is in an advanced state No disease modifying therapeutic options
LifeTime innovation	<ul style="list-style-type: none"> Diagnostic/prognostic biomarkers Risk stratification/ treatment selection biomarkers Novel targeted drugs 	<ul style="list-style-type: none"> Risk analysis/ patient stratification via early biomarker New drug targets, targeted therapies
Expected benefit	<ul style="list-style-type: none"> Overall cure rate to reach 75% (breast cancer up to 95%) Diagnosis/treatment selection improved by 40% 	<ul style="list-style-type: none"> Delayed onset of disease by 5 years Better quality of life Lower informal care costs/ treatment costs and family burden Earlier/more accurate diagnosis
Economic impact in Europe	<p>EUR 6 billion from productivity gains across all cancer cases (EUR 1.3 billion for breast cancer)</p> <p>Up to EUR 840 million savings from reduced inaccurate treatment prescriptions</p>	<p>EUR 150,000 per patient whose disease onset is delayed by 5 years. For early-onset patients (before 65 years old), the total amount saved each year of delayed onset corresponds to EUR 4 billion</p>

Source: PwC analysis⁶

⁶ PwC Research 2020, Assumptions on potential future health benefit for all disease areas have been generated with LifeTime experts, based on their expectations and working hypotheses and assuming a minimum of EUR 100 million per disease area is invested over 10 years

Infectious diseases	Chronic inflammatory diseases	Cardiovascular and metabolic diseases
COVID-19	Inflammatory bowel disease	Heart failure
<ul style="list-style-type: none"> Some patients develop a severe respiratory disease, leading to a long ICU stay 	<ul style="list-style-type: none"> Response rate declines to 50% after 1 year of treatment 	<ul style="list-style-type: none"> Some patients show signs before acute event, but others appear healthy
<ul style="list-style-type: none"> Disease course evaluated at day 8-10 of hospitalisation Immunotherapy starts once patient is in ICU 	<ul style="list-style-type: none"> Not possible to determine disease course and/or treatment response Very expensive treatment 	<ul style="list-style-type: none"> For sudden cases, nothing can be done before the acute episode
<ul style="list-style-type: none"> Early prognostic biomarkers for disease course 	<ul style="list-style-type: none"> Novel biomarkers Targeted therapy 	<ul style="list-style-type: none"> Early disease onset biomarkers Targeted therapy for high risk patients with family history
<ul style="list-style-type: none"> High-risk patients would start immunotherapy earlier ICU stay shortened, or avoided 	<ul style="list-style-type: none"> Increase response rate after 1 year up to 75% Better quality of life Lower healthcare spending on medication 	<ul style="list-style-type: none"> Prevention of 25-50% of all familial heart failure cases (estim. ca. 500'000 cases) Better quality of life, Increased productivity Lower hospital/ drug costs & family burden
In spring 2020 COVID-19 outbreak, each ICU day saved would have led to EUR 155-360 million per day of savings and faster patient recovery	EUR 10 billion from productivity gains across Crohn's disease and ulcerative colitis patients	EUR 2.1-4.1 billion savings in direct medical costs

Healthcare Cost Savings

Medicine and healthcare are rapidly expanding pillars of our economy. The increasing prevalence of chronic conditions is putting a heavy strain on the healthcare budget, as suggested by WHO⁷ data, showing a global spending on healthcare of USD 7.8 trillion in 2017. Specifically, the public spend in health in Europe in 2018 amounted to EUR 944 billion, or 7.0% of GDP on average⁸, for its 445 million citizens. According to the projections, the public expenditure on healthcare and long-term care will rise by 1.7% of GDP by 2045⁹.

LifeTime represents a new approach for healthcare systems to help spend “better” the limited resources, limiting the waste that derives from lengthy diagnoses and ineffective treatments.

For the five key disease areas: cancer, neurological and neuropsychiatric diseases, infectious diseases, chronic inflammatory diseases and cardiovascular and metabolic diseases, LifeTime can bring considerable improvement over the current clinical practices. If LifeTime research is implemented as recommended in this Strategic Research Agenda, innovation occurring in 10+ years from now (e.g. novel omic biomarkers and targeted therapies entering the market) will improve health outcomes, and determine considerable direct and indirect healthcare cost savings across Europe.

Today, 25% of global cancers occur in the European region. At the current rates, in 2030 almost 4 million new cases and 1.8 million deaths will occur, representing a total productivity loss of EUR 99 billion. LifeTime research and innovation will improve today's ability to cure cancer. In breast cancer, a 11% improvement in the cure rate would lead to EUR 1.3 billion of productivity gains in 2030 - which is only a small part of the overall benefits related to increased survival for women and their families. The gain across all cancer cases could amount to at least EUR 6 billion. Single-cell based approaches are also expected to improve diagnosis precision to guide treatment selection. Improving diagnosis accuracy by e.g. 40%, Europe would save up to 840 million compared to today by reducing prescriptions of incorrect cancer treatment.

Neurodegenerative diseases are another significant growing burden on the European healthcare systems. For example, if most Alzheimer's disease patients are diagnosed later in life, their diagnosis places a considerable emotional and financial burden on their families, predicted to grow up to EUR 256 billion in 2030. LifeTime research will focus on developing early biomarkers to identify and better stratify patients before severe brain damage occurs. If the disease was delayed by 5 years in early-onset patients (before 65 years old), more than EUR 20 billion could be saved across Europe compared to today.

LifeTime is also intensively focusing on the emerging threat represented by COVID-19. Early predictive biomarkers would enable patients to be treated earlier and relieve hospitals from excessive intensive care occupancy during new waves of infections. Assuming a similar number of cases (2 million) as in spring 2020, in the range of EUR 155-360 million would be saved across Europe for each day of shorter ICU stay.

⁷ Global spending on health: a world in transition. Geneva: World Health Organization; 2019 (WHO/HIS/HGF/HFWorking-Paper/ 19.4).

⁸ https://ec.europa.eu/eurostat/statistics-explained/index.php/Government_expenditure_on_health

⁹ Brändle and Colombier (2017), Healthcare expenditure projections up to 2045, FFA Working Paper No. 21, Economic Analysis and Policy Advice (EAPA)

Considering the dramatic effect of the pandemic on global productivity, better patient management would also have in addition a much larger economic impact.

LifeTime can also help better predict response to therapies by developing novel prognostic biomarkers and/or in-vitro organoid models. In inflammatory bowel disease, half of the patients stop responding to treatment after one year. A good predictive biomarker may increase the response rate up to 75%, translating into productivity gains for EUR 10 billion overall in 2030. Also, healthcare systems would be relieved from the resource-intensive process required for follow up today, including repeated hospitalisations.

Cardiovascular diseases are the leading cause of mortality in Europe. It is estimated that 1-2% of Europeans may suffer from heart failure, causing EUR 29 billion spent each year in relation to frequent hospitalisations and productivity loss. LifeTime has the potential to identify early biomarkers and novel medicines for young populations at high risk for heart failure, for example in familial cases. If even just half of the familial cases were prevented, Europe would save at least EUR 4.1 billion each year.

By considering specific economic components such as mortality- and morbidity-related productivity losses in the selected disease areas demonstrates that investing in LifeTime research would grant an enormous economic return.



2.5 Strengthening Citizen Engagement and Ethical Responsibility

LifeTime's goals will require active information campaigns and the commitment from the involved workforce to engage with the citizens. Through educational and outreach activities organised by collaborative efforts of LifeTime's ethics and training teams, LifeTime will promote critical thinking, and contribute to a more knowledgeable and empowered society, thereby providing a service to citizens. Citizen empowerment will support patients and will be key to initiate a necessary public dialogue together with relevant stakeholders including patient organisations, researchers, clinicians, policy makers and insurers, strengthening citizen involvement in the design of scientific partnerships, medical treatments and key policy decisions.

Transparent communication with the public is crucial, contributing to openness and trust that will be of central importance for the responsible implementation of the present Strategic Research Agenda. Promoting active public participation, together with the recommended ethics empirical research strategy, LifeTime will initiate a public dialogue about new technologies and the ethical issues they raise, in real-time throughout the scientific and technological advances. This strategy will permit the early identification of problematic societal aspects and will allow a rapid uptake of citizens' feedback steering technology development and application into the recommended directions. Bringing scientists and clinicians in close contact with ethics experts, social scientists and policy-makers, LifeTime can have an effective role in European policies, promoting harmonisation and changes in patients' consent procedures or in the use of patient's data and samples. Moreover, LifeTime will promote a fair balance between the public interest and the legitimate interest of private companies involved in the initiative. The proposed principle of benefit sharing will ensure a constant loop of investment in societal aspects. Profits originating from products generated based on research using patients' samples should be partially used to invest in aspects of relevance to society such as fair pricing of drugs and reimbursements, or investment of private funds in the public sector. We believe that open communication and increased public awareness of the social implications of LifeTime will promote trust and active public participation, enabling the successful adoption of a novel mentality in medical practice and basic research directed to the patient.



2.6 Benefits for All European Member States

The European Research Area was established to create European added value, through a single market for research, education and innovation, reducing the performance gap between Eastern and Western Europe. So far, we have not arrived at a truly united Europe. Many of the EU13 countries have made substantial economic advances. In terms of GDP per capita, many former Eastern Bloc nations have made big steps forward, with some having overtaken EU15 countries¹⁰. These developments, however, are not reflected in the EU13's innovation potential. All 13 countries are still below the EU average in the 2019 European Innovation Scoreboard country ranking¹¹, even if a general upward trend is recognisable. In the category of Scientific publications among 10% most cited the EU13 are still trailing behind, with the notable exception of Estonia. Most EU13 countries also score low in the categories of international scientific co-publications and while participation in the EU Framework Programmes has had some positive effect, most collaborations seem to be taking place between the new member states rather than entering established networks of scientists located in the EU15¹².

While many EU13 countries could economically profit from investment through the EU and other member states, this effect has not proved to be easily transferable to research and development, especially in disciplines that require high investment in infrastructure and equipment, such as the life sciences. Low scientist salaries and often the lack of a sufficient critical mass to shape and stimulate the research environment have led to a brain drain that is not compensated by an influx of foreign talent¹¹. Presently, this general trend is also evident in the composition of the LifeTime community. It can be assumed that the lack of previously established collaborations and networks has been a defining aspect, especially during the current conception phase of the initiative. This has been reinforced by limited research capabilities due to factors such as the size of the scientific workforce or the nature of the available infrastructure. However, the comprehensive LifeTime concept offers excellent opportunities for institutes and scientists from the EU13 but also from less developed EU15 countries such as Greece or Portugal, to not only gain access to highly innovative infrastructure but also to training and education programmes in breakthrough technologies and an innovation framework supporting the commercial exploitation of research results. Collectively developed standards for data and data sharing ([section 3.1.2](#)) will further foster participation in collaborative research and help raise excellence across the board. The organisation in an open network of European Cell Centres can provide stimuli for national investments, for instance, Poland has recently decided to invest in a LifeTime Single-cell Centre (IBCH PAS & NIEB PAS). LifeTime has the potential to make important contributions to creating a level playing field and closing the innovation gap present in Europe today.

10 https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?name_desc=false%26order

11 https://interactivetool.eu/EIS/EIS_2.html#a

12 Makkonen, T. and T. Mitze (2016), "Scientific Collaboration between 'Old' and 'New' Member States: Did Joining the European Union Make Difference?", *Scientometrics* 106, 1193–1215.



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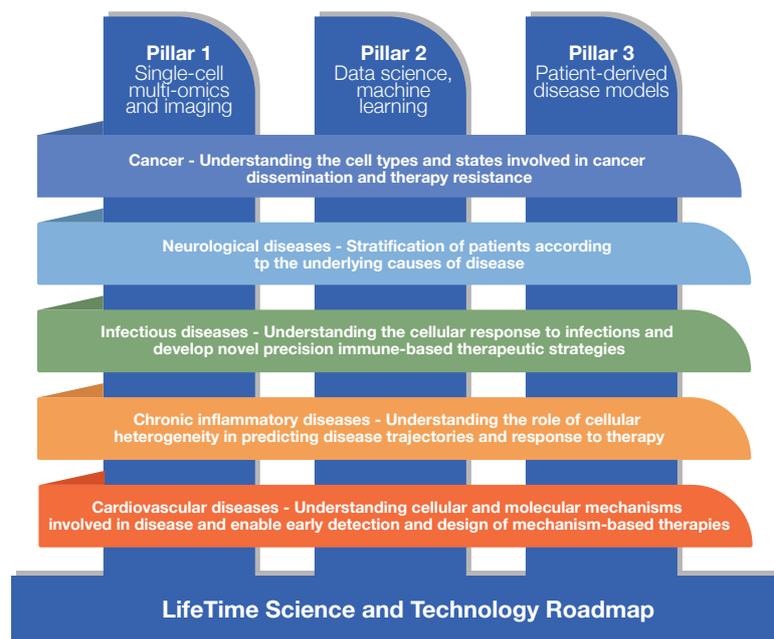
LifeTime Science and Technology Roadmap: Towards Cell-based Medicine in Europe

This Science and Technology Roadmap describes the technology and infrastructure developments required to implement cell-based interceptive medicine in Europe in the next decade. It details roadmaps to address key medical challenges in five disease areas and recommends funding of scientific programmes required to transition to a new way of detecting and treating diseases.

At the core of LifeTime's vision are **three technology pillars**: i) single-cell multi-omics and imaging; ii) data science, artificial intelligence (AI) and machine learning (ML); iii) patient-derived experimental disease models. The co-development and integration of these technologies will provide a suite of standardised technologies to address any key medical challenge and be subsequently deployed in the clinics.

LifeTime has identified **five key medical challenges** in different disease areas where the application of these integrated technologies will have a direct impact on patient care and outcome. The five disease areas are: i) cancer, ii) neurological and neuropsychiatric diseases, iii) infectious diseases iv), chronic inflammatory diseases, v) cardiovascular and metabolic diseases.

These medical challenges have been selected considering societal impact, evidence for cellular heterogeneity that limits current clinical avenues, availability of samples from biobanks, relevant pre-clinical models, existence of patient cohorts including those enabling longitudinal studies, clinical feasibility, issues relating to sex-and-gender-in research and ethical aspects, as well as alignment with national and EU funding priorities.



LifeTime recommends the establishment of a working group to ensure the sex-and-gender-in-research dimension and other relevant diversity aspects such as age or ethical background are taken into consideration from the very beginning in planning basic and translational research, including AI, activities.

Solving these medical challenges requires the synergistic combination of integrated technology developments in the three key technological pillars across five medical areas. Technology developments essential for introducing cell-based medicine at a population scale are described in three enabling technology sections ([sections 3.1.1 - 3.1.3](#)). These three technology pillars are built on a foundation of principles and infrastructures that will ensure that the technologies and data are fully Findable, Accessible, Interoperable and Reusable (FAIR) and secure when required ([section 3.1.2](#)). Through LifeTime, Europe has an opportunity to coordinate research efforts, standardise technologies and data formats, prevent duplication of efforts and ensure that citizens in each country have the opportunities to benefit from these developments.

The five ten-year disease roadmaps contain research programmes required to develop and apply these technologies to address key medical challenges ([section 3.2.1 - 3.2.5](#)), each disease roadmap follows the same structure with recommended investments in:

- 1. Immediate research into the identified medical challenge using established, scaled single-cell technologies, computational tools and disease models**
- 2. Development of new technologies required to address specific medical challenges, including the development of patient-derived model systems for longitudinal analyses**
- 3. Applying new, next-generation technologies for longitudinal analyses of patient samples, or patient-derived models, combined with machine learning to generate patient trajectories and predictive models of disease. Identification of biomarkers, drug targets and validation in clinical studies**

In addition to the challenges, aspects common to several diseases have been identified across disease areas and would benefit from coordinated research and use of standardised, interoperable technologies. These include inflammation-based mechanisms and the role of metabolism in disease, as well as links between infection/inflammation and cardiovascular diseases, cancer or neurological disorders.

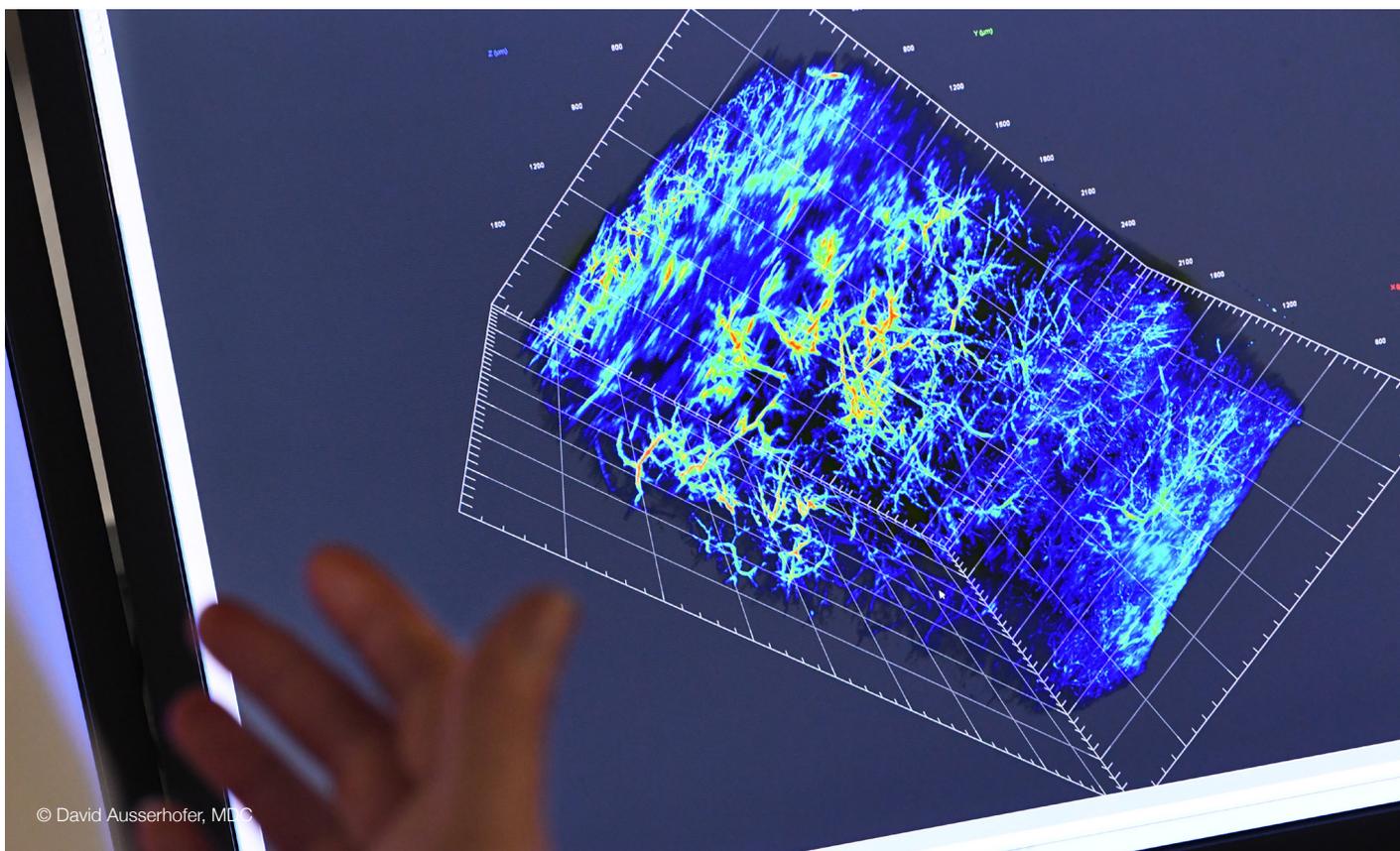
Together, implementation of the research programmes will drive the transition to data-driven and cell-based-medicine in Europe.

3.1 Developing Technologies for Cell-based Medicine

Implementing cell-based interceptive medicine requires the development and integration of single-cell multi-omics and imaging, artificial intelligence in particular machine learning and patient-derived experimental disease models. In the following sections, LifeTime identifies key technology development priorities that should be implemented in research activities addressing key medical challenges described in the disease roadmaps ([section 3.2.1 - 3.2.5](#)).

3.1.1 Single-cell Multi-omics and Imaging

Single-cell multi-omics and advanced imaging are technologies that simultaneously detect and enable the analysis of multiple types of macromolecules (DNA, RNA, proteins and metabolites) in individual cells. They are essential for cell-based medicine because disease processes within individual cells can occur on different molecular levels and no individual technology can provide a complete picture of a disease. Integration of single-cell technologies is needed to understand molecular mechanisms by describing the different molecular components, cell types and states in a tissue, the role of cell-cell interactions and tissue microenvironments and how these change through time. Realising their potential requires applying them to medical samples at different times, including during therapy, and patient-derived disease models ([section 3.1.3](#)) to reveal the status of hundreds of thousands of individual patient cells through the course of health and disease. Extracting meaningful information from these large, heterogeneous datasets using machine learning analytics ([section 3.1.2](#)) will provide a new level of information required to understand the cause of diseases, predict their future course and implement precision medicine.



Single-cell based technological solutions will impact our knowledge of disease in several ways. They will increase our resolution and understanding of disease mechanism diversity in patients diagnosed with a particular disease; enable the identification of single-cell based biomarkers to detect diseases earlier, stratify patients and select optimal therapeutic strategies; provide high-quality large datasets, including the consequences of genetic and molecular perturbations, to derive predictive models of disease; discover molecules and processes that will lead to new drug and therapy concepts based on understanding mechanisms; lead to new clinical trial designs and a new level of digital molecular pathology based on multi-dimensional data.

LifeTime recommends technologies to be developed in three main areas. The state-of-the-art of these areas is briefly described before outlining eight specific development priorities required to obtain mature single-cell multi-omics and imaging technologies.

Single-cell multi-omics. These approaches are typically performed in parallel on individual cells isolated from body fluids or from dissociated tissues. Methods for detecting single classes of macromolecules (DNA, RNA, protein or metabolites) are currently at different stages of development. Transcriptomics and chromatin accessibility are mature technologies that have been scaled and can be applied to hundreds of thousands of individual cells. Detecting mutations and structural variants in the genome, DNA and chromatin modifications or chromosomal contacts are still limited to thousands of cells. Unbiased single-cell proteomics and metabolomics technologies have not routinely reached single-cell resolution. So far, combined multi-omics approaches can simultaneously detect genome and transcriptome, combinations of transcriptome, chromatin accessibility and DNA methylation, as well as DNA-protein interactions and transcriptome or chromosomal contacts and DNA methylation, but do not include information on proteins or metabolites. The sensitivity of these integrated methods and the number of cells that can be analysed typically decrease. When further developed and integrated single-cell multi-omics will provide a complete view of the different molecular layers in a cell to reveal its status and underlying molecular mechanisms.

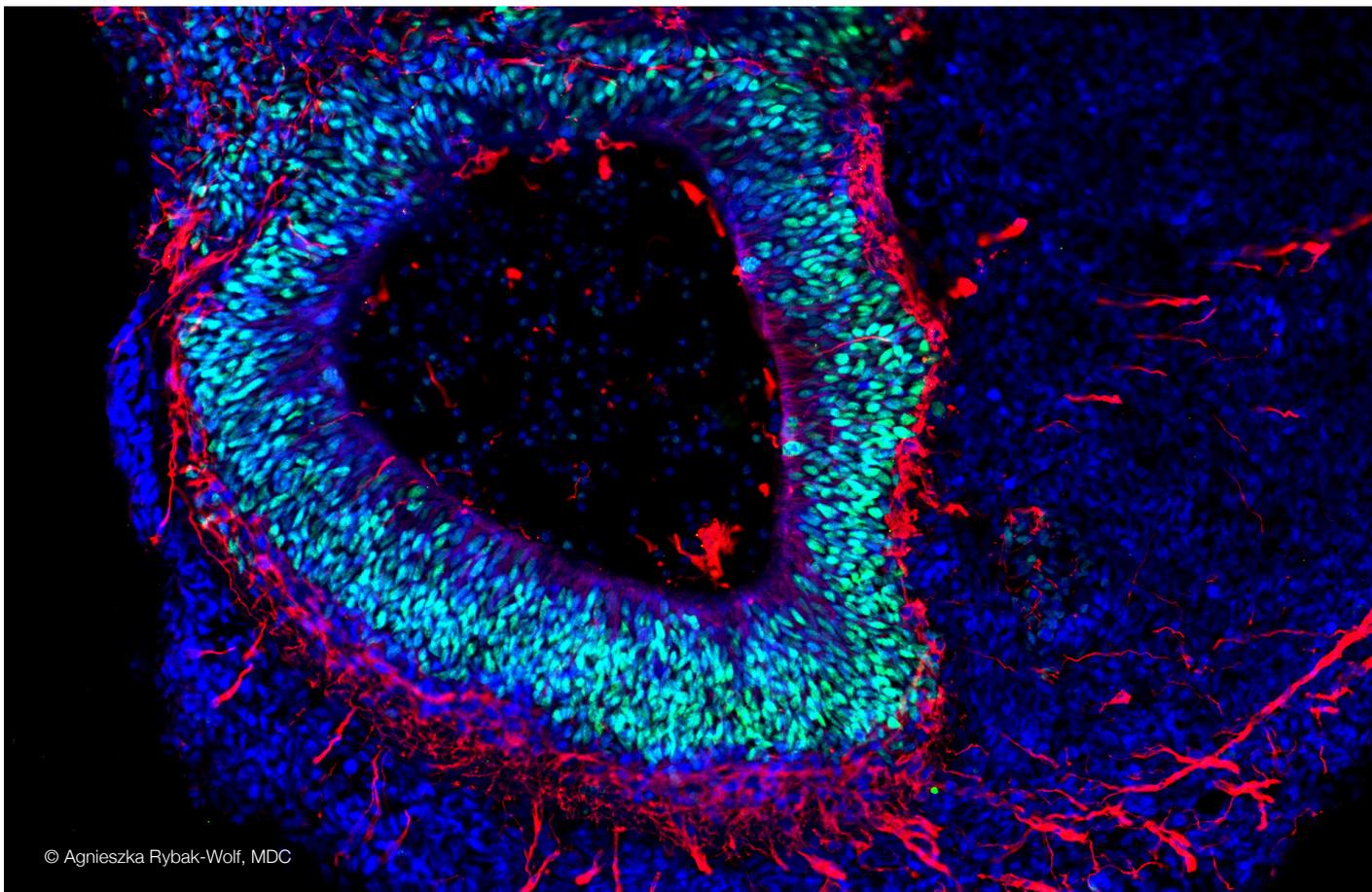
Imaging- and sequencing-based spatial omics. These approaches detect single types of macromolecules (DNA, RNA, protein or metabolites) in the context of tissue sections using sequencing or imaging approaches. They are important because they maintain information on the relative position of a cell within a tissue and its neighbouring cells and microenvironment - which are key to understanding diseases. Current spatial transcriptomics methods are based on either sequencing molecules from particular regions of tissues or imaging of labelled RNA to detect rare molecules with sub-micrometer precision. Similar approaches are being applied to detect DNA and proteins with spatial resolution: spatial genomics enables the tracing of the 3D structure of DNA in single cells, while spatial proteomics and metabolomics uses fluorescence or mass spectrometry-based imaging to detect proteins and lipids. Epitope-based methods that use tagged (fluorophore or metal) antibodies can detect up to a hundred different proteins in clinical tissue samples.

Spatial single-cell multi-omics and advanced imaging. Spatial multi-omics approaches detect multiple different types of macromolecules in tissues with spatial resolution. Imaging-based technologies offer the unique possibility to combine the detection of multiple molecular species in a single acquisition. For instance, 3D DNA structure can be traced while simultaneously detecting tens to hundreds of RNA

species, similarly, proteins and RNAs can also be monitored in the same cell within tissues. These technologies can be scaled and included in clinical workflows. Other advanced imaging approaches that can also detect different molecules in the same cell, such as multi-photon, light-sheet, or super-resolution microscopy can be difficult to transfer to the clinic, but will play a key role to understand disease mechanisms *in situ*. For instance for imaging deep within tissues at cellular resolution, for fast dynamic imaging of organoids and disease models, or for the visualisation of molecules and complexes in cells at sub-cellular resolution.

Building on a Fertile European Landscape

European research groups have pioneered many of these key technologies and are at the forefront of research for developing novel methods and applying them to study disease and therapy response. These include single-cell technologies for studying transcriptomes, genomes, epigenomes, proteomes and metabolomes. European groups are pioneering multi-omics technologies and integration with novel computational methodologies as well as imaging-based spatial genomics and multi-omics. They have established many approaches for spatial transcriptomics, proteomics and metabolomics, as well as super-resolution, multi-photon and light-sheet microscopy. Europe also has a dynamic ecosystem of companies with single-cell biology expertise, key proprietary technologies for single-cell isolation and single-cell analysis including spatial technologies. It also includes world leaders in the development of imaging hardware, components required for imaging, and software dedicated to image analysis. EU companies develop algorithms and computing platforms to analyse single-cell omics data and use AI to discover biomarkers. The expertise that is distributed across Europe is an excellent basis to drive the creation of next-generation single-cell multi-omics and imaging technologies, and to benchmark and standardise them to ensure rapid uptake in the clinics. More needs to be done to ensure that these technologies are taken up and commercialised in Europe to create a new single-cell technology-based ecosystem ([section 4](#)).



Priorities for Developing Next-generation Single-cell Multi-omics and Imaging Technologies

LifeTime has identified several technology developments that are required to address the disease challenges and enable large-scale profiling of patient cohorts. Implementation of these recommendations in specific research programmes is described in the individual disease roadmaps ([section 3.2.1 - 3.2.5](#)).

Development of robust, high-resolution and single-cell technologies for different macromolecules

Transcriptomic approaches have been scaled, standardised, benchmarked, are commercially available and can be performed on hundreds of thousands of cells. These gene expression data are used to identify different cell types and states in tissues but do not provide the whole picture. Understanding disease mechanisms requires additional knowledge of the genome and chromatin state, signalling pathways involved including post-translational protein modifications and lipids as well as the metabolic status of a cell. These molecules are not routinely assessed at large-scale at the single-cell level. High-resolution proteomics and metabolomics for analysis of small cell numbers, towards single-cell resolution with a useful depth of analysis, will require development of fast and sensitive mass spectrometry instrumentation (such as Orbitrap Fourier transform mass spectrometry and MALDI) and also new sample preparation strategies. For example, cell digestion strategies and methods for coupling of microfluidics platforms to mass-spectrometers should maintain the cell state and minimise the loss of the miniscule amounts of proteins and metabolites in individual cells.

Novel single-cell multi-omics modalities to understand disease mechanisms

Current single-cell multi-omics approaches have focused on combining transcriptomic and chromatin/epigenomic information. To reveal the complexity of cell states, novel multi-omics combinations are required that incorporate additional information on protein levels and modifications, metabolites and genetic variation. These will be applied to profiling of cells acquired from liquid biopsies, dissociated tissue biopsies or patient-derived organoids. They should also be integrated with techniques providing functional information on cells where required. For example, coupling with single-cell electrophysiology to record neuronal activity can inform about changes in the circuitry in neurological and neurodevelopmental diseases. Innovative multiplexing strategies, such as barcoding and cell hashing, using barcoded antibodies, lipids, or click chemistry are required to increase the throughput of approaches to make profiling at the cohort scale affordable and technically feasible. Coordinated efforts are required to develop reagents, protocols, and benchmarks to assist research groups with multiplexing strategies, which would accelerate the adoption of new methods.

Developing sensitive, high-resolution imaging- and sequencing-based spatial omics technologies

LifeTime has identified the development of next-generation spatial omics technologies to be a high priority. These developments will be important to address disease challenges, such as understanding the role of the tumour microenvironment in cancer, the functions of immune cells during homeostasis and immunotherapy, the link between cell types and pathological lesions in the brain, infections as well as specialised structural regions of the heart. The first step is to increase the sensitivity and resolution of technologies that detect specific types of macromolecules (either RNA, DNA, protein or metabolites). Sequencing-based spatial transcriptomics methods need to reach the subcellular resolution of imaging-based methods. In addition, the number of RNA species that can be profiled per spatial unit needs to be increased while acquisition times and costs should be drastically reduced. The number of RNA molecules and DNA loci detectable by imaging-based spatial transcriptomics/genomics is still relatively low (few thousands at most), which needs to be improved. Sample processing should be adapted and/or optimised, so these spatial methods can be applied to existing tissue collections, which are routinely stored as formaldehyde-fixed and paraffin-embedded sections. There is also a need for increased resolution, speed and sensitivity in spatial proteomics and metabolomics approaches. Typically these involve mass spectrometry-based technologies, which require development and improvement in instrumentation and data interpretation. Instrumentation needs to be simplified and commercialised to make it widely applicable, especially in clinical settings. Furthermore, development of new reporter chemistries is needed to increase sensitivity, resolution and the number of proteins and metabolites that can be simultaneously detected.

Novel spatial single-cell multi-omics and advanced imaging technologies

Next-generation spatial transcriptomics, genomics, proteomics and metabolomics approaches need to be integrated to create novel spatial single-cell multi-omics technologies that can detect multiple types of macromolecules in the same cells within tissues. This is required to discover hidden morphological features, facilitating the development of digital molecular pathology by visualising localisation of disease or patient-specific biomarkers, assisting early assessment of treatment, and improving prognosis. This



will require improvements in acquisition and analysis pipelines to achieve robust, fast, reliable and user-friendly imaging-based multi-scale spatial omics. This will enable acquisition of tissue-wide (millimeter-scale areas), spatial information on the presence and abundance of hundreds of thousands of different molecules in conjunction with other molecular features at cellular resolution. These developments should be accompanied by the establishment of standard data formats and validation datasets. Super-resolution and light-sheet microscopy should be further developed to achieve higher spatial resolutions, higher throughput and multi-scale imaging capabilities in tissues, organisms and organoids. Altogether, the coordinated development, optimisation, standardisation and cost-scaling of these technologies will accelerate the introduction of spatial multi-omic applications to medicine.

Computational methodologies for data integration and analysis

Creating new single-cell multi-omics and imaging technologies cannot occur without parallel advances in computation. Integration of multiple modalities requires new computational approaches, including those to register images and omics profiles. Analytic computational approaches are to reduce confounding factors, visualise highly multiplexed data from hundreds of thousands of cells or more, reveal molecular features and subpopulations hidden behind noise, and ultimately discover links between cell types, phenotypes, and states and their molecular networks. Approaches are required to provide molecular and spatial multi-scale models ranging from molecules to organs and humans ([section 3.1.2](#)).

Integration of perturbation screens and lineage tracing with single-cell multi-omics

Establishing the causative molecular changes that lead to disease and identifying the cells-of-origin will require integration of CRISPR-based technologies with single-cell multi-omics approaches. CRISPR-Cas technologies can be used to remove specific molecules from patient-derived disease models ([section 3.1.3](#)) and the disease-relevant consequences monitored using single-cell multi-omics approaches. Genetic lineage tracing approaches, including those using CRISPR-Cas modifications, provide information about the number of progeny that derive from a cell of interest, as well as their location and their cellular state. Coupling CRISPR-perturbation with spatial multi-omics technologies will provide much needed spatial information in the context of genome-engineered and patient-derived disease models. This will not only be important to understand the early events during disease onset or progression, but also to identify key molecules and cells for drug or therapy development. These approaches will also provide the large datasets required for the development and iterative evaluation of machine learning-based computational models of diseases, which will be critically needed to predict disease outcomes.

Benchmarking and standardisation

Newly developed multi-omics technologies need to be optimised, benchmarked and standardised to ensure that they produce high-quality data required for rapid adoption by the community and downstream analyses including machine learning-based computational approaches. Coordinated efforts will provide

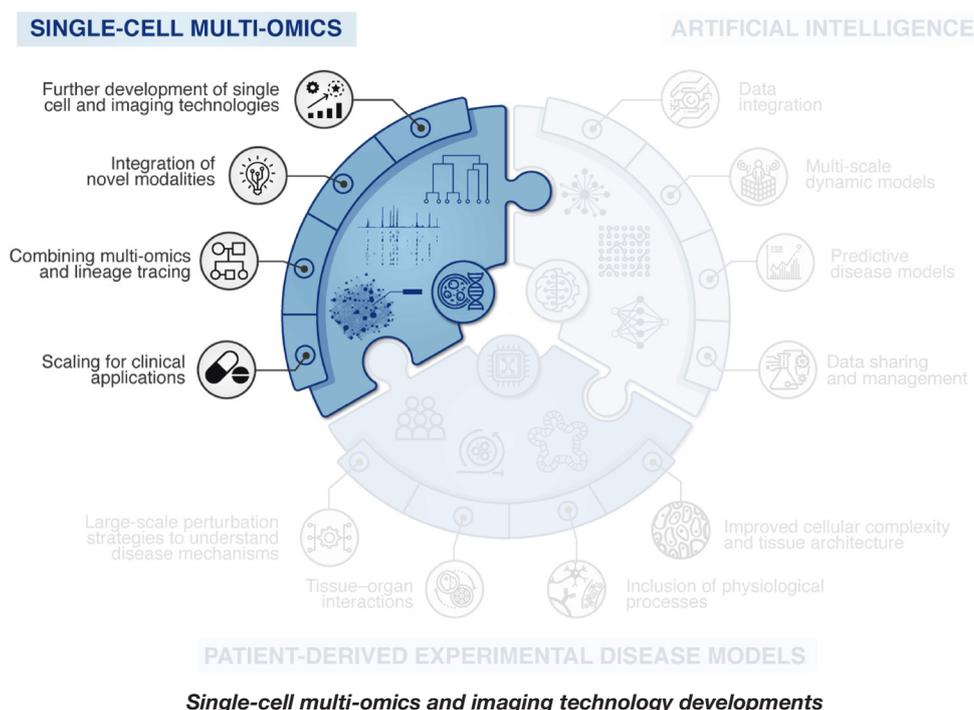
standardised protocols to ensure robustness and reproducibility and assure interoperability of datasets. This will also include reagents, for example establishing antibody standards for spatial proteomic approaches including cell lines for validation and longitudinal normalisation, as well as standardisation of procedures for clinical sample acquisition or recording of the sampling procedure and sample fixation.

Robust clinical sample acquisition and processing

For many diseases, most of the sampled tissue is composed of many “normal” healthy cells, while the cells relevant for pathology can be extremely rare. Major challenges to routinely applying single-cell approaches to clinical samples include the cost and ability to systematically process patient blood samples and tissue biopsies from the site of pathology. Strategies and technologies are required in order to obtain patient material containing high-quality dissociated cells for live processing. This will require development of affordable instrumentation for routine portable/robust acquisition of single-cells in the clinics, for example, new devices for single-cell processing of needle biopsies. Importantly, introduction of single-cell acquisition protocols into clinical procedures will facilitate acquisition of high-quality single-cell samples during routine diagnostic or operation procedures.

Preservation of patient samples (e.g. in single-cell biobanks) maintains the natural state found in a tissue and is required for subsequent sampling and downstream analysis. This will require the development of standardised protocols for cell or nuclei preparation that maintain an unbiased composition and unperturbed state of the tissue.

For patient sample processing, high-throughput microfluidic technologies for enriching specific types of cells will enable sampling of thousands of rare, disease-relevant cells (e.g. circulating tumour cells, circulating immune cells from tissue) routinely from thousands of patients across multiple centres. This will enable longitudinal monitoring of patient disease progression, response to treatment and relapse.



Expected Scientific Impact

In the short term:

Currently available technologies will be used to study disease processes to identify the cell types and pathways involved in disease and develop biomarkers

New technologies will be developed and scaled, so that they can provide additional levels of information that is crucial to understanding disease mechanisms and discovering ways to target the cells involved

Development of instrumentation from prototypes to successful commercial products will be done in partnerships between academia and industry. This should be supported by joint technology development programmes and adoption platforms across Europe ([section 4](#))

As technologies mature and are integrated, Europe should take a lead in benchmarking and setting standards to ensure interoperability

In the long-term:

Innovative multi-omics technologies will be able to profile and map hundreds of thousands of patients' cells for entire patient cohorts. Their scaling should ensure robustness and affordability, so that they can be applied to in-depth analysis of longitudinal human samples

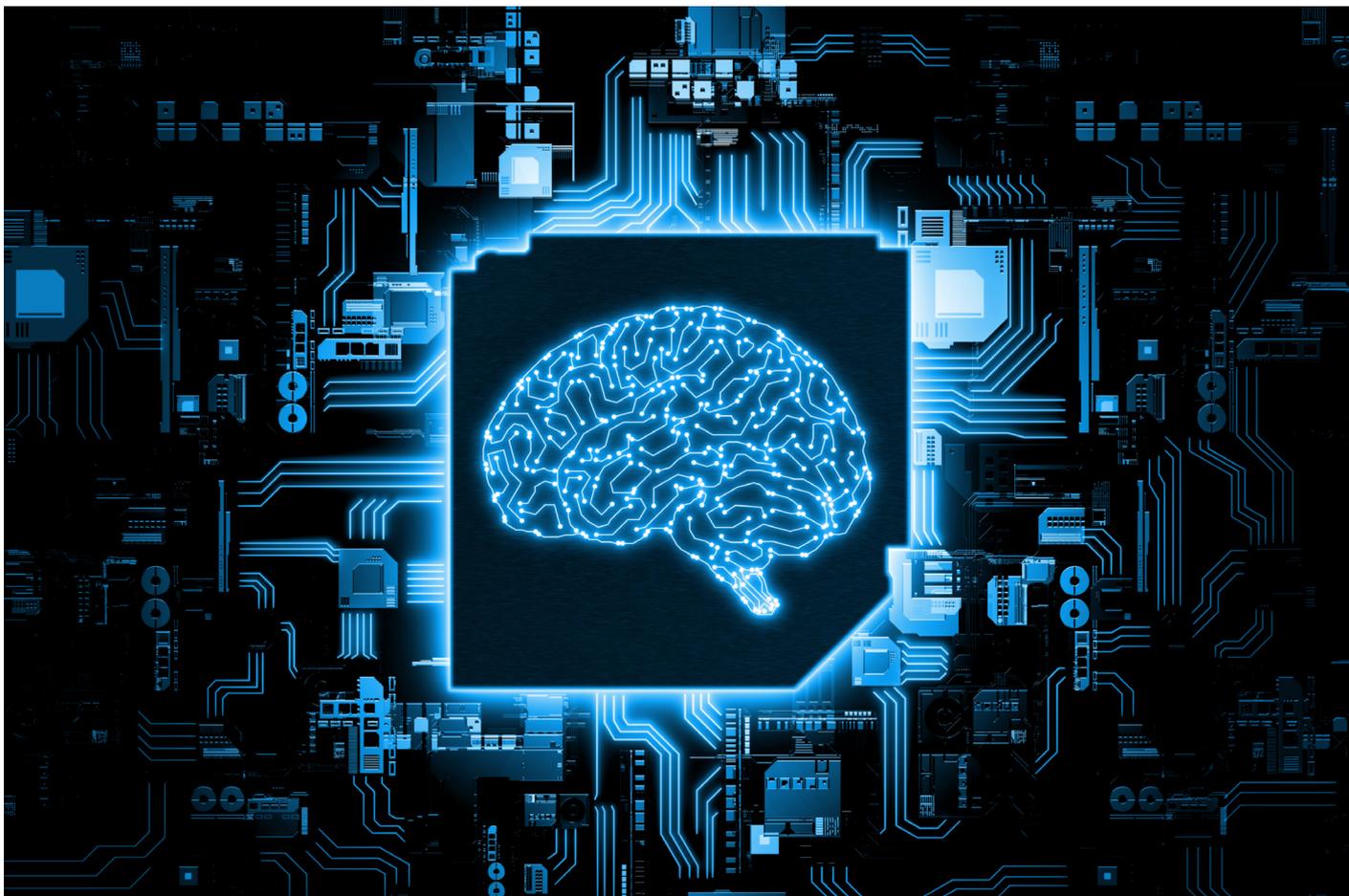
Multi-dimensional descriptors of cell states from patients taken from different stages of disease or therapy will be used to derive new biomarker panels and guide therapeutic strategies. This information for earlier detection of diseases depending on a patient's particular single-cell profile provides a rational way for interceptive medicine

Eventually, these technologies would be incorporated into digital molecular pathology and together with clinical and medical imaging data, the machine learning-based models used to inform physicians

3.1.2 Data Science, Artificial Intelligence and Machine Learning

Data-driven cell-based medicine - the real-time integration of molecular and cellular data generated using cutting-edge technologies with clinical information - will provide critical information for clinicians as they diagnose their patients, transforming healthcare across Europe and globally. Its successful implementation depends on the development of new computational methods - using advances in artificial intelligence, in particular machine learning, to identify complex associations between different molecular features and distinct clinical outcomes. Unlocking the full potential of novel molecular features depends upon access to large amounts of high-quality training data, so that complex patterns can be reliably learnt and their output can be made interpretable for humans. LifeTime's vision is to create the required high-quality big data at unprecedented scale and resolution ([section 3.1.1](#)). These will form the basis for the development of novel predictive computational models of diseases based on changes in thousands of molecular and clinical readouts from hundreds of thousands of individual cells at different stages of health and disease from large cohorts of patients. The derived predictive machine learning-based models will be tested and refined in an iterative manner, by performing systematic large-scale perturbations in patient-derived experimental disease models monitored by single-cell multi-omics and imaging approaches ([section 3.1.1](#) and [3.1.3](#)).

Computational and big data solutions will provide unique opportunities to drive early detection and interception of diseases. They will enable the discovery of unanticipated disease relationships, derivation of novel hypotheses and facilitate making predictions for disease prognosis and optimal therapeutic strategies. To fully exploit the large amounts of molecular health data in infrastructures and national health systems, LifeTime will address key issues of securely storing, sharing, accessing and jointly analysing data across national borders.



LifeTime recommends developments in three main areas, including computational approaches and infrastructure. The state-of-the-art of these areas is briefly described before outlining specific development priorities that are required for data sharing and analysis.

Large-scale data sharing and management. Europe has invested in infrastructures for storing and accessing large scale biological and medical data (e.g. ELIXIR, European Open Science Cloud (EOSC), Federated European Genome-phenome Archive (EGA)). These infrastructures and frameworks provide the foundation for scientists to find and share data, exchange expertise, and define best practices on a European level. Differences in European healthcare systems render accessing and integrating data from Electronic Health Records (EHRs) for research across borders particularly challenging. Data are usually not accessible outside a national, regional clinical care system or specified data 'safe haven'. When data are accessible, accredited systems are often required for storing the data and information governance may be at the hospital, federal or international level. Recent international population and disease specific cohorts such as the UK BioBank, have associated molecular omics data generated at scale and represent an essential bridge to healthcare data. In the future, a flexible ecosystem of computational infrastructures will be required to enable data sharing, access and querying across Europe.

Computational analytics. Artificial intelligence and machine learning are already an integral component for biomedical data science. With the first applications being focused on biomedical images, machine learning is increasingly transforming analysis paradigms for virtually all data types and fields, including genomics, proteomics, metabolomics, imaging, EHR, medical imaging as well as clinical data. Machine learning approaches have been successfully applied to medical imaging where they are able to diagnose disease at a similar level as a clinician, as well as predict the onset of some diseases based on EHR. The field of machine learning is evolving rapidly, where, in particular, methods based on deep neural networks are gaining more and more importance. New developments will be essential for integration, scaling and analysis of different types of data to create predictive models that identify actionable disease features.

Data visualisation and dissemination. Extracting knowledge from complex biomedical data critically depends on the deep integration of algorithms, software, models and statistics, deep learning, and artificial intelligence with visualisation tools. Complex datasets are commonly visualised by projecting them into lower-dimensional spaces, for example using dimensionality reduction methods. As the volume of medically relevant data grows physicians increasingly depend on digital decision support systems to quickly identify the patient's most relevant medical data and patterns, apply the latest medical insights and explore the best treatment options. More advanced forms of these tools will need to be driven by sophisticated machine learning-based approaches on diagnostic and therapeutic data from real patients.

Building on a Fertile European Landscape

Europe is strongly placed to build on pan-European investments in computational infrastructure and computing capacity for biomedicine. The European Bioinformatics Institute (EMBL-EBI) provides central databases, tools and software to align, verify and visualise the diverse data and make that information freely available to all. The EGA is a service for permanent archiving and sharing of all types of personally identifiable genetic and phenotypic data resulting from biomedical research projects. EOSC aims to establish a trusted, virtual, federated environment in Europe to store, share and re-use research data across borders and scientific disciplines. Coordinated infrastructures such as ELIXIR for data, Euro-BioImaging for imaging and EuroHPC and Partnership for Advanced Computing in Europe (PRACE) for high performance computing provide the standards, interoperability strategies and computational power necessary to deliver LifeTime's vision.

Complementary to data infrastructure, initiatives such as the European Laboratory for Learning and Intelligent systems (ELLIS), foster excellence in machine learning research. This provides an excellent basis to develop an ecosystem where innovation at the interface of artificial intelligence and biomedicine in academia and industry can flourish ([section 4](#)). Investment is required to link biomedical research and clinical data and drive application of knowledge for patient benefit and to improve outcomes. European small and medium enterprises (SMEs) are developing tools for downstream functional interpretation and navigation of LifeTime-related data. They include bioinformatics and data science expertise, image analysis, patient omics data-driven medicine, as well as AI-based decision-aiding systems required to integrate and interpret available molecular, cellular, individual disease trajectory and imaging information. Several companies and EU-initiatives are providing solutions for secure and European General Data Protection Regulation (GDPR) compliant data management platforms. These platforms will make derivatives of data, which have been collected and are stored locally at hospitals and institutes, available for consolidation and subsequent AI-based analytics. Together, the European landscape is well positioned to rapidly provide returns on investment and implement data-driven and cell-based medicine within a decade and form a dynamic healthcare ecosystem.



Priorities for Developing Computational Infrastructure and Tools

LifeTime recommends prioritising the below computational developments to address the disease challenges and to enable the derivation of patient specific computational models that can be used to predict disease outcome and guide treatment. Implementation of these recommendations in specific research programmes is described in the individual disease roadmaps ([section 3.2.1 - 3.2.5](#)).

Large-scale Data Sharing and Management

LifeTime has broad infrastructural and data management requirements, encompassing support for methods development, bioinformatics, clinical informatics and imaging and with the assumption that the data conform to the Findable, Accessible, Interoperable and Reusable (FAIR) principles. Consequently, a 'LifeTime ecosystem' of interoperable resources will be required and linked to and expanding on infrastructure that are either available or in development by existing projects (e.g. Human Cell Atlas (HCA), Global Alliance for Genomics and Health (GA4GH)), as well as leveraging investment in European infrastructures (e.g. ELIXIR, EOSC, Federated EGA). LifeTime's data platform will be based on a federated approach with control of the data, especially with respect to clinical data or controlled access data, such as EHR, and is likely to remain within national or federal jurisdictions.

/// Data storage and coordination

Biomedical data sharing has advanced considerably with the creation of large and complex datasets based on single-cell and imaging technologies. These include the development of the Human Cell Atlas Data Coordination Platform (HCA-DCP) - a unified cloud based modular system for single-cell transcriptomic data offering end to end data management and analysis. While the platform appropriately covers biological data management it requires improved integration of clinical and image data. LifeTime therefore recommends the development of a flexible and extensible ecosystem of resources linking existing infrastructures such as ELIXIR and Euro-Biolmaging, Clinical Systems and project specific efforts. This will require significant investment in computing, cloud storage, novel visualisation and query technologies and is an unparalleled opportunity to shape Europe's research data landscape. Optimising cloud usage for analyses, and delivering rapid integration via technologies such as Jupyter NoteBooks will enable access to data in specialised cellular atlases and improve integration with clinical data providing lasting impact by delivery of an extensible ecosystem and by cloud portability of analysis pipelines. As the number of disease atlases increases, these technologies will be extended to a scenario of federated atlases with common semantics and linked to omics datasets.

LifeTime recommends the implementation of common metadata standards to ensure that data are interoperable across technologies and with clinical data such as EHR. The initiative has the potential to generate a resource that has an even greater impact than the Human Protein Atlas (HPA), which provides large scale reference datasets and browsing tools. The HPA has invested significantly in the annotation and presentation of datasets and such investment is required also for LifeTime, to ensure data is accessible by the user community both for analysis and for incorporation into the clinical practice. With the integration

of large and complex datasets LifeTime recommends the inclusion of domain experts to coordinate the acquisition, quality control and curation of data. LifeTime should not only implement but also evolve technical standards for data quality, metadata as well as data sharing, similarly to those recommended by the GA4GH designed to bring omics data and clinical data standards together. These activities will be aligned with the European GDPR.

For controlled access to omics data, LifeTime proposes a federated solution involving local EGA installations using the ELIXIR developed Local EGA infrastructure. A Local EGA can be operated within the GA4GH data security framework and has the potential to be deployed on a secure cloud with GA4GH encryption standards. For LifeTime this will provide the necessary collocated access to the data and to computing, for example at existing high-performance computing facilities or via private clouds. This will address challenges of sharing data across borders by co-locating storage and analysis with data, and enabling federated analyses via common application programme interfaces.

Access to open and controlled data

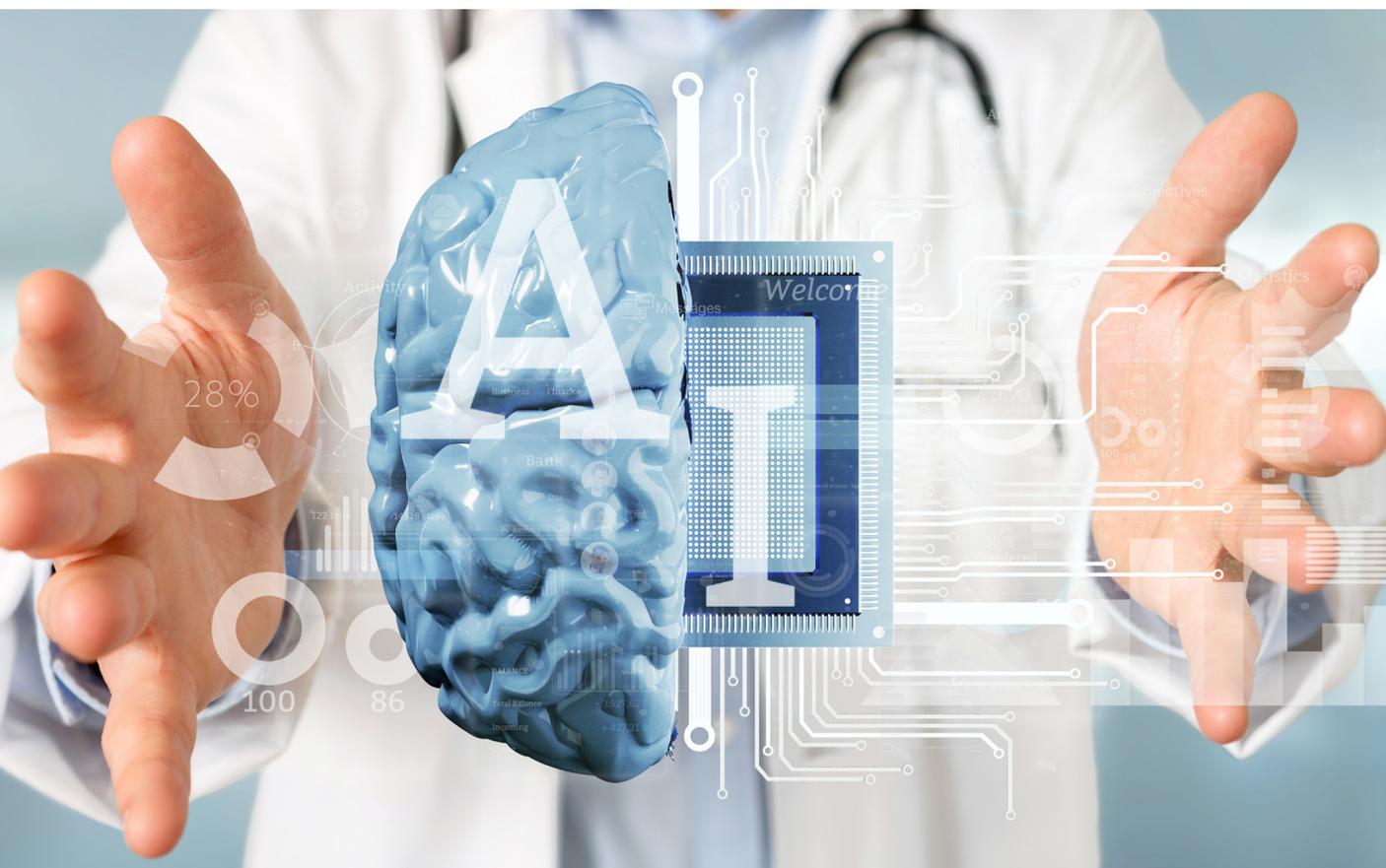
LifeTime's data platform will need to provide access to federated data subject to ethical constraints associated with national and pan-European models. Existing Authorisation, Access and Identification (AAI) protocols such as ELIXIR AAI can be deployed across national platforms and pan-European platforms enabling secure access to health records that typically reside in safe havens, and/or national mandated secured platforms residing in accredited national infrastructures or accredited national or institutional private clouds.



LifeTime provides an exemplar use case for driving European strategy for sharing health data across national borders, as part of the European Commission's Digital Single Market strategy by exploring open EHR exchange standards as a tool for improving portability of data. Such a standard could be driven by LifeTime and data consumed by LifeTime and we identify an opportunity to extend LifeTime's constituency with representatives of the OpenEHR community. Such activities may be considered as part of LifeTime's infrastructure network, though in the short-term access is likely to be within, or transfer of analysis to, pipelines in a secured environment. Where EHR or other health data is accessed within LifeTime, de-identified data can also be supplied for some research questions, using the UK BioBank model of linked clinical data.

/// Federated queries and analyses

European healthcare systems contain large amounts of rich health data. Today it is feasible to collect longitudinal health data on a national as well as cohort scale, which should be used to improve the quality of delivered healthcare. Analysis of this large-scale data by machine learning algorithms requires large training datasets to make accurate new discoveries. Beyond the technical challenges involved in producing such high-dimensional records, there are concerns about re-identification and associated privacy concerns. Regulations addressing access to clinical data necessarily introduce higher security standards, but anonymisation is intrinsically limited when dealing with high dimensional data such as medical records. LifeTime therefore recommends focusing on developing federated learning approaches for training of machine learning models while keeping records in decentralised trusted data warehouses at the hospital, avoiding single points of failure. Standardisation of federated access using minimal data models for harmonisation has been demonstrated in projects such as OSIRIS in cancer genomics. Both OSIRIS and PhenoPackets, a GA4GH standard for phenome/genomic data sharing have the potential to be adopted for cross border data sharing and interoperability with PhenoPacket already used internationally.



Computational Analytics

/// Computational approaches for integrating data from different modalities

While integrating data obtained from different experimental modalities will be extremely powerful to understand the molecular basis of disease, there remain significant challenges. These include the indirect relationships between different types of features (genes, chromatin regions, proteins, metabolites), differing coverage of the data as well as the multi-scale integration of complex datasets. Additionally, approaches are required to link single-cell data across scales, to make clinically relevant predictions on patients and their future health trajectories at the level of organs and patients. LifeTime proposes to focus on developing machine learning principles, such as multi-view learning and variational autoencoders, to project data from different modalities, including both multi-omics and spatial data, onto a common coordinate system, and construct a multi-space similarity measure that takes into account the different omics layers. A major avenue of future research is to derive methods that span different scales and have latent representations for individual cells while simultaneously accounting and modelling patient covariates and clinical variables. Concepts such as transfer learning will be important developments to fill in incomplete missing information from the different molecular layers.

/// Scaling computational analyses to higher dimensional data

Computational scalability and extensibility of computational approaches to cope with unprecedented volumes of single-cell imaging and omics data across large patient cohorts is essential. Currently, most analyses are based on compiling large datasets at a central location where analytical models are trained, which is problematic both for scaling as well as data sharing and privacy reasons. The scale of data that will be generated by LifeTime will foster novel innovations. LifeTime recommends developing modular models and software to support dynamic and online training, directly connected to data influx. The federated nature of European data deposition will require sharing of trained models and training schemes whereby the same models are iteratively refined based on the data available at different locations. Finally, there are important opportunities to compress large-scale datasets into models rather than sharing raw data to promote new modes of collaboration. This model-based dissemination of data proposed by LifeTime, for example using highly parameterised models such as deep neural networks, will permit sharing insights and democratising access to complex insights without the need for users to train these models on local high-performance computing systems and having access to potentially GDPR-protected data.

/// Integration of multi-omics molecular data into electronic health records

Data accessibility and governance have been, and remain, the primary challenges in accessing and integrating data from EHRs for research purposes. To integrate molecular data into health records and present data in a meaningful way to clinicians, LifeTime will address several challenges. These include: i) representing multi-omics data in clinical records, ii) a lack of reference data structures, iii) rapidly changing omics data and different evolution cycles between omics data and clinical standards, iv) lack of data and EHR

relevant standards as well as analysis pipeline execution standardisation, and v) application programming interfaces amenable to clinical data workflows.

LifeTime recommends prioritising the development of tools to process standardised data, such as single-cell data or summaries for inclusion in EHR, in collaboration with clinical information standards bodies such as Health Level Seven International (HL7). Molecular data from LifeTime will be made available via simple and lightweight data sharing tools aligned with the Human Cell Atlas Data Coordination Platform approach. LifeTime will work towards making EHR data formats consistent and interoperable, with a view to cleaning and standardisation of the data required to describe disease progression using machine learning. To address this, the initiative will explore the different standards pioneered by initiatives such as the PhenoPackets proposed by GA4GH to ensure interoperability of data with EHR. PhenoPackets 'packages' genomic information into a standard format, and adheres to the FAIR principles by the use of ontologies to describe individual phenotypes. A data exchange format compatible with Fast Healthcare Interoperability Resources (FHIR) and supporting software libraries could be extended to handling image data and new applications, such as biomarkers based on cellular data. LifeTime recommends this path is followed to leverage the momentum and impact of GA4GH. Projects such as the federated European Health Data and Evidence Network (EHDEN) goes beyond individual records as it provides an effective way of analysing large quantities of data (millions of EHRs). It relies on the Observational Medical Outcomes Partnership (OMOP) model providing a "common data model" for databases to label and structure their data consistently.

Generating predictive models based on patients' cellular trajectories

Cell-based medicine involves the longitudinal sampling of patients. This requires integration of additional dynamic information into computational approaches for inferring continuous changes in cell types and states across disease and time. To infer additional information on cellular trajectories during disease onset and progression LifeTime recommends incorporating extra information such as multiple modalities, experimental time and spatial information. This will provide a more complete picture of cell transitions and lineage relationships. Creating predictive trajectory models requires additional information on directionality and dynamics such as that provided by sampling and temporal information, lineage tracing, and information on the dynamics of biochemical reactions. Such predictive models will infer future dynamics from observed data, combining sparse and incompletely sampled data at multiple time points with adequate models of uncertainty.

With a particular focus on spatial multi-omics approaches ([section 3.1.1](#)) LifeTime recommends developing computational tools to combine information from several time points as well as multiple patient samples with lineage tracing and multi-modal, including spatial, readouts. Functional single-cell readouts from spatial omics approaches such as morphometries could be used to determine cell state and transitions across lineages, these would improve lineage reconstruction and produce more accurate trajectories.

To robustly identify and annotate the resulting cell dynamics, it is paramount to be able to map to a reference atlas as for example generated in healthy subjects within the Human Cell Atlas project using machine learning and deep learning-based projection methods. These data integration tasks need to be sufficiently constrained to guarantee that disease states are not regressed out and thus need to be benchmarked accordingly.

Differentially comparing cellular trajectories between cells in a tissue, between organs or between individuals through time will require not only method transfer from the field of time series analysis (such as change point detection) but also the use of a coordinate system, as proposed by the Human Cell Atlas. This will be challenging, since various factors (e.g. age, height, gender) can lead to differences in an organ's morphology, making mapping onto a common template challenging. LifeTime recommends leveraging machine learning methods to account for covariates to robustly describe the underlying integrated latent space.

Establishing causality for molecular mechanisms

Modelling disease progression based on longitudinal cellular readouts will not only enable predictions but also enable discovery of the underlying molecular mechanisms. While the proposed machine and deep learning techniques allow for the scalable and robust incorporation of variation across samples, the resulting network architectures make interpretation of the sources of variation difficult. LifeTime proposes to address this limitation by going beyond pure statistical approaches and constrain the networks towards interpretable models, which will be key for explainable AI-based approaches to be accepted for clinical use. This would include backpropagating variation in classification in supervised learning, or incorporation of mechanistic models in the network and extend these tools to the mostly unsupervised and non-localised/convolutional



methods employed in single-cell omics. This will reveal sets that jointly explain certain variation and hence fully data-driven pathways, which will be complemented by traditional annotation-based efforts. Integrating learned trajectories, time series information with spatial structure, will identify gene regulatory motifs and causal networks, cell-cell interaction graphs and dynamic transitions affecting disease. Enriching inference methods with epigenomic data will lead to interpretable disease regulatory motifs that can be translated to more effective treatments.

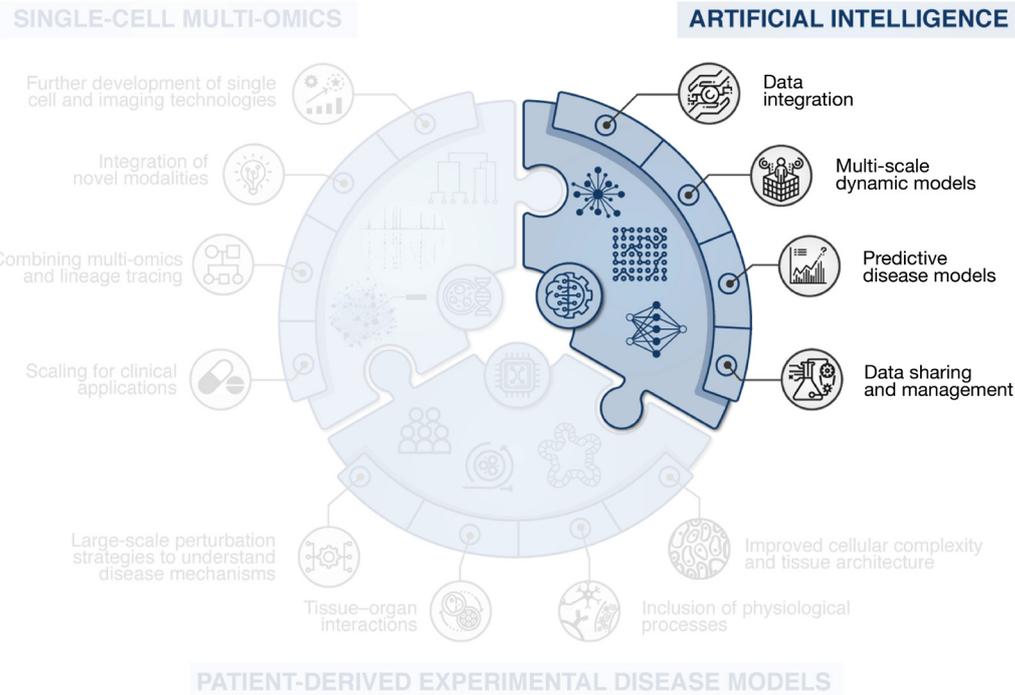
The resulting molecular mechanisms will need to be integrated within a multi-scale model of a patient, to address tissue, organ and organism-level covariates beyond a purely statistical setting. Multi-scale models of organs, generated by integrating information from tissues, cells and molecules, will simulate the dynamic interplay of factors during disease progression and treatment. LifeTime will develop the needed computational frameworks to integrate machine learning and multi-scale modelling to identify causality by modelling molecular mechanisms and predicting their effects at the tissue, organ or system level.

Validation and benchmarking computational tools

Ensuring comparability between multiple analyses will require validation and benchmarking of computational approaches. Through LifeTime, Europe is well placed to implement standardised benchmarks for datasets and methods needed for data-driven medicine. LifeTime recommends defining datasets (where possible with known ground truth) and metrics for systematic benchmarking of the developed methods. This includes defining which aspects of analysis can be performed using common strategies across multiple biological contexts and which require genuine context-specific tools. The initiative will drive the identification of more



accurate metrics for assessing the quality, robustness and impact of different computational strategies on downstream biological inference to be implemented in clinical settings. These metrics will include self-consistency under subsampling, robustness with respect to outliers and noise, performance on gold standard data sets or more broadly identification of independently validated medical knowledge. LifeTime recommends promoting the regular development of such standards as well as open community-based competitions, also involving industry ([section 4](#)), which could lead to benchmarks - similarly hackathons and other community efforts could be leveraged to build compatible and “best-of” computational pipelines. LifeTime will ensure that such benchmarking will be done in collaboration with related initiatives such as the GA4GH and Human Cell Atlas.



Computational, artificial intelligence, machine learning developments

Data Visualisation and Dissemination

The outputs from large-scale machine learning and mechanistic models may be difficult to interpret. A key challenge is developing intuitive, comprehensible visualisation and dissemination tools and strategies that are useful to all user groups including computational and experimental researchers as well as clinicians to facilitate better diagnoses and treatment.

Complex datasets are commonly visualised by projecting them into lower-dimensional spaces, for example using dimensionality reduction and latent-space learning methods. These approaches provide accessible entry points for practitioners and non-experts to explore the complexity of data and gain insights. Resources and computation infrastructures that provide such functionality and then allow mapping model results on top of the raw data are critical to enable data and models to be widely used in the community. LifeTime recommends building upon existing efforts and in particular existing portal infrastructures and systems developed in the context of the Human Cell Atlas and other efforts. This approach will ensure that LifeTime visualisation is closely interlinked and connected to existing infrastructures, such as the bio data resources offered by the European Bioinformatics Institute. This will require approaches for the visualisation and connection of spatial omics data together with genomic data and modelling results, thereby connecting mutational, genomic and epigenomic data to tissues and their two-dimensional and three-dimensional makeup.

LifeTime recommends working closely with clinicians to create the next-generation clinical support systems to produce new AI-based decision-aiding systems that will integrate and interpret available molecular, cellular, individual disease trajectory and imaging information. Using interpretable and accountable AI systems will also provide the basis for the predictive models and clinical recommendations. Simple dashboards will enable these clinical teams to exploit data produced during the patient journey, from the patient narrative to rich imaging and genomic data. They should highlight predictive scenarios as well as actionable targets identified by modelling, as well as link these targets to available clinical performance indicators. Alongside dashboards, browsers capable of handling genomes as graphs, such as those used by the 1+ Million Genomes Initiative, would enable population genomics. These approaches will provide new medical knowledge and be used for visual purposes or as the foundation for tools such as decision support systems.

Expected Scientific Impact

In the short term:

Machine learning methods for single-cell data analysis and integration will be accessible to a wider community for broad application.

Newly developed methods will translate disparate European datasets from diverse samples into mechanistic insights of disease.

Standardisation and sharing of data by openly releasing datasets via a federated approach that is FAIR and can be computationally treated from different locations across Europe.

Standardised common formats for incorporating molecular data into EHR.

Implementation of benchmarked methods with different standard datasets and in different scenarios in clinical settings.

Integration of existing infrastructures by promoting an ecosystem of data resources with common standards and cloud portability. Scaling beyond traditional approaches and hybrid architectures will be ideal for data-driven analyses.

In the long-term:

Scaling of newly developed methods and visualisation tools to very large federated cohort datasets to enable the detection of early onset of disease and inform medical doctors of the best possible treatment not only for the specific disease but also for the current status of the disease in the specific patient.

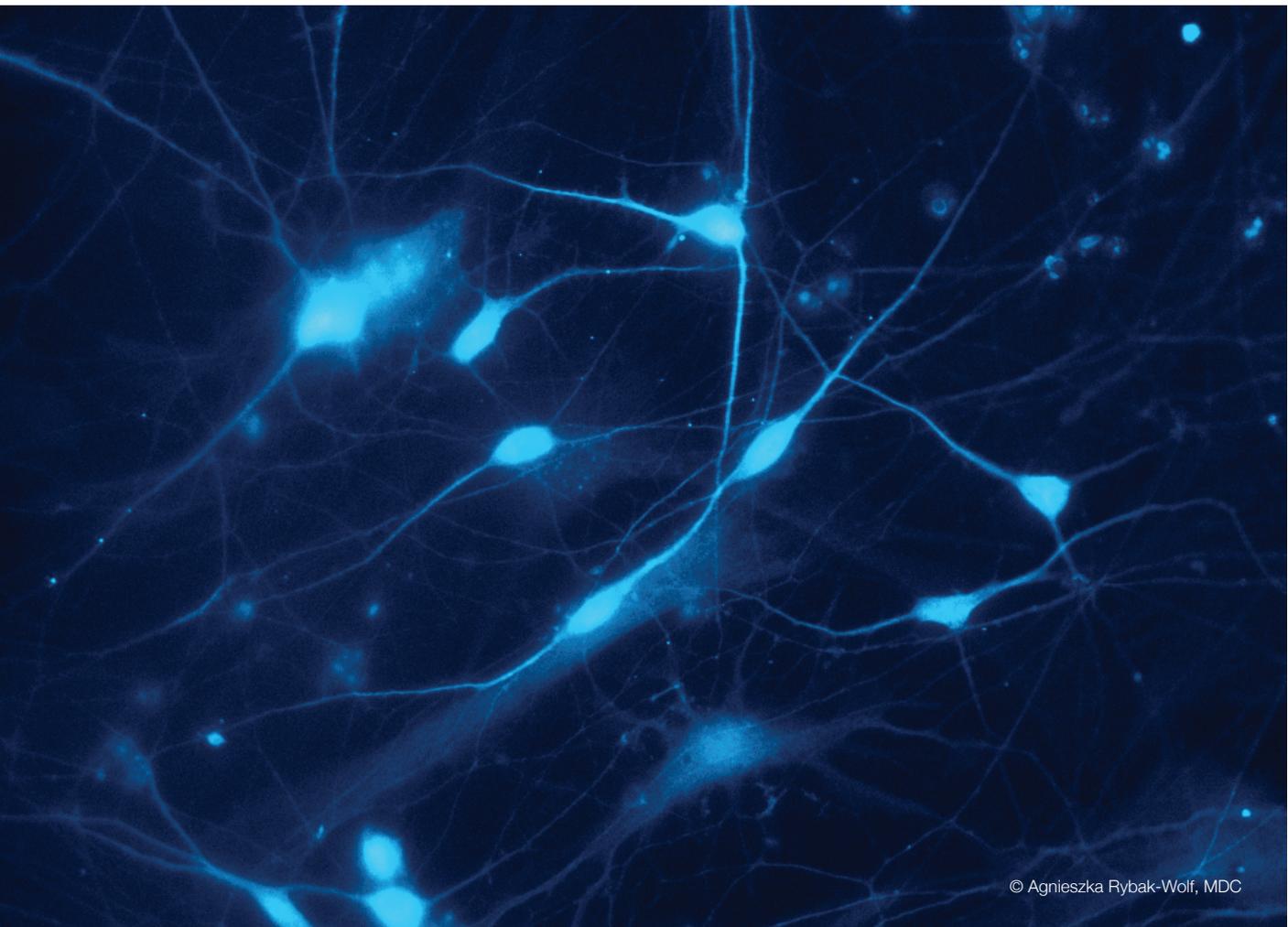
Accurate machine learning approaches to enable multi-scale models of disease in patients to make data-driven decisions on treatment.

Inclusion of novel resources into the infrastructure ecosystem to enable users to access and analyse large datasets relying on federated approaches for the benefit of patients. Such distributed learning models will need to be processed in near real-time.

3.1.3 Patient-derived Experimental Disease Models

Patient-derived experimental disease models are cell or organism-based systems that recapitulate the pathophysiological processes involved in disease. As they are derived from adult, pluripotent human stem cells or tissues, and can capture individual features that are unique to each patient. Importantly, by comparing patient-derived models from diseased and healthy individuals, unique features can be extracted even without knowing the specific genetic cause of the disease. They are especially important for studying diseases where repeated acquisition of patient tissues is limited or impossible, for instance for neurological disorders or cardiovascular disease, or genetic disorders that are caused by combinations of many unknown genes. Developing these key technologies will provide a range of models that reflect human biology and pathophysiology as closely as possible. Together with single-cell multi-omics and imaging ([section 3.1.1](#)) and large-scale genetic and molecular perturbations they will be used to understand disease mechanisms and iteratively test machine learning-based predictive computational models ([section 3.1.2](#)) that predict outcomes or most effective treatments for an individual patient.

Patient-derived models will have a major impact on the understanding of disease mechanisms. They will help discover new drug targets based on identifying the molecular cause of disease, new concepts for cell-based therapies as well as more accurately predict potential drug toxicity. Developing biobanks of patient-derived models will lead to new concepts for screening platforms that cover a wide range of the worldwide population genetic variance. Functioning as patient ‘avatars’ they will be tools for predicting disease prognosis and testing tailored therapeutic strategies and drug combinations on patients cells before administering them.



LifeTime recommends developments in three main technology areas. The state-of-the-art of these areas are briefly described before outlining specific development priorities required to create the necessary patient-derived disease model technologies and tools for cell-based medicine:

/// Patient-derived organoids. Organoids are emerging multi-cellular three-dimensional experimental systems that model aspects of organ development, regeneration and pathophysiology. Derived from adult or pluripotent human stem cells, they have been created for most healthy tissues, as well as from diseased tissue e.g. tumours. Organoids have tremendous potential for disease research, especially for organs such as the brain where key developmental and physiological processes can only be studied in a human setting as well as enabling routine genetic analysis in human tissues. They can be used to characterise potential disease risk factors, disease specific cell types, disease-specific molecular changes and mechanistic analysis in human tissues, bridging gaps between biological research and medicine. Therapeutically, patient-derived organoids have been also used to test the likelihood with which a patient will respond to a given therapy. Further development of organoids is required in order to more faithfully recapitulate key physiological features in human tissues and to understand more precisely disease processes and mechanisms.

/// Advanced animal models containing human genes and cells. *In vivo* model systems such as patient-derived xenografts (PDXs) and genetically engineered mouse models are necessary to translate the science from bench to bedside. They are important for understanding 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. Additionally, these models capture the cellular heterogeneity required to understand disease progression and therapy response, which is not possible in many *in vitro* systems. Advanced models are required that more closely represent specific disease processes in humans and will be used in parallel with animal-free research until *in vitro* models are sufficiently developed to reduce their use.

/// Large-scale perturbation tools. Understanding the molecular causes of disease in a personalised manner in human tissues will require the development of tools for systematically perturbing molecules in disease models and analysing their consequences on the single-cell level. These include both genetic (CRISPR-Cas) and pharmacological inhibitors (e.g. small molecules or next-generation therapeutics such as conjugated antibodies or protein degradation agents) combined with single-cell multi-omics approaches and imaging or lineage tracing.

Building on a Fertile European Landscape

Europe is well placed to develop and implement next generation patient-derived disease models in cell-based medicine. The recent surge in the development and use of patient-derived models, especially organoid systems, has been driven by European research groups. This includes the development of these models to study normal physiological and developmental processes, disease mechanisms and pre-clinical applications. Europe has invested in large-scale infrastructure with the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-ERIC) which links over 600 biobanks across Europe and facilitate the use of disease models and standards as well as the EuroPDX initiative which facilitates the exchange of disease models and avoids duplication in pre-clinical cancer research. Europe also has a dynamic ecosystem of SMEs involved in the standardised production and maintenance of organoid collections of different organs and diseases for drug discovery screens, drug and companion diagnostics development and pre-clinical patient stratification. Investment in European expertise and know-how would enable a coordinated effort to further develop these models, standardise and scale them to be routinely used for precision medicine. Research is required into the fundamental biology of these models and how they can be improved, which should happen hand-in-hand with model development and integration with single-cell multi-omics and imaging technologies.



Priorities for Developing Next-generation Patient-derived Experimental Disease Models

LifeTime has identified five priorities for developing next-generation patient-derived disease models. Implementation of these recommendations and integration with other technologies are described in specific research programmes in the individual disease roadmaps ([section 3.2.1 - 3.2.5](#)).

Increasing cellular, structural and functional complexity of organoids

Organoids are derived from homogenous cell populations that are directed into specific lineages using a variety of signalling molecules that are present in the *in vivo* tissue environment. Despite their potential, they need to be extended to create tissues from multiple distinct origins and contain the full complement of organ-specific cell types. Currently, they are typically more representative of fetal rather than mature tissues. LifeTime recommends increasing the complexity and maturity of organoids to create improved pre-clinical models and enable the further understanding of disease mechanisms. More precise control of tissue structures will require the development of more complex and manipulatable extracellular matrices, tissue engineering approaches such as biofabrication and synthetic biology. Increasing the reproducibility and cellular complexity of organoids needs more accurate spatial and temporal control of signalling pathways to better mimic the intracellular microenvironment.

Organoids lack many key features of tissues such as the presence of nerves, blood vessels, immune cells and microbes. These are key to understanding various aspects of neurological, cardiovascular, chronic inflammatory and infectious diseases, cancer as well as precision immunotherapies. LifeTime recommends establishing coculture systems where relevant progenitors are incorporated into the organoids at precise times during development. Engineered vasculature systems will need to be developed to facilitate diffusion of oxygen and nutrients. Microfluidic based systems to apply mechanical forces such as fluid shear stress and solid mechanical forces are required for full maturation of certain tissues. Studying disease mechanisms will require establishing protocols and careful benchmarking to ensure that different types of organoids can be studied using single-cell multi-omics, spatial and imaging technologies ([section 3.1.1](#)).

Organoid integration to study tissue-tissue and organ-organ interactions

Many disease relevant biological processes involve interactions between different tissues or organs. Modelling these processes will require the integration of different organoids. For example, the assembly of organoids from different regions of the brain (assembloids) to recapitulate mature functional circuits that may be perturbed in neurological or neurodevelopmental disorders. LifeTime recommends expansion of those technologies towards the reconstruction of major functional brain circuits are required for further insight into neuropsychiatric diseases. Fusion of organoids resembling different interacting organs and engineered tissues will allow the assembly of functional units of organs and create distinct microenvironments. For example, the multi-layered alveolar–capillary unit in the lung, which is composed of closely interacting alveolar epithelial cells and pulmonary microvascular endothelial cells which interact with air and blood to study respiratory infections. Likewise, fusion of organoid systems resembling heart muscle and blood

vessels will allow for unprecedented modelling of cardiovascular diseases. Such bioengineered systems enable the introduction of physiologically important mechanical or shear stress of fluid flow forces required to mature organoids. Since many diseases involve dynamic systemic interactions between different organs, microfluidic-based platforms will connect different organoids to simulate multi-organ interactions. Such structured organoids require novel microchip concepts that account for the stereotypical organisation of organoids and the incorporation of real-time monitoring of single-cells in the tissue context using for example electrodes for electrophysiological recordings, cell-cell interactions and metabolic processes in tissues.

Standardisation, automation, scaling and benchmarking of organoid propagation and banking

Generation of organoids is currently based on manual laboratory procedures that result in extensive inter-organoid variability. Although this allows for remarkable precision in recapitulation of endogenous processes, more reproducible and robust three-dimensional structures are required. In partnership with industry ([section 4](#)), LifeTime proposes establishing common guidelines and common practices for different tissues and organs. Scaling of organoidogenesis requires automation, optimisation of protocols and microengineering and miniaturisation of procedures and assays to reduce costs, this will require use of robotic cell handlers, three-dimensional bioprinting and microfluidic chips. To reduce costs of longitudinal single-cell multi-omics profiling of patient-derived organoid cohorts or genome-wide perturbation studies, LifeTime proposes the development of strategies for multiplexing of samples. Standardised protocols will need to be benchmarked against cell type composition of healthy tissues based on current atlas studies of healthy tissues such as the Human Cell Atlas, using several single-cell based technologies. Standardised protocols for biobanking and recovery will be developed in collaboration with BBMRI-ERIC to ensure quality control checks, so samples are comparable across different countries, facilitating reproducible and reliable data.



Advanced animal models for studying human pathophysiology and therapy response

Studying specific disease related processes that cannot be easily recapitulated in organoids will require models in which patient-derived tissues are integrated into *in vivo* models. For example, differences in the immune system between humans and mice means that successful engraftment of PDXs requires the use of immunocompromised organisms, which prohibits studying the tumour microenvironment and human-specific therapy such as immunotherapy. To overcome this limitation, LifeTime proposes developing models with an intact/functional human immune system. Mice with induced pluripotent stem cell-derived xenografted human cells will be important pre-clinical models for studying interactions between these cell types and neurodegenerative pathologies associated with human proteins over longer periods of time. Alternatively, neurodegenerative disorders could be modelled under physiological conditions by engrafting human brain organoids into an adult immunodeficient mouse brain. These would contain key human cell types, functional neuronal networks, blood vessels and have the potential to model sensory inputs. Investment is required in advanced animal models for different disease applications that faithfully reflect human population dynamics, cellular heterogeneity, disease risk factors, age, lifestyle and chronic environmental exposures.

LifeTime also recommends developing models to study early events in disease such as for example mechanisms involved in tumour initiation, early tumour development or early biochemical alterations in Alzheimer's disease when clinical symptoms are not yet present and dementia can still be prevented. Precise modelling of disease progression requires replicating the natural course of events, for example for cancer, ranging from tumour initiation to metastatic outgrowth or the inflammatory response in Alzheimer's disease. Studying the early events in disease onset will require the further development of Genetically Engineered Models (GEMs). CRISPR-Cas systems have great potential incorporating human alleles, loci or pathways to study diseases. These will be particularly important for modelling human disease for personalised medicine to address the great variability between individuals, including response to treatment and clinical trajectories.

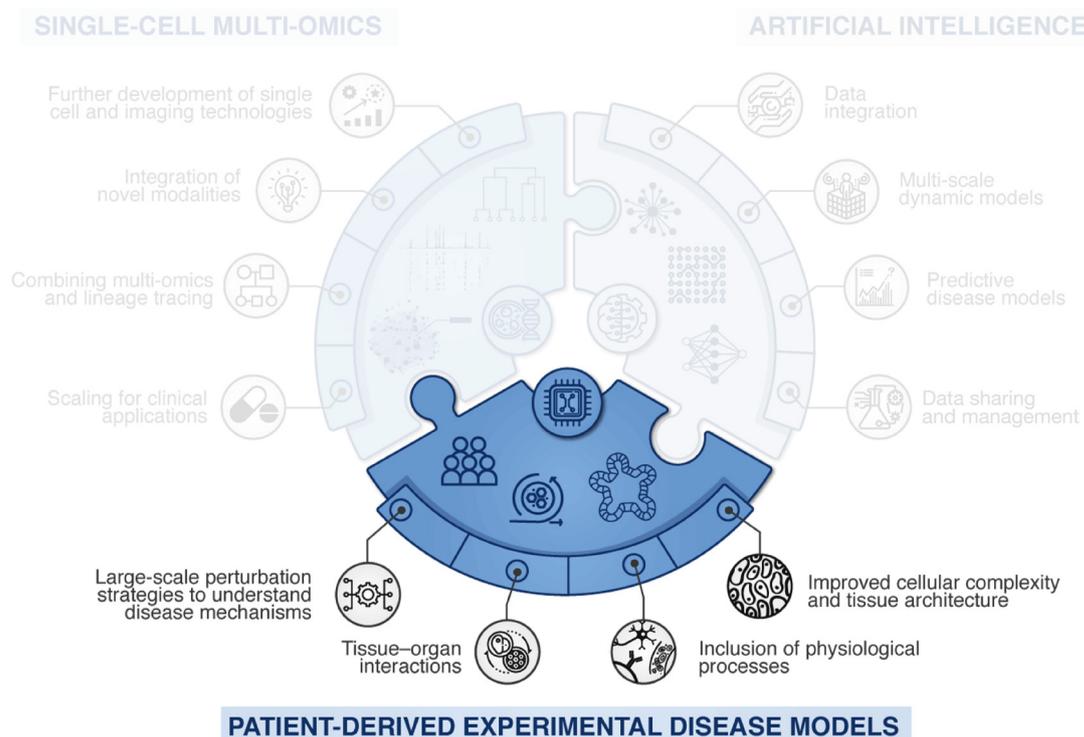
Adaptation of technologies will be required to study disease processes in these next-generation models such as expanding intravital imaging to all tissue sites and techniques that allow for quantitative dynamic information *in vivo*, such as lattice-light sheet microscopy, or single-cell sequencing-based methods ([section 3.1.1](#)). Development of imaging-based spatial multi-omics will capture spatial relationships and cellular heterogeneity and cell-cell interactions within intact tissues at single-cell resolution.

Large-scale perturbation tools to establish causality in model organisms

Understanding the causes of disease requires integration of new methods for large-scale perturbation experiments. These involve reducing the levels or activity of specific molecules in advanced disease models and monitoring the consequences on disease processes. Large-scale perturbation screens have been described in using CRISPR-Cas technologies with a single-cell transcriptome readout. LifeTime proposes to develop strategies for combinations of perturbations to reveal biological mechanisms that are controlled by parallel processes. Also tools are required for the targeted perturbation of the human epigenome and of protein signalling pathways to determine cause and effect among these highly interconnected layers. Large-

scale perturbation screens will profit from the development of high-throughput sequencing- and imaging-based multi-omics assays, especially those that can provide single-cell and spatial resolution ([section 3.1.1](#)), and testing predictive computational models ([section 3.1.2](#)). Moreover, CRISPR-based methods for lineage-tracing and molecular recording of cellular events and environmental exposures (including the storage of transcriptional events into the genome) will make it possible to capture each cell's developmental history, its present regulatory state, and its epigenetic potential for future plasticity.

Large-scale perturbation experiments, in combination with elements of synthetic biology, have the potential to accelerate the development of cell-based therapies, both in cancer immunotherapy and regenerative medicine, for example by enabling the rational, data-driven design of application-specific gene-regulatory networks. Clinical trials provide a rigorous, standardised path for the clinical validation of novel therapies. Unfortunately, a large percentage of clinical trials fail to reach their primary endpoint, often for unclear reasons. To improve insight into the molecular basis for success or failure of clinical trials (especially phase I/II) LifeTime recommends reproducing them in suitable experimental disease models including patient-derived organoids together with single-cell technologies and high-throughput perturbation analyses.



Patient-derived experimental disease model technology developments

Expected Scientific Impact

In the short term:

Currently available disease models will be used to study disease processes with established single-cell technologies, which will provide insights into cell types and pathways involved in disease

Generation of next-generation disease models containing increased complexity of cell types and containing tissue elements e.g. vasculature and immune system components or tissue engineering to study respiratory infections in the lung, that are key to addressing the disease challenges

Standardisation, automation and scaling of patient-derived disease models to create the required large cohort scale model biobanks and for perturbation screens



In the long-term:

Patient-derived disease models will be required at scale to be able to understand the patient-to-patient heterogeneity in mechanisms underlying disease

Disease models and iterative large-scale perturbations will be used to test and train machine learning derived predictive computational models of disease to increase their accuracy

Avatars of patient-derived material disease models will be used to test therapeutic strategies based on predictions from machine learning-based computational models

3.2 Solving Medical Challenges - Disease Roadmaps

3.2.1 Cancer

Medical Challenge

Cancer will kill almost 2 million citizens in Europe every year. It affects everyone regardless of age, gender or social status and represents a tremendous burden for patients, families and societies at large. Almost half of cancers are diagnosed after 65 years and, considering the ageing European population, a tidal wave of cancer cases will sweep across Europe within the next decades. If no further action is taken, the number of people newly diagnosed with cancer every year in Europe will increase from the current 4.2 million to 5.2 million by 2040. Preventing such an increase, as a minimum goal, would require a 0.75% annual reduction in risk and 1% reduction in risk of death. Such challenges call for coordinated European efforts, rational strategies, implementation of new structures and interdisciplinary research initiatives that are able to address major challenges in cancer diagnostics and treatment.

Cancer is a broad medical field with hundreds of individual tumour types, each with their own clinical presentations, molecular portraits, diagnostic and treatment strategies and prognostic outlook. Nevertheless, there are critical knowledge gaps that are common for all cancer entities, including early dissemination and therapy resistance. Metastatic dissemination of a subpopulation of cancer cells is a leading cause of death in almost all cancer types. Successful treatment of advanced and metastasised forms of cancer remain difficult, despite the development of targeted therapies and immunotherapies, due to the emergence of drug or therapy resistance.

Although tumours originate as single-cells, during disease progression some cells accumulate mutations and/or epigenetic changes to evolve into spatially and temporally distinct lineages and subclonal populations. These changes lead to intratumour cellular heterogeneity (the specific cell types and states involved) which contributes to early dissemination with subsequent metastasis and the development of therapy resistance. Until recently there has been a lack of technologies that are able to resolve the underlying mechanisms, the role of cellular heterogeneity as well as the complex interactions between cancer cells and the tumour microenvironment and metastatic niche. This level of complexity can be deconvolved using a combination of single-cell technologies providing cellular spatial resolution, machine learning and patient-derived disease models.

Driven by cancer genomics, technologies to resolve cellular heterogeneity and molecular risk stratification, the cancer field has been a "first mover" in the precision medicine field. Cancer can, therefore, serve as a template for other diseases. Identifying cancer at the earliest stage possible will enable **interception of the disease** before it becomes too advanced or spreads via dissemination and metastasis. A European strategy for early cancer detection and interception of small tumours curable by surgery +/- radiotherapy as

well as/or tailored drugs will **increase survival of European citizens**. Alongside prevention strategies, this will require implementation of new translational research strategies focused on identification and targeting of the driving cancer cell population(s).

To address the **key challenge of cancer spread**, LifeTime's approach should address the following medical challenges to provide the greatest impact for cancer patients in the next decade:

Understanding the cell types and states - malignant cells and their microenvironment - involved in early stages of cancer dissemination

Understanding the reprogramming of cellular states during disease and their impact on therapy resistance

Cancer Roadmap

LifeTime proposes the following objectives to deliver an understanding of tumour evolution leading to dissemination and therapy resistance of cancer cells:

- Define the cell types and states involved in early cancer dissemination using patient biomaterial (tissue and liquid biopsies) and pre-clinical models (patient-derived organoids and advanced animal models)**
- Understand the molecular mechanisms and reprogramming events underlying cellular diversity and acquisition of properties essential for disease progression (including metastatic dissemination) and the development of therapy resistance with temporal and spatial resolution. Use this knowledge to generate new single-cell based molecular and cellular biomarkers for early disease detection and interception**
- Integrate clinical phenotypes (responders versus non-responders as well as metastasis versus primary tumours) with molecular mechanisms, using machine learning to generate *in silico* models of cancer progression, metastasis and relapse to guide therapy selection and treatment**

Addressing these objectives will enable: i) the stratification of patients based on biomarkers derived from disease mechanisms in single-cells; ii) early disease detection and prediction of disease prognosis for an individual patient; iii) the systematic identification of key molecules/pathways for drug targeting and/or repurposing and development of effective, preventive or early interception treatments. Together, these insights will enable newly designed clinical trials by bridging clinical with molecular/cellular endpoints and therapeutic approaches on the basis of validated patient-specific disease mechanisms. For this roadmap, LifeTime's expected impact on breast cancer is used as a specific showcase example, but similar impact has been identified for colorectal and pediatric cancer, melanoma, glioblastoma and acute leukemia in the broad field of cancer.

Development and integration of novel multi-omics approaches with machine learning to reveal mechanisms involved in early cancer dissemination and therapy resistance

Understanding underlying molecular mechanisms requires the integration of information from different molecular networks as well as the functional importance of cellular location, cell-cell interactions and the tumour environment. LifeTime proposes prioritising the development and integration of several spatial-based multi-omics single-cell technologies ([section 3.1.1](#)) to provide a longitudinal view of the changes involved in early dissemination and resistance mechanisms of aggressive and deadly cancers. The important role of signalling pathways, metabolism and interactions of cancer cells with immune cells, stromal cells and vascular cells in the tumour microenvironment requires advances and integration of imaging and sequencing-based spatial transcriptomics/ genomics with proteomics and metabolomics. This will be done in combination with advanced methodologies for non-invasive live-cell imaging of disease models at subcellular resolution (light-sheet and multi-photon microscopy). Linking these molecular data with clinical data-sets and medical imaging modalities (i.e. radiomics) will provide insight into patient outcomes.

These technologies and new machine learning approaches ([section 3.1.2](#)) will go beyond gene expression programmes and substantially enrich mechanistic insights. They will begin to generate new predictive models for disease based on cell states and trajectories for disease interception. Discovery of the relevant biomarkers, cell types and their molecular characteristics for innovative targeted and immunotherapeutic treatment approaches will most likely provide a new level of treatment efficacy compared to current precision oncology approaches. These approaches would be validated immediately in new clinical trials and also initiate a new level of digital molecular pathology, based on spatial multi-omics, as the resulting information and models can be provided to clinicians to help guide decision making.

Development of advanced patient-derived cancer models

Obtaining longitudinal tumour tissue samples is challenging. Therefore, LifeTime proposes a particular focus on deriving advanced patient-derived models for major cancer entities, which can also be used to investigate underlying disease mechanisms ([section 3.1.3](#)), using newly developed single-cell and machine learning approaches ([section 3.1.1](#) and [3.1.2](#)). More representative patient-derived organoids or human-on-chip models require increased cellular complexity, to ensure that all key cell types are represented including tumour cells, stromal cells, immune cells and vascular cells with predictable spatial organisation and accurate cell-cell interactions. The need for vascularisation will require the use of microfluidic systems and long-term culture. Protocols that model different tumour microenvironments and metastatic niches (i.e. bone marrow, liver, brain or lung) must be developed to recapture cell-cell interactions in the respective environments. Longitudinal drug response measurements require the development of human-on-a-chip methodologies, in which organoids are grown within 3D-scaffold in proximity to niche cells. Disease models should be developed in conjunction with strategies to implement large-scale perturbation screens (e.g. CRISPR-Cas, small molecule) with single-cell multi-omics readouts and lineage tracing to understand causation in resistance and dissemination mechanisms ([section 3.1.1](#) and [3.1.3](#)).

These advanced models will not only serve as a driving force for understanding cancer metastasis and resistance mechanisms but are required to close the gap between basic research and translation of these findings into the clinics. They will also enable optimisation of therapies, where applicable, by testing tailored strategies and therapy combinations for individual patients.

Longitudinal studies using patient cohorts and advanced disease models to understand tumour resistance and identify new drug targets

Understanding diversity in individual patient disease trajectories will require complementary studies using non-invasive liquid biopsies and newly developed patient-derived disease models. These will be generated from samples of patients obtained from clinical trial cohorts, that either respond or not to new treatments. These large-scale cohorts will be investigated using the newly developed, benchmarked and standardised imaging and sequencing-based multi-omics technologies (described above and [section 3.1.1](#)), and integrated with clinical and medical imaging data. In the process, the large high-quality datasets will be generated that are required for predictive computational models using machine learning algorithms ([section 3.1.2](#)) for early disease detection, interception and identification of novel mechanism-based drug-targets. Disease mechanisms and new potential drug targets will be studied using a combination of classical chemotherapy, molecular and immunotherapeutic approaches as well as novel large-scale CRISPR and small molecule screens in newly developed disease models.

Identified biomarkers will enable the stratification of patients based on the underlying disease mechanism. New modes of digital molecular pathology based on single-cell and machine learning approaches will create predictive models that will facilitate the selection of treatments for individuals. Where the disease course allows these treatments will be first tested in patient-derived model 'avatars' to ensure the required therapeutic response. Based on these models the portfolio of druggable targets will be systematically expanded targeting the driving cancer cell populations and subsequently lead to more efficient combination therapies.

Validation of biomarkers for patient stratification, disease interception and prevention in newly designed clinical trials

Promising new therapies would be tested in relevant and accurate models, allowing fast translation to the clinics for stratified groups of patients. Mechanism-based biomarkers for early dissemination and therapy resistance will be validated in patient cohorts and used to stratify patient groups for clinical trials for existing and repurposed drugs, and also for novel therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models. These biomarkers will provide the basis for secondary disease prevention and would be used to molecularly screen at risk populations for early disease detection. We expect that such sensitive diagnostic and progression biomarkers as well as promising new combination therapies for major aggressive cancer entities would be identified and validated within the five to ten years.



Validation of biomarkers for patient stratification, disease interception and prevention in newly designed clinical trials



Longitudinal studies using patient cohorts and advanced disease models to understand tumour resistance and identify new drug targets



Development of advanced/next generation personalised cancer models



Development of novel multi-omics approaches and machine learning to reveal mechanisms involved in early cancer dissemination and therapy resistance



Longitudinal mapping of cancer cell types/ states involved in early dissemination and/or treatment resistance using available single-cell approaches

Y1

Y5

Y10

Cancer Roadmap timeline

Expected Scientific Impact

SHORT-TERM (1-7 years):

Identification of cell types and states involved in early metastatic dissemination and treatment resistance

Single-cell spatial methods to understand infiltration/dissemination in the tumour microenvironment and metastatic niche

New pre-clinical cancer models for testing and predicting drug responses in patients

Identification of novel drug targets, biomarkers and molecular signatures suitable for risk stratification for early disease detection and interception

LONG-TERM (8-15 years):

Assessment of biomarkers, risk stratification schemes and targeted treatments in personalised clinical trials. Prospective validation of biomarkers within clinical trials

Introduction of biomarkers and molecular-guided therapeutic interventions into clinical practice

Single-cell based predicted prognosis of cancer entities will enable the development of preventive and interception therapeutic strategies and stratify tumours for appropriate aggressiveness of treatment

Application of machine learning will create new tools for early diagnosis and to define prognostic factors

Technologies to enable physicians to delay/prevent metastatic spreading and diagnose cancer much earlier and more effectively as well as predict the future course of the disease and select the optimal treatment for an individual cancer patient

Medical Challenge

- Understanding the cell types and states involved in early cancer dissemination and therapy resistance
-

Outputs

- Increased understanding of the cell types and states responsible for cancer dissemination and therapy resistance and how they cause relapse and/or metastasis
 - New technologies for understanding the cellular basis and evolution of tumours in the context of the microenvironment
 - Next generation patient derived cancer models for longitudinal cohort studies and testing of new or predicted personalised therapies
 - Novel multi-dimensional biomarkers for patient stratification for therapeutic strategies
 - Identification of new targets for drug development or repurposing based on cell types and states involved in metastasis and drug resistance
 - Development of machine learning enabled systems for new molecular pathology of tumours that can be used for secondary prevention applications
-

Impact

- Increased likelihood of curing cancer at an early stage, increased patient survival
- Less burden on health systems and less individual suffering through early detection of cancer and emergence of drug resistance based on informative multi-dimensional biomarkers to enable disease interception, before metastasis or resistance occurs
- Improved patient outcomes through precision therapeutic strategies to intercept disease, based on predictive and personalised models of disease
- Faster and better validation of therapies based on new technologies and preclinical models as well as newly designed clinical trials using clinical and cellular/molecular endpoints

Example – Impact on Breast Cancer

- // Identification of disease-relevant cell types/states involved in early dissemination and therapy resistance, how these cells interact with each other and the tumour microenvironment to cause local relapse and/or metastasis. These disease-driving cell populations would be used to identify relevant molecular targeted approaches and immunotherapies for disease interception.
- // Increased knowledge of disease mechanisms and new computational predictive models for disease course based on cell states and trajectories. Novel single-cell multi-omics and imaging technologies will form a basis for a new level of digital molecular pathology.
- // Advanced patient-derived disease models will serve as a driving force for understanding cancer metastasis and resistance mechanisms as well as accelerate translation.
- // Stratification of patients based on multi-dimensional biomarkers and the underlying disease mechanisms. Together with predictive computational models these biomarkers will facilitate the selection of treatments for individuals. Where disease course allows these treatments will be first tested in patient-derived disease model 'avatars' to ensure required therapeutic response to provide optimised treatments. Based on these models the portfolio of druggable targets will be systematically expanded targeting the driving cancer cell populations and subsequently to more efficient combination therapies.
- // Mechanism-based biomarkers for early dissemination and therapy resistance will be validated in patient cohorts and used to stratify patient groups for clinical trials for existing and repurposed drugs, and also for novel therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models. Biomarkers will provide the basis for secondary disease prevention and would be used to molecularly screen at risk populations for early disease detection. It is expected that such sensitive diagnostic and progression biomarkers as well as promising new combination therapies for major aggressive cancer entities could be identified and validated within the next 5 to 10 years.

3.2.2 Neurological and Neuropsychiatric Diseases

Medical Challenge

The majority of chronic neurological diseases are currently incurable. Collectively they are the leading global cause of Disability Adjusted Life Years and the second-leading global cause of deaths¹. Brain disorders affect the quality of life of **over 160 million European citizens**, constituting an ever-growing social and economic burden that threatens the stability of the EU's healthcare systems.

In cases where treatments are available, they mostly attempt to alleviate the symptoms of the disease but are not able to cure or even slow its progression. This situation coupled with an ageing European population, offers poor future prospects for patients and their families. After more than a decade of failed clinical trials, drug discovery is increasingly limited to academia and SMEs, with the pharmaceutical industry progressively withdrawing from translational brain research programmes due to failing returns on large early investments. As a result, brain diseases are currently among the most understudied clinical conditions, with new strategies and approaches urgently required to tackle this unmet challenge. A key factor explaining the poor translation of research outcomes to the clinic is the complexity and heterogeneity in disease causes, mechanisms and presentation, which could not be adequately addressed using previous approaches. Consequently, clinical trials have so far included patients with both diverse symptoms and underlying disease biology, and who are often at late stages of disease, which complicates developing effective disease-modifying drugs.

A major barrier to implementing personalised medicine is the large knowledge gap in our understanding of the human brain structure and function at the cellular level and how this relates to clinical phenotypes captured through functional brain imaging studies. Due to the cellular complexity of the brain, revealing these mechanisms requires single-cell approaches, including spatial and imaging. These would identify the specific cell subpopulations and corresponding molecular pathways associated with specific functions or disease. Being able to map specific cell (sub)types to specific brain locations is key as specific brain regions are selectively or predominantly affected in several brain diseases. Another major barrier is the difficulty of studying disease biology, especially early events, in humans due to a lack of routine access to tissue from patients to study disease onset and progression. Longitudinal sampling of disease states will require highly innovative *in vitro* models that fully reproduce human biology, including ageing and disease. These include developing human induced pluripotent stem cells (hiPSCs), advanced animal models containing hiPSC-derived specific human cell types that can be exposed to human pathology, for example amyloid plaques composed of human proteins. Alternatively, brain organoids generated from hiPSCs recapitulate *in vitro* salient features of the *in vivo* developing brain, especially the sequential emergence of progenitor and neuronal subpopulations that capture aspects of spatial organisation of several brain regions.

1 the Global Burden of Disease Study 2015

Understanding the cellular and molecular mechanisms that underlie diseases in individual patients will reveal the heterogeneity and diversity of causes of neurological disorders. This will provide new multi-dimensional biomarkers that can be used for **earlier disease detection**, and most importantly, used to **stratify patients according to disease mechanism** to re-test previous, as well as new therapeutic concepts for **disease-modifying drugs and therapies**. Such biological information is also needed to design tailored treatment strategies for specific patient subgroups and disease stages.

Therefore, LifeTime has identified:

The stratification of patients according to the heterogeneity of cell states and trajectories in neurodegenerative and neurodevelopmental diseases

as the key transforming challenge to provide the greatest impact for patients in the next decade.

Neurological and Neuropsychiatric Diseases Roadmap

LifeTime proposes the following objectives to deliver an understanding of the diversity of neurological and neuropsychiatric disease mechanisms in patients:

- Define the cellular states in disease-relevant contexts and analyse how they are altered due to an individual's complex genetic constitution using combinations of patients' primary samples (biopsies, cerebrospinal fluid and peripheral blood), brain organoids and advanced animal models**
- Understand the cellular trajectories and mechanistic pathways underlying neurodegenerative and neurodevelopmental diseases with temporal and spatial resolution**
- Integrate clinical phenotypes with molecular mechanisms, using machine learning to generate *in silico* models of Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, epilepsy and autism spectrum disorders**

Addressing these objectives will enable: i) a rational stratification of patients on the basis of biomarkers empirically linked to pathogenic cascades; ii) the systematic identification of key molecules/pathways for drug targeting and/or repurposing; iii) early disease detection and better prediction of disease prognosis. Together, these insights are poised to transform the design of clinical trials by bridging clinical with molecular/cellular endpoints and therapeutic approaches on the basis of validated patient-specific disease mechanisms. For this roadmap, LifeTime's expected impact on autism spectrum disorders and Alzheimer's disease is used as showcase examples for the broad field of neurodevelopmental and neurodegenerative disorders.

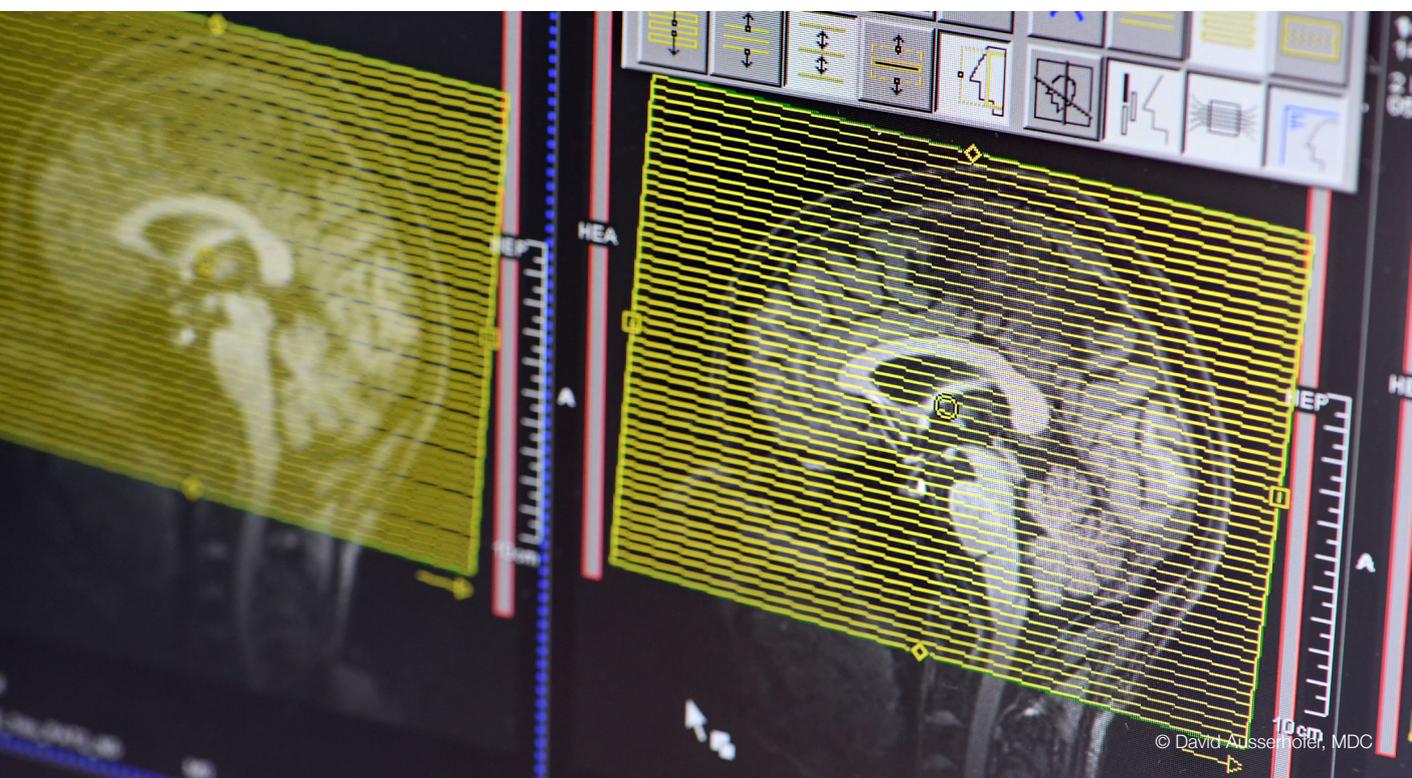
Required Investments for Neurological and Neuropsychiatric Diseases

To address the above objectives LifeTime recommends the implementation of the following multidisciplinary research programmes:

Longitudinal mapping of disease cell states and types in established patient-derived models using available single-cell multi-omics approaches

To understand the early pathophysiological events that occur during neurodevelopmental and neurodegenerative disorders, LifeTime proposes to immediately apply currently established single-cell multi-omics approaches (transcriptomic, chromatin accessibility, epigenetic approaches on dissociated cells) and spatial technologies (spatial transcriptomics and proteomics). For neurodevelopmental disorders longitudinal multi-omics analysis will be pursued in patient-derived brain organoids to uncover the molecular pathways and derangements in cellular trajectories. As organoid models for neurodegenerative diseases still require significant technological development (see below), initial longitudinal analyses will use disease models in which reprogrammed cells from patients with a high risk of developing a specific disease (based on polygenic risk score) are grafted into the mouse brain to uncover major disease-relevant phenotypes. This would be linked to ongoing efforts towards generating brain atlases, in particular the Human Cell Atlas, the Human Brain Project, and the H2020 project BRAINTIME (molecular atlas of the brain across the human lifespan).

These studies will provide insight into disease mechanisms at the single-cell level. For Alzheimer's disease they will reveal the specific cell types (neurons, glia, vascular cells) involved, the early responses to amyloid pathology and how these cells interact with each other to ultimately cause neurodegeneration. Most importantly, they would begin to reveal where and when the many genes associated with risk of Alzheimer's disease are expressed and exert their function. Analysing the cellular reaction in different brain areas will provide insights into regional vulnerability. Comparing cell states of patients with various genetic



risks of Alzheimer's disease and especially healthy centenarians will provide information on the cellular mechanisms of resilience. For autism spectrum disorders, longitudinal organoid modelling will reveal the changes in developmental trajectories, the timing of their deviation from normal development and the effect on neuronal-network architectures. These are necessary for the meaningful stratification of patients and the rational design of clinical trials and drug repurposing pipelines.

Development of novel multi-omics approaches to study disease mechanisms in brain models

Based on the functional importance of cellular location, cell-cell interactions and the local environment in the brain, LifeTime proposes prioritising the development of several spatial-based multi-omics single-cell technologies ([section 3.1.1](#)) together with machine learning ([section 3.1.2](#)). These will provide an integrated view of the molecular layers involved in brain diseases using patient-derived models required for cohort scale analysis below. Increasing cellular resolution and sensitivity as well as the throughput of spatial transcriptomic approaches is required to reveal the roles of different cell types including both neurons and glial cells, the neurovasculature and, in the case of neurodegeneration, protein aggregates. Unravelling the important role of signalling events, proteostasis, cellular inflammation and lipid metabolism requires advances and integration of spatial proteomics and metabolomics as well as advanced methodologies for non-invasive imaging of disease models, including live cell imaging at subcellular resolution ([section 3.1.1](#)). Integration of data-sets and other medical imaging modalities will require novel machine learning based approaches for extraction of meaningful features that can be used as biomarkers for disease onset and progression ([section 3.1.2](#)). Since pathology will also result in changes in cellular activity it will also be essential to integrate functional assays, such as electrophysiology, within these spatial approaches.

These technologies will substantially enrich the mechanistic insights obtained from current established technologies, since changes in the proteome and especially the lipidome cannot be reliably predicted based on gene expression. For both Alzheimer's disease and autism spectrum disorders this will reveal the cell types responsible for pathophysiological changes. In the process revealing the alterations in proteins, protein modifications and turnover, and metabolites including lipids both in these cells and in the surrounding tissue. The outcome will be a detailed view of disease progression at high spatial and temporal resolution.

Development of advanced patient-derived disease models for neurological disorders

Obtaining longitudinal patient brain samples is particularly challenging for neurological disorders. Therefore, LifeTime proposes a particular focus on deriving advanced patient-derived models for both neurodegenerative and neurodevelopmental diseases ([section 3.1.3](#)) to dissect the underlying molecular and cellular mechanisms and identify and validate new drug targets. More representative patient-derived organoids require increased cellular complexity, to ensure that all key cell types are represented, including neurons and glia, with predictable spatial organisation and accurate cell-cell interactions. In addition, there is a need for vascularisation, which will require the use of microfluidic systems, and for long-term culture. Since symptoms in patients originate in distinct functional neural circuits, new research, analysis and

therapy concepts depend on the reconstruction of brain circuitry on a histological and functional level. While assembly of circuits in organoid model systems is currently in its infancy, the fusion of organoids resembling different brain areas is an example of a promising approach to establish more sophisticated brain circuit organoid systems with the correct neuronal connections. Analysing these circuits requires the parallel development of optogenetic tools in organoids, fluorescent readouts for neuronal activities and - most importantly- readouts for neural firing patterns compatible with single-cell multi-omics.

Longitudinal activity measurements require the development of brain-on-a-chip methodologies in which organoids are grown within a 3D-scaffold in proximity to inbuilt electrodes that enable measurement of real time electrical activity. Disease models should be developed in conjunction with strategies to implement large-scale perturbation screens (e.g. CRISPR-Cas, small molecule) with multi-omics readouts and lineage tracing to understand causation in disease mechanisms ([section 3.1.3](#)). Profiling of disease trajectories (see below) at a cohort-wide scale will require that organoid production be scaled, standardised, automated and benchmarked to primary tissues as described in detail in [section 3.1.3](#).

These advanced models will not only serve as a driving force for understanding disease mechanisms but they are essential for closing the gap between basic research and translation of these findings into the clinics. For example for Alzheimer's disease current models based on human cells are in their infancy and have the potential to revolutionise how the disease is understood, but also explore the potential of new therapeutic strategies in a human *in vitro* pre-clinical trial platform. For autism spectrum disorders, complex hiPSC-based models have already been developed and used to study monogenic autism spectrum disorder syndromes, and non syndromic autism spectrum disorders would also benefit from these advanced models.

Longitudinal studies of disease onset and progression using advanced patient-derived models to understand disease mechanisms and identify new drug targets

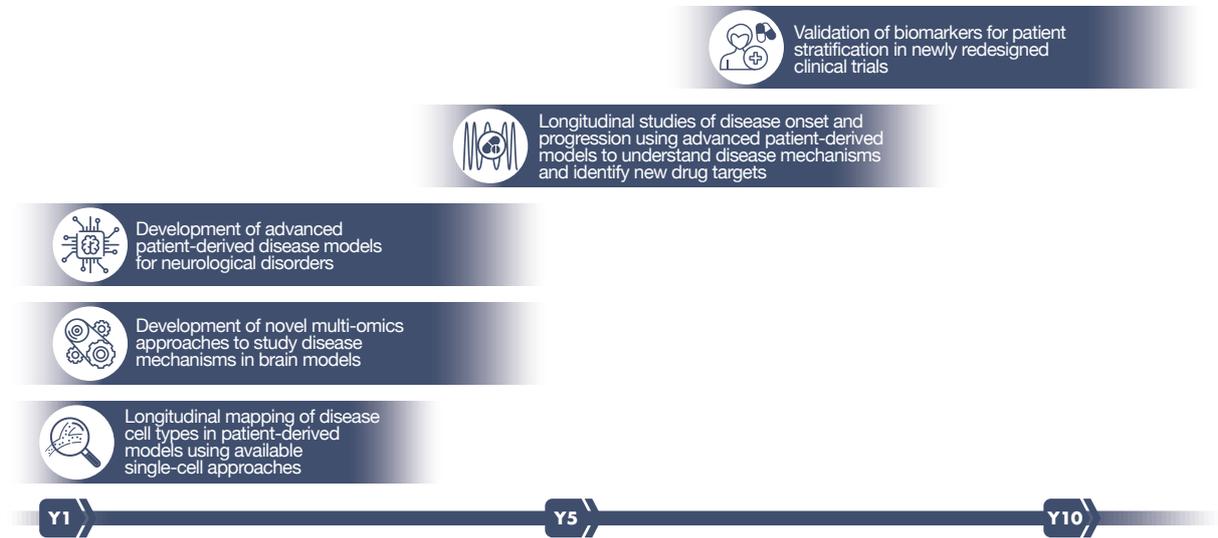
To understand both normal ageing and disease trajectories of individuals and to identify novel meaningful biomarkers for patient stratification will require longitudinal studies of advanced models based on hiPS cells derived from established patient cohorts. For example, the EMIFAD MBD (European Medical Information Framework for Alzheimer's disease Multimodal Biomarker Discovery) study or national cohorts such as the Dementia Platform UK for Alzheimer's disease; and the EU-AIMS (European Autism Interventions - A Multicentre Study for Developing New Medications) study or the Italian autism network (ITAN) Rome cohort and Milan Cohort from the San Paolo Research Hospital for autism spectrum disorders. Newly developed patient-derived disease models described above will be generated from selected patients from cohorts. This will be based on extremes in the polygenic risk scores to identify extreme high-risk and extreme protected individuals (for instance healthy centenarians) with different pathophysiological mechanisms e.g. inflammation or defects in lipid metabolism. These large-scale model cohorts will be investigated using the newly developed, benchmarked and standardised single-cell multi-omics and imaging technologies (described above and [section 3.1.1](#)), which will be integrated with clinical and medical imaging data. These approaches will generate the large high-quality datasets required for generating predictive computational models and identify novel mechanism-based drug targets. Machine learning-based models will be developed to generate *in silico* predictions of the most promising therapeutic targets, using mechanistic knowledge.

They will predict which type of intervention will be the most efficacious for a particular disease phase ([section 3.2.2](#)). Disease mechanisms and new potential drug targets will be studied using a combination of classical molecular and genetic approaches as well as newly developed large-scale CRISPR and small molecule screens in novel disease models ([section 3.1.3](#)).

For both Alzheimer’s disease and autism spectrum disorders this will identify biomarkers that enable the stratification of patients based on the underlying disease mechanism and lead to a considerable expansion of the portfolio of druggable targets. This will also allow antisense and genetic therapies to be rapidly tested in clinical trials over the coming years, and encourage the pharmaceutical industry to re-invest much more than today in R&D for brain diseases.

Validation of biomarkers for patient stratification in newly redesigned clinical trials

Promising therapies that have previously failed to prove efficacy in clinical trials will be re-tested in relevant and accurate models, allowing fast translation to the clinics for targeted groups of patients. Mechanism-based biomarkers will be validated in patient cohorts and used to stratify populations for clinical trials for existing and repurposed drugs, and also for therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models. It is expected that such sensitive diagnostic and progression biomarkers would be identified and validated within the next five to ten years, putting an end to the “one-size-fits-all” approach to treating brain diseases.



Neurological and Neuropsychiatric Diseases Roadmap timeline

Expected Scientific Impact

SHORT-TERM (1-7 years):

For Alzheimer's disease:

Stratification of patients according to the main cellular mechanisms driving the disease (biological pathways, neuroinflammation, vascular defects, lipid metabolism, etc.)

New design of clinical trials to re-evaluate drugs that were tested without patient stratification (eg amyloid directed therapies)

Broaden the drug target portfolio beyond amyloid and tau biology, initially to inflammatory and vascular targets and perform pre-clinical validation in relevant advanced patient-derived models

For neurodevelopmental disorders:

Advanced patient-derived models reflecting specific disease aspects to identify pathways that can be targeted, whenever possible by repurposed drugs, to drive cell states into a healthy trajectory

Pre-clinical testing of new drugs or therapies in relevant and accurate models to drive faster translation to the clinics

LONG-TERM (8-15 years)

These approaches will revolutionise the field of brain diseases research and change the way drugs and therapeutic strategies are developed and diseases diagnosed. Focusing on the initial cellular phases of these disorders will provide opportunities to intercept them at an earlier stage, to halt or even prevent disease manifestations

LifeTime will shift the focus to the early cellular biology of these diseases in the complex context of the brain. This will provide a novel arsenal of therapies addressing pathological cell states in brain disease and replace our traditional and obsolete battery of diagnostic tools and symptomatic treatments

Patients will be treated in a personalised manner, using combinations of therapies that target the right cellular responses at the right time

Medical Challenge

- // The stratification of patients according to the heterogeneity of cell states and trajectories
-

Outputs

- // Increased understanding of the molecular mechanisms and cell types and states causing disease
 - // New technologies for understanding the molecular mechanisms, cell types involved, their activity and spatial interactions in the brain. Organoid systems recapitulating main human brain circuits
 - // Tools for circuit-level analysis of neurological disorders in organoids and neural firing patterns on the single-cell level compatible with other single-cell level analysis
 - // Next generation patient-derived organoids to create 'cohorts' to study early events in disease and progression and used as a pre-clinical trial platform to test new drugs and therapies
 - // Identification of biomarkers for patient stratification in clinical trials based on underlying molecular mechanisms and pathways involved
 - // Systematic identification of new drug targets and therapeutic concepts for disease modifying drugs and a much broader drug target portfolio
-

Impact

- // Rational development of disease modifying drugs and therapies that can slow or cure of diseases to improve patients' quality of life
- // Faster translation of therapies to clinics using advanced pre-clinical models and applying improved clinical trial design according to patient subgroup's underlying mechanisms
- // Improved patient outcomes based on earlier detection of neurological diseases; more precise therapy selection using machine learning enabled systems for predictive computational models of brain diseases

Example - Impact on Alzheimer's Disease

- /// New insight into disease mechanisms at the single-cell level, including the specific cell types (neurons, glia, vascular cells) involved, the early responses to amyloid pathology and how these cells interact with each other to ultimately cause neurodegeneration. Reveal where and when the many genes associated with risk of Alzheimer's disease are expressed and exert their function and provide insights into brain region vulnerability.
- /// Enriched mechanistic insights from novel single-cell multi-omics and imaging technologies that incorporate changes in the proteome and the lipidome in addition to gene expression and epigenome. Reveal which cell types are responsible for pathophysiological changes and the alterations in proteins, protein modifications and turnover, and metabolites including lipids in these cells and in the surrounding tissue. Provide a detailed view of disease progression at high spatial and temporal resolution.
- /// Advanced patient-derived models as a driving force for understanding disease mechanisms and closing the gap between basic research and translation of these findings into the clinics. Revolutionise how the disease is understood and also explore the potential of new therapeutic strategies in a human *in vitro* pre-clinical trial platform.
- /// Stratification of patients according to single-cell based biomarkers and understanding the underlying disease mechanisms will lead to a considerable expansion of the portfolio of druggable targets. This will encourage the pharmaceutical industry to re-invest much more than today in R&D for brain diseases.
- /// Re-testing of promising therapies that have previously failed to prove efficacy in clinical trials in relevant and accurate models, allowing fast translation to the clinics for targeted groups of patients. Mechanism-based biomarkers will be validated in patient cohorts and used to stratify populations in clinical trials for existing and repurposed drugs, and also for therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models.
- /// Sensitive diagnostic and progression biomarkers could be identified and validated within the next five to ten years, putting an end to the "one-size-fits-all" approach to treating brain diseases.



MEDICAL REPORT

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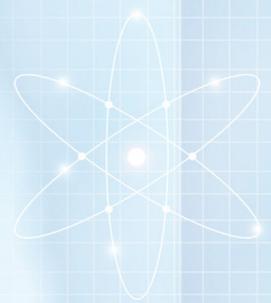
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3.2.3 Infectious Diseases

Medical Challenge

Infectious diseases remain one of the most challenging areas in medicine and responsible for one in four deaths worldwide. Antimicrobial resistance is increasing, and epidemics and pathogens such as SARS, Influenza H1N1, multi-resistant bacterial pathogens, novel fungi such as *Candida auris* and very recently SARS-CoV-2 continually emerge. Difficulties in treating persistent chronic infections, increasing resistance and pandemic outbreaks such as COVID-19, call for the rapid development of novel therapeutic strategies.

Despite the need for new treatments, only a handful of new antibiotics have been launched over the past 40 years and many companies have abandoned their R&D programmes in infectious diseases. In addition, antimicrobial therapy is unlikely to provide full protection for a weakened patient and novel, personalised, intervention strategies are required to boost an individual's immune response. Importantly, interception of infections using recent medical breakthroughs such as immunotherapy, which has transformed the therapeutic landscape of autoimmune diseases and cancer, has not yet been successfully implemented for infectious diseases. Previous immunotherapeutic approaches, for example in sepsis, have been unsuccessful due to the "one-size-fits-all" approach, which does not consider the immune status of patients. This has resulted in the failure of important therapeutic concepts in infection biology such as hyperinflammation or immunoparalysis. An important factor explaining the difficulty in translating new molecular insights into novel therapies is the complexity and heterogeneity in the causes, mechanisms and presentation of infectious diseases.

Implementing novel therapeutic approaches such as immunotherapy for infectious diseases requires a more comprehensive understanding of the cellular basis of disease heterogeneity, as well as the underlying mechanisms and dynamics. For example, in pneumonia or sepsis there is a complex cellular immune response that continuously changes during the course of the infection. Selecting the most effective available therapy at a particular time or developing new immunotherapies will require knowledge of the phase of the immune response, e.g. hyperinflammation or immunosuppression, and take into account an individual's preconditions, genetics and environmental factors. Understanding and targeting host-pathogen interactions requires longitudinal single-cell level analyses of the cell types, sub-types, functional cell states and cellular memories involved. Disease mechanisms will require patient-derived disease models of anatomically complex tissues such as the lungs to resolve spatio-temporal interactions within diverse microenvironments that can be exploited by pathogens. Infectious diseases offer a unique opportunity to combine single-cell multi-omics and imaging approaches with both cohort-based studies and human controlled experimental infections to decipher pathophysiology before and after challenge (e.g. with a vaccine) as well as during therapy.

Reducing the burden of infectious diseases requires a coordinated, international, multi-dimensional approach that encompasses increased research, development and innovation in areas such as improved diagnostics, patient stratification, new and precise therapeutic strategies and more effective vaccines. This will provide new multi-dimensional biomarkers that can be used for **earlier disease detection**, and selection of **tailored immunotherapy** and combination strategies to specific patient populations to identify optimal strategies for treating patient subgroups and disease stages.

In order to achieve these goals, LifeTime has identified the following key transformational challenge to be studied in the next decade that could have the greatest impact for patients:

Understanding the cellular response to infections and develop novel precision immune-based therapeutic strategies to combat infectious diseases

Infectious Diseases Roadmap

LifeTime proposes the following objectives to deliver a transformative improvement in the monitoring and treatment of infectious diseases:

- // Identify single-cell multi-omics-based biomarkers for cellular immunopathology and patient stratification**
- // Develop new immunotherapy concepts for infections based on single-cell resolution of patient disease trajectories**
- // Develop novel approaches to improve vaccination efficacy in at risk patients (e.g. elderly, immunosuppressed), including using novel controlled models of human infection**

Addressing these challenges will: i) provide a single-cell resolution spatio-temporal map of infections and the trajectory of the immune response from the initiation of the infection towards the recovery; ii) identify biomarkers to stratify patients for immunotherapy; iii) increase our understanding of disease mechanisms based on single-cell multi-omics analysis, machine learning and patient-derived disease models for earlier detection and therapy selection and monitoring immunotherapy response; iv) develop novel approaches for improving vaccination by modulating host immune pathways and cells. For this roadmap, LifeTime's expected impact on COVID-19 and sepsis are used as showcase examples for the broad field of infectious diseases.

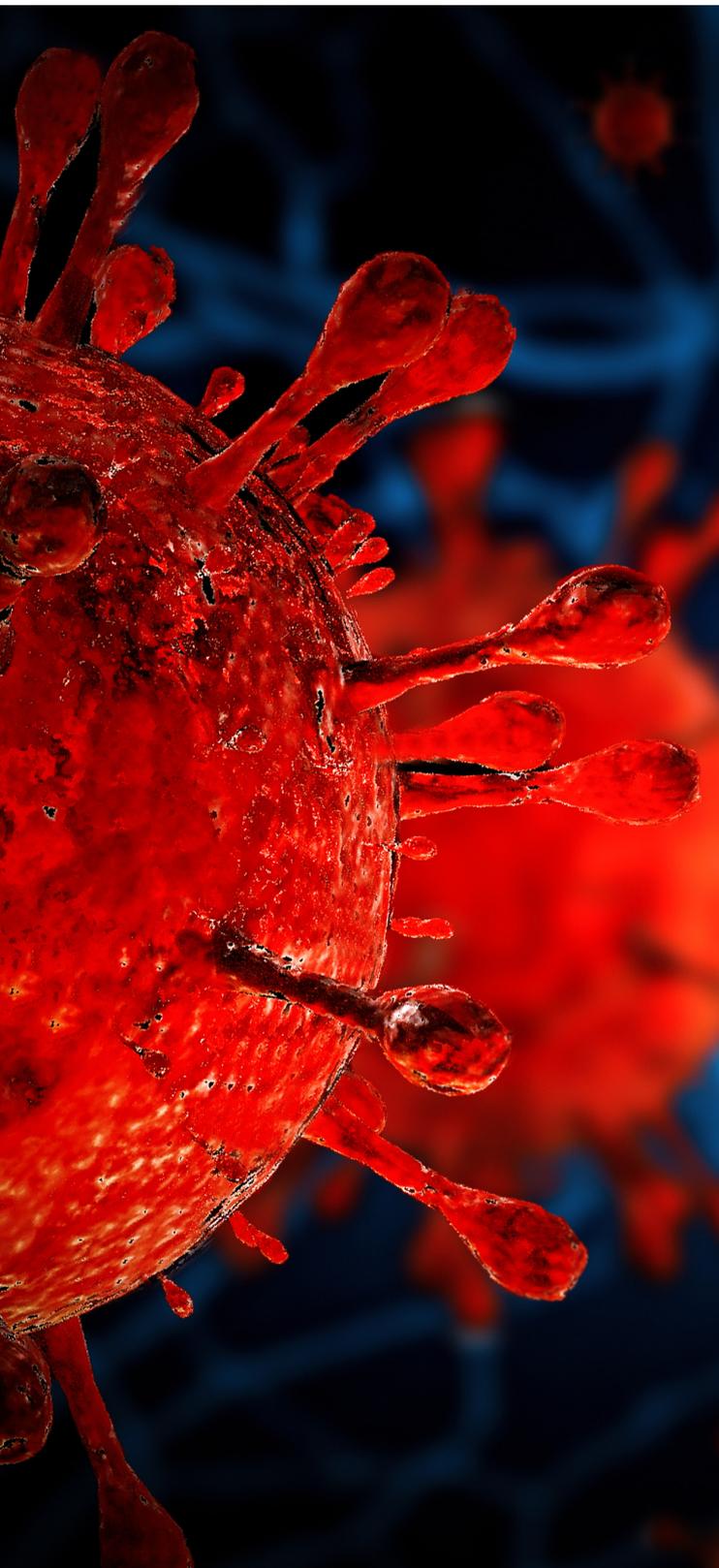
Required Investments for Infectious Diseases

To address the above objectives LifeTime recommends the implementation of the following multidisciplinary research programmes:

- // Longitudinal single-cell multi-omics analysis of patients' immune response to infection**

To understand the immune response to infection and vaccination, LifeTime proposes to immediately apply established and scaled single-cell approaches to body fluids and tissue biopsies from (1) acute lower respiratory tract infections or (2) sepsis patient cohorts or (3) individuals undergoing controlled infections or vaccination programmes. Immediately deciphering the heterogeneity in a patient's immune response

to infection will be initiated using current single-cell technologies such as transcriptomics, epigenomics and proteomics. These will be performed on accessible patient material (peripheral blood mononuclear cells, plasma, nasal scrapings, bronchoalveolar lavage for respiratory diseases and whole blood for sepsis) from patient cohorts with standardised clinical data longitudinally across key timepoints. Immune responses during respiratory diseases will also be characterised at the site of infection using minimally invasive tissue sampling and spatial transcriptomic approaches depending on the pathogen and infection site (i.e. spatial transcriptomics on lungs, bronchial linings). This will be complemented with studies using established patient-derived airway and lung organoid models to model infections and disease progression and combined with medical imaging (computerised tomography scans) to facilitate early diagnostics.



For COVID-19 this will reveal immune dysregulated pathways in patients with disparate symptoms and enable screening of available immunomodulatory drugs in established disease models. These will identify biomarkers of disease severity. These will be used to select the immunotherapies that have the greatest potential to restore body/lung homeostasis for specific patients and facilitate the initiation of rapid clinical trials with particular drugs.

For sepsis this longitudinal analysis will reveal the dynamics of sepsis progression, including the timing of hyperinflammation and immunosuppression phases. It will identify cell types or states that are associated with early events that could be used as biomarkers for early detection and stratify patients based on the type of immune dysregulation and organ dysfunction and stage of sepsis. This will indicate the optimal immunotherapies and timing of administration to ensure they have the greatest potential to restore immune homeostasis in combination with antimicrobial therapy.

For vaccinations this will provide insight of immunological mechanisms and molecular pathways involved at the single-cell level. It will reveal individual heterogeneity in the response to vaccination and how these cells interact with each other to ultimately determine an efficient or defective immune response. Most importantly, these technologies and analyses will reveal which pathways should be modulated for improved vaccine design, and how the individual variability should be approached for maximum efficacy.

Developing advanced patient-derived models that recapitulate pathophysiology and reveal infection/disease mechanisms

Obtaining tissue samples for longitudinal analysis of disease progression is particularly challenging for infections that target particular organs. While iPSC lung organoids and air-liquid interface are key to deciphering the immediate response to respiratory virus infection, they need to be further developed to go beyond the epithelial layer and to integrate components of the basal, stromal and endothelial cells to more accurately reflect complex lung tissue ([section 3.1.3](#)). They also require the incorporation of resident and recruited immune cells that play a role during the infection. Advanced models should also mimic age-dependent structures since lower respiratory tract infections depend on age. Establishing causality in dysregulated pathways and host manipulation strategies by the virus and creation of predictive computational models requires integration of organoids, single-cell multi-omics and genome-scale gene perturbation screens e.g. CRISPR based technologies to resolve the complex intertwined host-pathogen interaction ([section 3.1.2](#) and [3.1.3](#)). Creating organoids from population cohorts will provide an opportunity to investigate individual susceptibility and pathology. The respiratory tract is highly structured in successive compartments such as the conductive airway and the respiratory airway. Studying lung-specific processes requires development of novel tissue engineering approaches such as lung-on-a-chip that approximate the whole organ ([section 3.1.3](#)). Microfluidics-based approaches will be used to model complex structures that also contain multiple layers of stromal cells and immune cells that play a major role in mounting an efficient immune response and tissue repair.

For COVID-19 these models will provide a means to study temporal aspects of infections and patient-to-patient variability and sensitivity to infections. When coupled with CRISPR-Cas screens they will play a key role in understanding the molecular mechanisms involved in host pathogen interactions and the immune response.

Developing novel multi-omics approaches to study infection disease mechanisms longitudinally

Timely intervention of infectious diseases requires development and optimisation of antimicrobial and immunotherapeutic strategies. LifeTime prioritises understanding the mechanisms that contribute to cellular heterogeneity in the pathogen and the immune response by integrating longitudinal changes in transcriptomes, intracellular signalling pathways, including phosphoproteomes, metabolomes, lipidomes, and cell-cell interactions, using machine learning ([section 3.1.1](#) and [3.1.2](#)). This requires investment in the development of untargeted single-cell proteomics and metabolomic approaches. These are particularly key to understand the states of immune cells, including the regulation of inflammatory responses and immunoparalysis in sepsis and how pathogens manipulate host signalling pathways and metabolism during infection. Interactions between host and pathogen are also influenced by cell-cell interactions and the lung tissue microenvironment. Interception of the early stages of infections requires the identification of cell types/states that are targeted by pathogens, the molecules involved and the temporal and cellular response of the immune system. These require systematic studies including longitudinal approaches using patient-derived samples or models. These molecular data will be integrated together with clinical data collected for lower respiratory tract infections such as computerised tomography scans and X-rays to improve diagnosis

([section 3.1.2](#)). This approach will also be tested in the context of treatment (companion diagnostics) which could potentially accelerate the development of new therapies.

For COVID-19 and sepsis, integration of these approaches and creation of computational models will provide mechanistic insight into the regulation of the various molecular networks in cells. In the process revealing the roles of cell types and subtypes involved in viral infection and host defense mechanisms, especially those that lead to acute respiratory distress syndrome (ARDS) and sepsis.

Apply novel single-cell multi-omics approaches to study infections longitudinally using patient cohorts and patient-derived disease models

To understand the role of heterogeneity of infections and the corresponding immune response, including sepsis, as well as response to treatment within individual patients and across cohorts LifeTime recommends applying the single-cell multi-omics and machine learning approaches as well as patient-derived disease models described above to systematically analyse patient disease trajectories. Next generation multi-omics technologies will be used to analyse samples from multiple patient cohorts and biobanks, including with comorbidities (e.g. cardiovascular or renal). This will include body fluid samples from patients with respiratory infections and sepsis caused by a variety of pathogens, to reveal general and pathogen specific signatures, and also include samples obtained from controlled human infections and vaccination programmes. The later will provide longitudinal data, prior to and during infection through to therapy response and clearance as well as subsequent timepoints. Machine learning approaches will be used to integrate these data with clinical and imaging data, as well as single-cell multi-omics analysis in patient-derived organoid and tissue models and include perturbation studies to create predictive causal mechanistic models of infections for individual patients ([section 3.1.2](#)).

For COVID-19 and sepsis, integration of novel multi-omics technologies with machine learning approaches at a cohort/population scale will enable the creation of predictive models for disease progression based on multi-dimensional datasets. Elucidation of disease mechanisms will systematically identify therapies, including combinations, as well as new cellular drug/antiviral targets to be validated in patient-derived models.

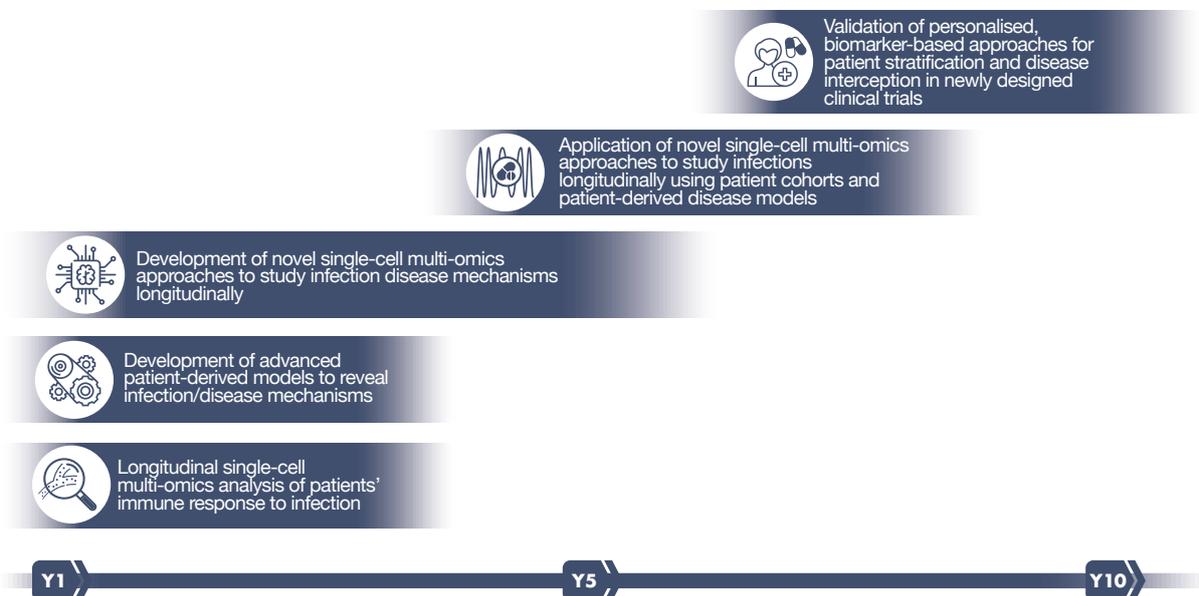
For sepsis this will provide a better classification of disease and enable early detection and accurate diagnosis of sepsis from the very first hours of the patient admission. The informative biomarkers based on enhanced disease classification will be developed into easy-to-perform clinical and laboratory tools to allow tracing the subgroups and provide patient stratification at the bench-side. Together these cellular and molecular biomarkers will help guide the physician in selecting the most effective therapies to intercept the progression of sepsis in individual patients.

For vaccination, new mechanistic insight from longitudinal analyses using next generation multi-omics technologies will reveal the specific cell types and molecular pathways involved in the heterogeneity of the response to vaccination. This will provide new strategies for enhancing vaccine efficacy. Enhanced mechanistic understanding of host-response to infections will lead to new systematic strategies for developing host-directed therapies, new vaccine leads and novel antiviral drugs, which differs from current candidate screening approaches.

Validation of personalised, biomarker-based approaches for patient stratification and disease interception in newly designed clinical trials

For COVID-19 longitudinal studies in patient cohorts will identify therapies and combinations (e.g. anti-IL-1 approaches, anti-IL-6 antibodies, interferon-beta, passive immunisation with hyperimmune serum, anti-SARS-CoV-2 monoclonal antibodies) that will be effective in specific patient subgroups. These will be tested in relevant and accurate patient-derived models, allowing fast translation to the clinics for targeted groups of patients. Furthermore, novel cellular-based therapy concepts will be likely identified in the process of understanding disease mechanisms at the single-cell level and can be tested in advanced pre-clinical models. Mechanism-based biomarkers for disease onset and therapy response will be validated in patient cohorts and used to stratify populations for clinical trials for existing and repurposed drugs, and also for novel therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models. Multi-dimensional diagnostic and progression biomarkers as well as promising new combination therapies for immunotherapeutic intervention will be validated and implemented in the next seven to ten years.

For sepsis biomarkers based on multi-omics single-cell technologies for patient immune stratification at the bench-side will be validated in large-scale randomised clinical trials. Personalised treatment of infections of the critically ill patients will use an algorithm guided by the sepsis classification tool and deliver specific treatment tailored to each patient's needs. The outcome will demonstrate the treatment's potential to prolong sepsis survival compared to the standard-of-care modalities.



Infectious Diseases Roadmap timeline

Expected Scientific Impact

SHORT-TERM (1-7 years):

Increased understanding of infectious diseases in space and time and classification of the cell types, states and localisation required to predict disease progression based on cellular biomarkers

Quantification of immunotherapy treatment efficiency, and stratification of patients for the appropriate type of immunotherapy

Development of early diagnostics and therapy response based on study of patient cohorts

LONG-TERM (8-15 years):

Introduction of novel biomarkers into clinical practice for disease detection and guided therapeutic intervention

Circulating immune cells will be used as cellular biomarkers to stratify patients and predict the disease progression based on data-driven multi-omics

Design of guided-therapeutic interventions (both therapeutic and prophylactic, such as vaccines) based on single-cell multi-omics profiles

Design of new clinical trials for targeting precisely novel immune cell types and sub-types

Medical Challenge

- // To understand the cellular response to infections and develop novel precision immune-based therapeutic strategies to combat infectious diseases
-

Outputs

- // Increased understanding of the cellular basis of the immune response to infections and vaccination
 - // New technologies for understanding the cell types and molecular mechanisms involved in the early events during infection through to immunotherapy response
 - // Advanced patient-derived models to recapitulate pathophysiology and understanding infection mechanisms and immune response
 - // Identification of biomarkers for patient stratification for specific immunotherapy regimens
 - // New immunotherapy concepts to combat infectious diseases
-

Impact

- // Earlier diagnosis of infectious diseases based on circulating immune cells obtained through minimally-invasive diagnostics
- // More effective treatment of patients using precision immunotherapies and response based on multi-dimensional biomarkers used to stratify patients according to underlying pathophysiology
- // Enhanced prevention by developing more long-lasting and effective vaccines based on understanding immune response

Example - Impact on COVID-19

- /// Reveal immune dysregulated pathways in patients with disparate symptoms and enable screening of available immunomodulatory drugs in established disease models. Identify multi-dimensional biomarkers of disease severity and immunotherapies that will have the greatest potential to restore body/lung homeostasis in specific patient subgroups. Facilitate the initiation of rapid clinical trials with selected drugs.
- /// Advanced disease models will enable the analysis of the temporal aspects of infections and patient-to-patient variability and sensitivity.
- /// Integration of single-cell multi-omics, advanced disease models and creation of machine learning-based predictive computational models will provide mechanistic insight into the regulation of the various molecular networks in cells and reveal the roles of cell types and subtypes involved in viral infection and host defense mechanisms, especially those that lead to acute respiratory distress syndrome.
- /// Integration of novel multi-omics technologies with machine learning approaches at a cohort/population scale will enable creation of predictive models for disease progression based on multi-dimensional datasets. Elucidation of disease mechanisms will enable systematic identification of therapies, including combinations as well as new cellular drug/antiviral targets to be validated in new patient-derived models.
- /// Longitudinal studies in patient cohorts will identify therapies and combinations that could be effective in specific patient subgroups. These will be tested in relevant and accurate patient-derived models, allowing fast translation to the clinics for targeted groups of patients.
- /// Novel cellular-based therapy concepts will be likely identified in the process of understanding disease mechanisms at the single-cell level and tested in advanced pre-clinical models.
- /// Mechanism-based biomarkers for disease onset and therapy response will be validated in patient cohorts and used to stratify populations for clinical trials for existing and repurposed drugs, and also for novel therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models. Multi-dimensional diagnostic and progression biomarkers as well as promising new combination therapies for immunotherapeutic intervention will be validated and implemented in the next seven to ten years.



3.2.4 Chronic Inflammatory Diseases

Medical Challenges

Chronic inflammatory diseases (CIDs) are a group of non-communicable, currently incurable diseases involving the immune system. They are characterised by relapsing inflammatory activity and disease-specific secondary diseases, in which uncontrolled inflammation leads to tissue destruction. Lifetime prevalence of CIDs is estimated at over 10% in Central Europe.

Although CIDs are defined by the symptoms of the inflammatory reaction in the affected organ, they are considered to be systemic diseases with overlapping phenotypes and manifestations. Although disease-onset occurs during specific timeframes, often during early adulthood, they remain difficult to detect and there is a diagnostic delay of 12-24 months in Europe. Diagnosis relies on a combination of clinical symptom and/or organ damage scores together with additional information from endoscopic, radiologic and histological procedures. These methods are rather crude, only describe the magnitude of inflammation and often contain subjective patient reported outcome measures (e.g. intensity of pain, disability) that are difficult to use in clinical trials. The scores are unable to define the disease entity or predict outcome, meaning there is an urgent need for a more granular set of molecular biomarkers for early disease detection and stratification of patients.

The high burden of CIDs is caused by chronicity and long-term debilitating consequences due to structural destruction of the affected organ or tissue. Current therapies only treat the symptoms and do not cure or fully control the chronic inflammatory pathophysiology. While many different targeted therapies exist they are expensive and are limited by high rates of non-response to treatment. For example, while anti-TNF therapy has significantly improved the quality of life for many patients by reducing disease symptoms and slowing disease progression, full therapeutic benefit is achieved in less than 20-30% of the patients with inflammatory bowel disease or rheumatoid arthritis at an economic cost of approximately €9 billion in Europe.

The difficulty in treating CIDs is due to the observed large degree of heterogeneity in disease progression. This includes both disease activity (i.e. mild, moderate and severe) and complexity that can range from easily controlled disease to a severe destructive course, which ultimately leads to permanent impairment of organ function with a severe impact on the quality of life. Understanding the cellular basis for disease heterogeneity and the pathogenic cell-types and states involved is required to impact the future clinical management of the diseases. This requires single-cell level approaches to reveal the cellular complexity and heterogeneity of the immune system that links to disease type and disease behaviour. Single-cell based biomarkers and innovative pre-clinical models are required for early disease detection, to identify new therapeutic mechanisms, extend indications and guide therapy selection. Longitudinal analyses have the potential to go beyond simply guiding the selection of therapy and define the optimal timing of intervention (decision support) during the course of CID, which would result in a higher degree of disease control than is possible today. Future mechanism-based therapies must address the molecular cause of the disease to enable interception and deliver a cure.

Therefore, LifeTime has identified:

Understanding the role of cellular heterogeneity in predicting disease trajectories and response to therapy

as a pivotal challenge of translational research to provide a disruptive impact for CID patients in the next decade.

Chronic Inflammatory Disease Roadmap

LifeTime proposes the following objectives to generate an understanding of the molecular and cellular heterogeneity of CIDs:

- Define the full functional cellular heterogeneity in disease-relevant context and analyse the impact of inter-patient genetic variation and microbiome on regulatory molecular networks**
- Develop approaches for predicting disease trajectories based on disease mechanisms and endotypes**
- Understand the heterogeneity of response to targeted therapies for optimising disease control**

This will lead to: i) a molecular taxonomy of CIDs across individual disease entities empirically linked to pathogenic cascades and individual immune network states to unambiguously detect and diagnose them earlier; ii) a systematic identification of cell populations and molecular pathways that must be targeted (by potentially different therapeutic principles) to overcome the problem of heterogeneity of disease progression; iii) a personalised predictive computational model for therapy selection and optimisation. For this roadmap, the expected impact of LifeTime's approach on inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis are used as showcase examples for the broad field of CID.

Required Investments for Chronic Inflammatory Diseases

To address the above objectives LifeTime recommends the implementation of the following multidisciplinary research programmes:

Longitudinal mapping of disease cell states and types in CID patients using single-cell based multi-dimensional analyses: novel markers for unambiguous diagnosis

To understand early pathophysiology requires increased knowledge of the roles of different cell types, including immune cells, epithelial (neuronal and glial cells for multiple sclerosis) and stromal populations (endothelial cells, fibroblasts). LifeTime proposes to apply currently established single-cell approaches (transcriptome, epigenome, chromatin accessibility) on purified cell populations (from biopsies, stool, cerebrospinal fluid and peripheral blood) and relevant disease models (organoid, pre-clinical models). Particularly important will be analyses related to life history events (e.g. treatment changes, triggers for flare) in longitudinal datasets. As regional differences of inflammatory responses are known (e.g. skip lesions in inflammatory bowel disease or specific joints being affected in rheumatoid arthritis), spatial transcriptomic analyses will link impaired cellular response states to anatomical structures and compartments to provide a currently unknown dimension to understanding the underlying disease mechanisms. Simultaneous analysis of microbiota and bacterially derived metabolites will provide additional insight into host-microbe crosstalk that shapes heterogeneity of immune cell lineages and subpopulations. These investigations will be linked to high-dimensional well curated clinical data sets and generalised clinical features such as fatigue, depression or metabolic comorbidities.

Ultimately, such studies will resolve a molecular taxonomy of disease beyond the organ-based manifestation and lead to early predictors of disease trajectories for earlier detection. As an example, for multiple sclerosis this will comprise molecular and cellular stratification markers, which reflect specific disease behaviour and comorbidities. Such an approach will enable the meaningful stratification of patients and the rationale design of future clinical trials.



Development of novel patient-derived disease models and spatial multi-omics approaches to study disease: therapy selection and new therapeutic concepts

Emerging contributions of epithelial and mesenchymal cells in CID etiology require that models comprise more than just a singular layer of cellular complexity to recreate the dynamic cell-cell interactions within specific tissue compartments. LifeTime recommends developing novel patient-derived *in vitro* disease models of CIDs ([section 3.1.3](#)). This will involve microfluidics and other solutions to model perfusion, tissue oxygenation, the role of vascular cells and immune cell recirculation. iPSC-based technologies will enable also the generation of tissue compartments, which are usually not accessible to routine tissue sampling (e.g. microglia and immune cell reactions in iPSC-derived brain organoids in multiple sclerosis or synovial organoid cultures). Promising organoid models such as the intestinal mucosa in inflammatory bowel disease, from which patient samples are accessible and can be repeatedly taken, will be further developed to capture specific aspects of disease. For example, further miniaturisation and the addition of environmental factors such as microbial communities in trans-well systems will allow a more detailed and robust view on immune-mediated processes and the parallel testing of therapeutic compounds (“clinical trial in a dish”). The integration of defined genetic models (e.g. cells derived from patients with rare monogenic phenocopies of CID) will provide invaluable insight into the role of genetic variants in influencing disease processes in susceptible individuals. Findings and hypotheses from the models should be validated in pre-clinical *in vivo* models and in smaller sets of patients in order to corroborate the relevance of the systems.

Understanding the mechanisms underlying the complex biology of cell-based CID models will require spatial-based multi-omics single-cell technologies, including spatial transcriptomics, proteomics and metabolomics as tissue compartmentalisation is particularly important ([section 3.1.1](#)). Physiological spatial gradients such as oxygen and microbiota-dependent metabolites are deregulated in inflammatory bowel disease and understanding and defining pathological microcompartments will provide essential insights into mechanism of disease manifestation and progression. To capture dynamic spatial interactions multi-omics approaches will be complemented and integrated with advanced imaging approaches to decipher the complex multicellular processes in the inflammatory niche. Imaging methodologies will also delineate processes at subcellular resolution or to decipher migratory dynamics and interaction kinetics using live-imaging ([section 3.1.1](#)). CID models offer the opportunity to develop strategies for large-scale perturbation screens (e.g. CRISPR-Cas), which can be assessed using these single-cell multi-omics technologies ([section 3.1.1](#) and [3.1.3](#)).

Ultimately, such refined cell-based models will substantially enhance our mechanistic understanding of CIDs and identify cellular compartments which might be specifically accessible by targeted treatment approaches. These systems will be important tools to test therapeutic principles, which will include new drug targets, repurposed available compounds as well as completely new approaches (e.g. site-specific epigenetic reprogramming to overcome differentiation impairments). For example, for inflammatory bowel disease, the current challenge is to mimic the disease process between epithelial, mesodermal (immune cells, vasculature and fibroblast compartment) and neuronal cells to understand the impairment at each layer. Overcoming current limitations (e.g. modelling influx/efflux of inflammatory cells) will enable another crucial layer of understanding and rapid pre-clinical testing of novel targeted therapies.

Development of advanced pre-clinical disease models to study CID progression and therapy response: testing new therapeutic concepts

Current animal models of CID only capture parts of the respective underlying pathophysiology. Genetically altered mice are often complete-loss-of-function models, which do not reflect specific genetic variants that are associated with CID. Therefore, LifeTime proposes a particular focus for advancing pre-clinical models for CID using CRISPR-Cas based technologies to create the required mutations in selected genetic background, introduce heterozygous SNPs and genomic regions genetically associated with CID in humans ([section 3.1.3](#)). These novel pre-clinical models will better mimic the effect of human coding variants or the effect of regulatory elements. Coupled to appropriate perturbation (e.g. by gnotobiotics, antigenic stimuli or cellular transfer), such models will be powerful tools for understanding human CID mechanisms and potential targets. Efforts to incorporate human aspects of such models will provide crucial additional insights to understand why translation from mice to humans has often failed in the past. Such models need to include the chronicity and co-morbidity aspects of CID, which reflect aspects of the respective disease e.g. fibrotic scarring and atrophy or metabolic consequences of chronic inflammation. Single-cell multi-omics technologies, including transcriptomic, proteomic and metabolic approaches developed above will enable the delineation of signalling events, cellular interactions, reconstruction of (immune)metabolic events and may also include non-invasive physiological measurements (e.g. of mitochondrial metabolism) at single-cell level ([section 3.1.1](#)).

These advanced pre-clinical models will be an important step towards closing the gap between basic research and translation of these findings into the clinics. In proof-of-concept studies, they will enable new cell-specific therapeutic concepts such as sequential immunotherapies, microbiota-based strategies to modulate specific cell types or delivery of targeted epigenetic modification therapies to be tested. This approach will lead to a disruptive advance in generating personalised pre-clinical models that will enable stratified testing of repurposed drugs and new therapies. For example, for rheumatoid arthritis and inflammatory bowel disease, one of the current challenges is to understand the exact impact of immunologically active cells, which do not belong to the classical migratory immune cell compartment, such as fibroblasts and epithelial cells. Advanced pre-clinical models to study human risk gene loci, epigenetic reprogramming of specific loci or the therapeutic transfer of autologous re-programmed cells will enable a radical paradigm shift in the treatment of CIDs.



Longitudinal studies of disease progression and response to therapy using advanced cell-based biomarkers and novel patient-reported outcomes to develop innovative clinical endpoints: earlier detection and interception

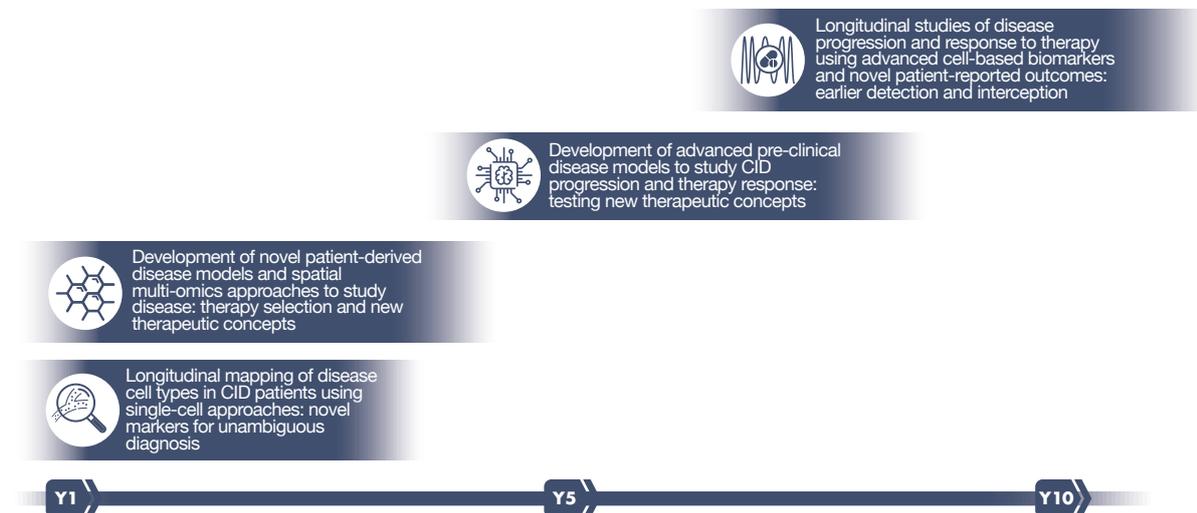
A major challenge in future CID patient care is the definition of actionable disease sub-phenotypes to reliably predict disease progression and to provide a rationale for disease interception and individual therapy selection. CIDs as a disease group share a common set of genetic variants, signalling pathways and environmental risk factors, however, determinants of disease etiology are distinct from biomarker predictors of disease behaviour or diagnosis. Exploiting longitudinal high-resolution data sets from well-characterised clinical cohorts will define molecular and cellular biomarkers that identify prognostic disease endotypes to clearly predict future disease behaviour. These biomarkers will address the problem of primary and secondary non-response to targeted therapies and tailor specific therapy concepts for individual patients. LifeTime recommends to build on efforts in several EU-funded projects (H2020 SYSCID, IMI2 3TR) that are collating large CID patient cohorts receiving first time targeted therapies in long-term observational studies using harmonised protocols. This includes harmonisation of follow-up schedules, clinical scoring systems and recording of co-morbidities. LifeTime's approach delivers a unique opportunity to exploit these and future systematic collections in the most meaningful sense by assessing the dynamics of cellular and functional heterogeneity in diseased organs and peripheral blood to extract meaningful predictive biomarkers. The approach will develop spatially-resolved single-cell multi-omics technologies into a disruptive clinical



diagnostics tool-set using machine learning-based algorithms and create predictive disease models (section 3.1.1 and 3.1.2). Successful translation requires benchmarking against state-of-the-art standard tissue-based methods, such as histological scores or routine lab tests. Defining deep remission on the cellular level, e.g by associating the presence or absence of particular cell states with prolonged response to therapy, will have an immediate impact as an innovative molecular endpoint in clinical trials. It will lead to improved and individualised usage of targeted therapies by employing quantifiable multi-modal biomarkers for a better anticipation of individual disease behaviour and definition of disease control.

Such single-cell multi-omics derived insights will provide novel concepts to clinically address disease severity and remission. Including innovative patient-centric outcome parameters will provide crucial insights into disease impact on patients' lives and integrate innovative objective measurements (wearables, smart patient home). This advanced dimensionality of patient-derived data will be important to close the gap between the high granularity and dynamics of molecular assessments and still more than crude ways to clinically describe disease behaviour (e.g. number of stools in inflammatory bowel disease).

Another important aspect of clinical diagnostics relies on innovative imaging-based methods (e.g. functional magnetic resonance imaging, *in vivo* microscopy), which offer the possibility of correlating results from cell-based molecular markers with non-invasive diagnostic principles. In proof-of-concept studies, such new combined diagnostic concepts should be tested longitudinally to demonstrate the predictive power of LifeTime's cell-based approach and enable earlier interception of disease. This requires interactions with different stakeholders (e.g. regulatory authorities and patient organisations) for communicating and proper benchmarking of innovative clinical and molecular endpoints.



Chronic Inflammatory Disease Roadmap timeline

Expected Scientific Impact

SHORT-TERM (1-7 years):

Identification of immune cell subtypes involved in disease heterogeneity and therapy refractoriness, resolving molecular taxonomy of disease beyond the organ-based manifestation will lead to early predictors of disease trajectories, which are necessary for the meaningful stratification of CID patients and the rationale design of future clinical trials.

Refined patient-derived models will substantially enhance the mechanistic understanding of CIDs and identify cell populations for targeted treatment approaches. These models will be important tools to test therapeutic principles, including new drug targets, repurposed available compounds as well as completely new approaches.

Advanced pre-clinical models will be an important step towards closing the gap between basic research and translation of these findings into the clinics. In proof-of-concept studies, they would enable the testing of new cell-specific therapeutic concepts.

LONG-TERM (8-15 years)

Larger, biomarker-informed basket trial for targeted therapeutic intervention (proof-of principle trial to optimise efficacy), development of targeted strategies for epigenetic reprogramming of immune cells.

Medical Challenge

- // Understand the role of cellular heterogeneity in predicting a patient's disease trajectory and response to therapy
-

Outputs

- // Increased understanding of the cellular basis for autoimmune diseases and variability between patients
 - // New technologies for identifying the cell types and molecular mechanisms involved during the onset of disease and response to immunotherapy
 - // Creation of advanced patient-derived models to recapitulate pathophysiology, drug repurposing pipelines and to test new immunotherapeutic concepts (sequential immunotherapy or targeting microbiota)
 - // Identification of new drug targets and novel cell-specific therapeutic concepts
 - // Identification of biomarkers for patient stratification for specific immunotherapy regimens
 - // Biomarker-informed clinical trials for targeted strategies of immune cells
-

Impact

- // Better quality of life for patients through improved disease management and control
- // Earlier detection and interception of diseases
- // Improved translation of new therapies based on next generation pre-clinical models and advanced cell biomarkers and clinical endpoints

Example – Impact on Inflammatory Bowel Disease

- /// Provide a molecular taxonomy of disease beyond the organ-based manifestation and lead to early predictors of disease trajectories for earlier detection. These will include molecular and cellular markers to enable the meaningful stratification of patients and the rationale design of future clinical trials.
- /// Advanced patient-derived models to enhance the mechanistic understanding of the IBD disease process between epithelial, mesodermal (immune cells, vasculature and fibroblast compartment) and neuronal cells. These models will be important tools to test therapeutic principles, which may include new drug targets, repurposed available compounds as well as completely new approaches (e.g. site-specific epigenetic reprogramming to overcome differentiation impairments). Advanced pre-clinical models to study human risk gene loci, epigenetic reprogramming of specific loci or the therapeutic transfer of autologous re-programmed cells will enable a radical paradigm shift in the treatment of CIDs.
- /// Single-cell multi-omics analyses will provide novel concepts to clinically address disease severity and remission. Including innovative patient-centric outcome parameters will provide crucial insights into disease impact on patients' lives and integrate innovative objective measurements (wearables, smart patient home). This advanced dimensionality of patient-derived data will be important to close the gap between the high granularity and dynamics of molecular assessments and the crude ways to clinically describe disease behaviour (e.g. number of stools).
- /// New combined diagnostic concepts based on combining innovative imaging-based methods (e.g. functional MRI, *in vivo* microscopy) with cell-based molecular markers for non-invasive diagnostic principles will enable earlier interception of disease.

3.2.5 Cardiovascular and Metabolic Diseases

Medical Challenge

Cardiovascular and metabolic diseases (CMD) are the leading cause of death worldwide today. In Europe, 45% of all deaths are due to CMD. With 29% of all deaths under 65 years, CMD is also the leading cause of premature mortality of which many cases are deemed to be preventable through timely and effective treatment. Despite enormous successes of interventional and drug therapies, they remain the world's largest health problem. Currently, over 85 million Europeans suffer from cardiovascular diseases, causing early disability and interfering with healthy ageing - a dramatic situation that represents an enormous economic burden.

Many CMDs lack effective therapies. These include heart failure with reduced and preserved ejection fraction, and inherited, toxic, viral, auto-immune and storage disease related cardiomyopathies, which when untreated also result in heart failure (HF). A major reason is that despite substantial progress in the understanding of epidemiology, physiology and pathophysiology of CMDs, knowledge of their cellular and molecular causes is still in its infancy. Current therapies generally do not take the underlying etiology into consideration and primarily alleviate symptoms accompanying the disease. Furthermore, the relationship between abnormal cardiac cell structure/function and pathophysiology is not sufficiently incorporated into clinical decision-making during HF therapy. A detailed characterisation of changes in cell-type composition and gene expression of individual cells in different types of HF is urgently required for a new molecular classification. This will enable subsequent patient stratification needed for optimisation and individualisation of HF treatments. In addition, the resulting novel insights into HF etiology-specific pathophysiology will trigger **novel therapeutic approaches** based on molecular profiling that will pave the way for **personalised HF treatment**.

New insight into the molecular and cellular basis of disease processes will open up a wealth of opportunities for new therapeutic and regenerative therapies as well as early recognition of CMD. This will require developing new technologies to investigate the complex interactions between different cell types, including immune cells, in the heart and the different autocrine, paracrine and endocrine signalling pathways involved, as well as various pathomechanisms such as fibrosis. Single-cell multi-omics approaches and particularly spatial technologies are needed to understand the complexity of cardiac cells and their relationships in health and disease. Single-cell multi-omics and spatial analysis should be integrated with cardiac medical technologies used to detect arrhythmias, vascular disease, or recognise acute cardiovascular events contributing myocardial infarcts to improve and automate analysis of digitalised data in cardiovascular imaging (going from electrocardiogram (ECG), echo to magnetic resonance) for **earlier disease detection and management**.

Given the emerging role of bone marrow derived inflammatory cells, which partially replace tissue resident immune cells, as drivers of pathophysiological remodelling and cardiac fibrosis, circulating cells could represent **new biomarkers** for identifying patients in whom inflammation may play a critical role in cardiac remodelling and fibrosis. Using this knowledge for early detection of CMD will allow early **interception**, which is especially important as chronification of the response to injury is of particular concern due to

the limited potential of the adult heart to regenerate. Early recognition of CMD will not only enable the prevention or an early treatment of CMD, it will also increase the sustainability of our healthcare systems.

Therefore, LifeTime has identified:

Understanding cellular and molecular mechanisms involved in CMD to enable early diagnosis and to design new mechanism-based therapies for precise clinical treatment

as a major unmet clinical challenge in the field of CMD.

Cardiovascular and Metabolic Diseases Roadmap

To address the key challenges in the field of CMD LifeTime proposes to address the following objectives:

- Identify the heterogeneous response of parenchymal and non-parenchymal cells (e.g. inflammatory cells, endothelial cells, fibroblasts etc.) and underlying molecular mechanisms involved in CMD in organoids, tissue engineering constructs mimicking disease states, established mouse models, and human samples**
- Deeply assess the contribution of immune cells to disease progression by determining the heterogeneity of circulating and tissue resident cells in mouse models and human samples**
- Use the mechanistic knowledge to identify targets for interfering with pathophysiological secondary disorders that lead to cardiac dysfunction and assess their therapeutic benefit in disease models. Use single-cell multi-omics and imaging technologies to guide the use of novel therapeutic interventions to treat patient subgroups that are predicted to respond to treatment**

For this roadmap LifeTime's expected impact for heart failure is used as a showcase example in the field of CMD.

Required Investments for Cardiovascular and Metabolic Diseases

To address the above objectives LifeTime recommends the implementation of the following multidisciplinary research programmes:

Elucidating cell states and types associated with pathomechanisms

To study changes in cell-type composition and gene expression profiles of individual cells in response to different triggers of HF, LifeTime proposes to immediately use established single-cell multi-omics techniques such as transcriptome profiling and measuring chromatin accessibility in individual dissociated cells as well as spatial transcriptomics. These approaches will characterise cardiac cell states and types, their expression networks and cellular circuits, and locate these in 3D space. This will require tissue sections from patients with different forms of heart failure to understand the cellular and molecular drivers that enable functional plasticity in response to different stress responses leading to heart failure. Such tissue is available through numerous tissue banks established in a variety of population studies that exist for cardiovascular diseases. These provide the material from clinically well characterised patients required to correlate cellular and molecular mechanisms underlying structural alterations with clinical, imaging and hemodynamic data. Understanding disease mechanisms requires the systematic integration of human tissue analysis with animal models for longitudinal sampling in the presence of systemic influences such as blood pressure and immune responses.

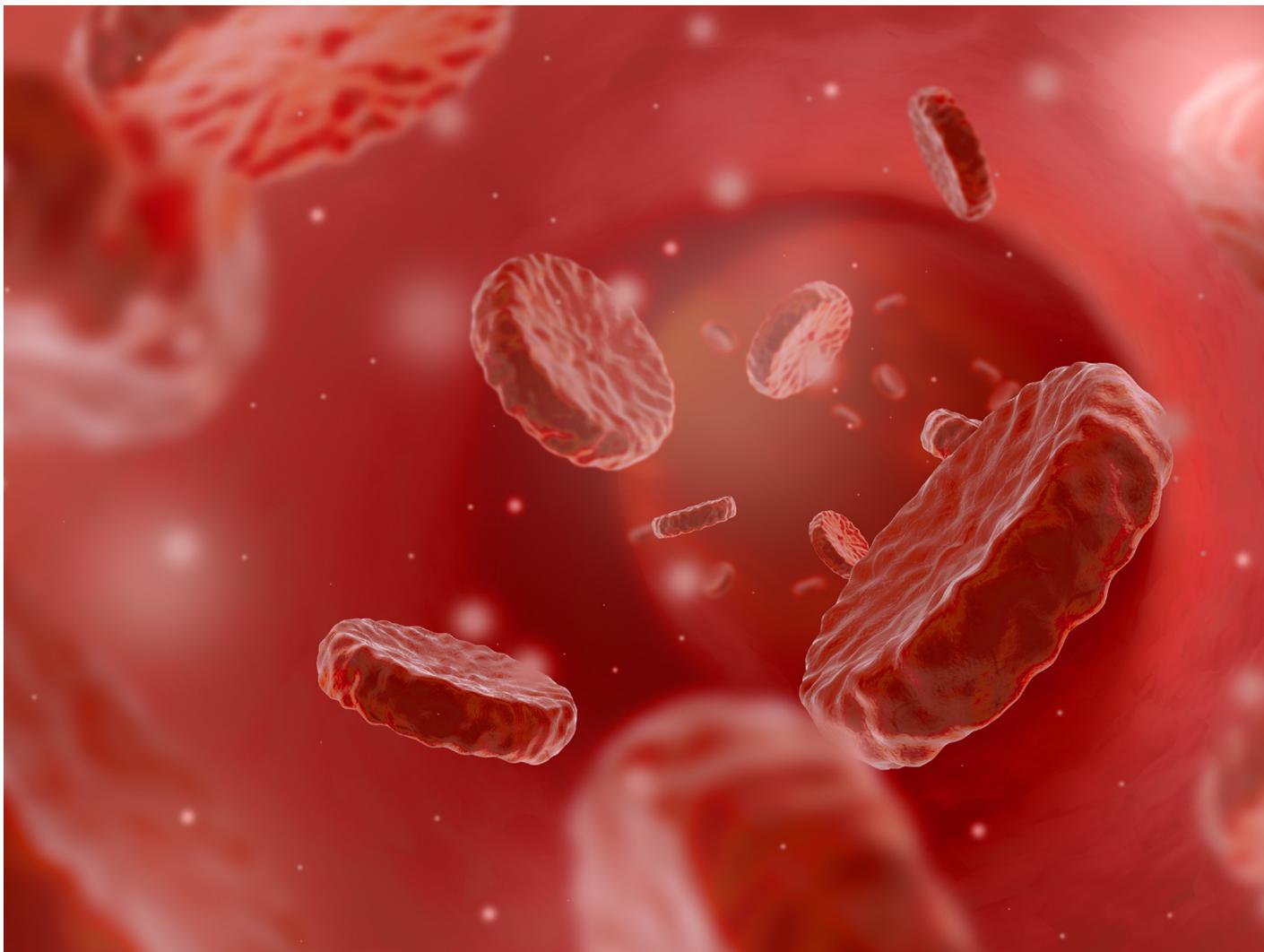
Molecular profiling together with clinical characterisation will serve as a starting point for a new molecular classification of HF and assessment of prognosis to significantly advance patient stratification for treatment and allow for a more informed interpretation of genetic testing results in the clinic. Comparing changes in cell type composition of cardiac tissue at different disease stages will provide new insight into the underlying molecular mechanisms driving the course of disease and identify early disease markers and new therapeutic targets for precision therapy of HF pathologies.

Development of novel multi-omics approaches to study cardiac disease mechanisms

Complexity of the heart and cardiac disease biology requires the development of new technologies to address specific aspects of pathology. For example, integration of single-cell full-length RNA-isoform will address currently unknown heterogeneity in isoform usage between cells, distinct cardiac regions and response to physiological stimuli as well as disease triggers. Its complex physiology means that spatial information is particularly important for the heart, and spatial knowledge of cardiac cell type arrangement in three dimensions is urgently needed to understand the heart at the single-cell level ([section 3.1.1](#)). For example, it is fundamentally important to comprehend how the swirling pattern of cardiac muscle tissue contributes to the heart's ability to pump blood effectively and how disease associated changes affect cardiac function. The cardiac conduction system initiates and coordinates the contraction of the heart across the entire organ – from atria down to the interventricular septum and along the ventricles. Dysfunction of the conduction system can cause arrhythmia and knowledge of how the specialised cells

involved are arranged in three-dimensions will lead to a better understanding of how changes predispose a person to complications such as stroke or HF. Studying cardiac cell type arrangement can be initiated using spatial transcriptomics in two dimensions, but requires tracing cells in three dimensions and ultimately in four-dimensional spatial trajectories ([section 3.1.1](#) and [3.1.2](#)). These will be key to elucidate how muscle tissue is built up, how neighbouring cells communicate and interact through autocrine/paracrine signals, electromechanical connectivity and biophysical interactions. Elucidation of immune cell interactions with connective tissue cells is especially important for understanding disease related cardiac fibrosis mechanisms such as cytokine release that can serve as novel therapy targets. Additional aspects of cardiac physiology require the integration of other spatial technologies ([section 3.1.1](#)). Spatial proteomics will enable the investigation of the important role of cell-cell communication in the heart based on, for example, receptor and ligand expression. Energy metabolism is of particular importance to the heart as it must contract perpetually which requires a tight coupling of ATP production and myocardial contraction. The heart is capable of remodelling the metabolic pathways in chronic pathophysiological conditions, which modulates myocardial energetics and contractile function. Therapeutic interventions have been clinically tested to target substrate preference, insulin sensitivity, and mitochondrial function to variable success. To fully understand the complexity of the cardiac metabolism in concert with cardiac contraction and cardiac tissue structures requires the development and integration of novel spatial metabolomic technologies.

The development and integration of spatial technologies will provide novel insights into structural and myocardial energetics alterations in three dimensions that will enable a detailed characterisation of contractile and cardiac conduction system dysfunctions. This will significantly expand the understanding of cardiac disease pathomechanisms and lead to the recognition of novel region-specific therapeutic targets.



/// Patient-derived experimental disease model development to enable longitudinal analysis of disease onset, progression and response to therapy

Cardiac organoids hold great potential in studying the molecular mechanisms driving disease progression ([section 3.1.3](#)). However, in addition to increasing the multicellularity and maturation of cardiac organoids to more accurately model the tissue it also needs to be considered that the human heart consists of specialised substructures that acquire different features during development and are physiologically and functionally distinct. Developing these aspects of human *in vitro* models is particularly important for stem cell-based regenerative, therapeutic purposes. For example, developing cardiac “patches” to recapitulate specialised substructures could be introduced into patients and replace damaged tissues. Also in disease modelling differences in cardiac tissue composition in the various heart regions is important since cardiac diseases can show structural alterations in particular regions. For example dilated cardiomyopathy affects the left ventricle to a far greater extent than the right ventricle. This clearly indicates the need for advancing cardiac organoids with the goal to achieve multicellularity including immune cells, maturing organoids to resemble adult cardiac tissue and to model the different cardiac substructures found in an adult human heart.

These new technologies will provide for the first time the possibility to perform pre-clinical screening of novel drugs and for testing of repurposing drugs in sophisticated models to provide a better understanding of their effectiveness and translatability to humans. Furthermore, patient-derived cardiac organoids can serve as personalised disease models to test new therapeutic approaches. The use of such models will significantly accelerate the bench-to-bedside process of novel therapeutic strategies based on basic research findings and will boost the field of engineered heart tissue grafts for regenerating diseased myocardium.

/// Identification of novel biomarkers for earlier disease detection and interception based on non-invasive liquid biopsies

Inflammation, fibrosis and microvascular dysfunction/regression are hallmarks of CMDs and comorbidities, including diabetes, liver disease, kidney disease and cancer. The early recognition and monitoring of these processes requires establishing minimally-invasive detection strategies to identify novel multi-dimensional biomarkers. Immune cells play an important role in not only inflammation but also fibrosis and microvascular dysfunction. To obtain minimally-invasive information on the status of these processes, LifeTime proposes to investigate the potential of circulating immune cells for their correlation with tissue resident immune cell populations. Longitudinally studying the relationship between circulating and resident immune cells in animal models and correlation with results from patient blood and tissue samples will reveal if circulating cell profiles reflect resident immune cells in humans at different stages and can be used in clinical decision making. Furthermore, LifeTime proposes to study clonal hematopoiesis of undetermined potential (CHIP) in peripheral blood cells by profiling single circulating cells to identify the impact of known and unknown CHIP mutations on cardiovascular diseases. Understanding the mechanisms underlying the connection between somatic mutation-driven clonal hematopoiesis and cardiovascular disease will be highly relevant in the context of personalised medicine, as it may provide key information for the design of diagnostic, preventive or therapeutic strategies tailored to the effects of specific somatic mutations. Multiple human cohorts such as the Flemengho study, The European network on database and biobanking in cardiomyopathies and

myocarditis, The LifeLines Cohort Study and The German National Cohort (GNC) exist with banked blood for single-cell profiling of immune cells and CHIP identification. In addition, numerous tissue banks exist for the validation of biomarkers identified in studying cardiovascular disease mechanisms.

Biomarkers based on blood samples will provide, for the first time, a measure to enable detection of early signs of HF risk and thus allow for early intervention. They will facilitate tracking of disease progression and clinical decision making aligned with the course of disease. Furthermore, such biomarkers will greatly aid the stratification of populations for clinical studies of existing and repurposed drugs as well as therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models.

Development and validation of novel biomarkers and cell-based therapies

We expect that in ten years we will have a significantly increased understanding of the cellular and molecular mechanisms underlying cardiovascular diseases and novel biomarkers for patient stratification. To serve as the foundation of new guidelines relevant for clinical decision-making, biomarkers will need to be validated in clinical studies or patient cohorts. The identification of novel therapeutic targets based on understanding HF mechanisms will lead to the development of new therapy approaches such as cell-based targeted anti-inflammatory and anti-fibrosis therapies as well as therapies addressing expanded somatic blood-cell clones. These approaches are already beginning to emerge, in a mouse model of cardiac injury it was shown that T cell immunotherapy can be used to limit cardiac fibrosis. Moving forward with engineered T-cell therapies in human heart failure is a promising strategy but requires further developments such as generation of T cells that can be turned on and off to limit unwanted activity. Cellular therapies need to be tested in animal models, followed by clinical studies.





Development and validation of novel biomarkers and cell-based therapies



Identification of novel biomarkers for earlier disease detection and interception based on non-invasive liquid biopsies



Patient-derived disease model development to enable longitudinal analysis of disease onset, progression and response to therapy



Development of novel single-cell multi-omics approaches to study cardiac disease mechanisms



Elucidating cell states and types associated with pathomechanisms

Y1

Y5

Y10

Cardiovascular and Metabolic Diseases Roadmap timeline

Expected Scientific Impact

SHORT-TERM (1-7 years):

Increased understanding of underlying HF disease mechanisms, including HF trigger-specific pathophysiology that will result in the recognition of novel targets for precision therapy.

Novel biomarkers will pave the way for a new molecular classification of heart failure and for the optimisation and individualisation of heart failure treatments based on understanding underlying molecular mechanisms.

Novel biomarkers will aid patient stratification for future clinical studies of existing and repurposed drugs as well as of therapies that demonstrate efficacy in proof-of-concept studies in advanced pre-clinical models.

LONG-TERM (8-15 years)

New molecular understanding of HF pathology will impact pathophysiological concepts and clinical decision making for therapy.

Novel therapeutic modalities will be tested in patient stratified clinical studies using molecular biomarkers. Together with the novel ability to track disease course, this strategy will lead to personalised treatments that target the cellular and molecular causes of disease at the right time and will make current symptomatic treatment obsolete.

Medical Challenge

- // Understand cellular and molecular mechanisms involved in CMD to enable early diagnosis and to design new mechanism-based therapies for precise clinical treatment
-

Outputs

- // Increased understanding of the cellular basis for pathomechanisms involved in CMD
 - // Development of new technologies for understanding the roles of cell types and spatial arrangements including cardiac regions
 - // Creation of advanced patient-derived models to recapitulate cardiac structure as well as pathophysiology and be used as a basis for regenerative therapies
 - // Identification of biomarkers using minimally-invasive biopsies for early CMD detection
 - // Biomarker-informed clinical trials for clinical decision making for novel therapeutic concepts
-

Impact

- // Earlier detection and interception of CMD risk and heart failure based on novel biomarkers and minimally-invasive liquid biopsies
- // Accelerated translation of novel cell-based therapies and repurposed drugs using next generation pre-clinical disease models

Example – Impact on Heart Failure

- // New molecular classification of HF and assessment of prognosis to significantly advance patient stratification for treatment and allow for a more informed interpretation of genetic testing results in the clinic.
- // New insight into the underlying cellular and molecular mechanisms driving the course of HF, including specialised contractile and cardiac conduction system dysfunctions. These will identify early disease markers and new therapeutic targets for precision therapy, including new region-specific therapeutic drug targets for HF pathologies.
- // New patient-derived model systems will enable pre-clinical screening of novel drugs and for testing of repurposing drugs to provide a better understanding of their effectiveness and translatability for HF in humans. The use of such models will significantly accelerate the bench-to-bedside process for novel therapeutic strategies and developments in the field of engineered heart tissue grafts for regenerating diseased myocardium.
- // Biomarkers based on blood samples will provide for the first time a measure to enable detection of early signs of HF risk and thus allow for early disease detection, interception, disease progression and clinical decision making aligned with the course of disease. These biomarkers will be used to stratify populations for clinical studies of existing and repurposed drugs and new therapies.
- // Validation of novel biomarkers for patient stratification in clinical studies or patient cohorts. The identification of novel therapeutic targets based on understanding HF mechanisms will lead to the development of new therapy approaches such as cell-based targeted anti-inflammatory and anti-fibrosis therapies (e.g. engineered T-cell therapies) as well as therapies addressing expanded somatic blood-cell clones.





04

A Multisector Strategy for Industry and Innovation

Creating a single-cell based biomedical innovation ecosystem in Europe, involving start-ups, established small, medium and large enterprises as well as research and technology organisations will form a solid basis for establishing personalised or precision medicine as the new standard of care. Only a pan European integration of efforts within the public and private sectors will offer sustainable, transformative solutions. Most of the technologies at the core of the LifeTime vision are at the Technology Readiness Level (TRL) of proof of concept, or validated in the laboratory, such as single-cell multi-omics, spatial transcriptomics, high-throughput imaging and single-cell computational models. These need to be further developed and integrated together with industry partners to a TRL where they have been tested and demonstrated in a clinical environment.

To join all necessary European stakeholders, the Industry Strategy introduced in this Strategic Research Agenda (SRA) identifies key priority areas divided into five industry engagement platforms: i) technology adoption and development, ii) strategic partnerships, iii) networking brokerage, iv) entrepreneurship and v) expert advising. Appropriate framework conditions including intellectual property (IP) policies for firms in the EU should ensure successful implementation and operation of these platforms as outlined in [section 7.6](#) to be able to succeed and compete globally.

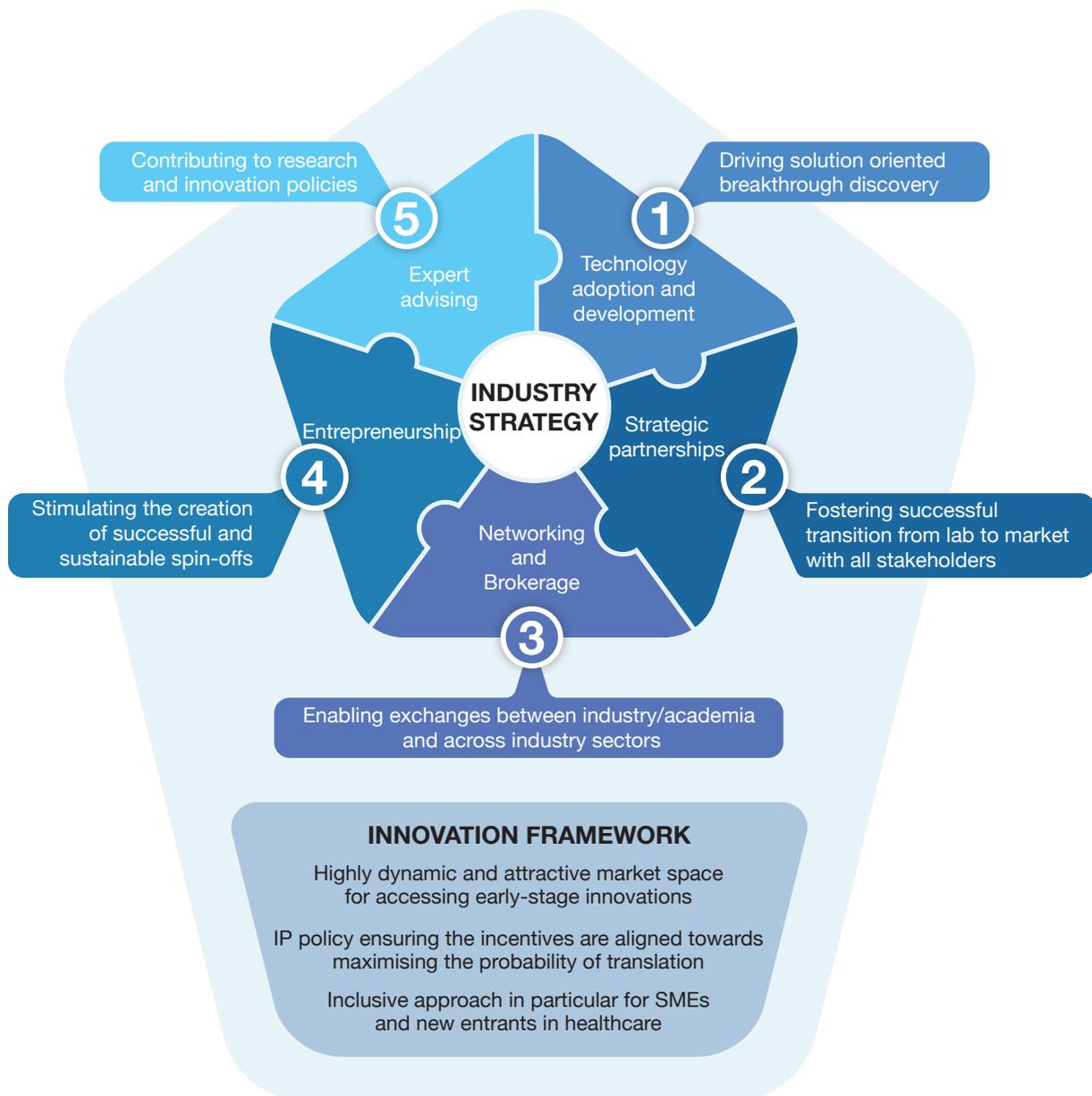
LifeTime has a unique potential for developing innovative technologies and discovering new drugs or diagnostic opportunities with a realistic chance of significant value creation. This could be very powerful in generating innovation, creating spinoffs and supporting sustainable and inclusive growth of companies, regions and countries ([section 2.4](#)).

In order to deliver on the ambitious objectives of this SRA, European public and private sectors need to join forces. LifeTime recommends addressing the key challenges described below to ensure a major role of the industry sector in the proposed path to transform healthcare for all citizens. Establishing five industry engagement platforms will facilitate involvement and coordinated co-operation between all stakeholders and foster the development of a competitive health industry in Europe. LifeTime will apply single-cell multi-omics to pathology, develop single-cell resolved organoids models for personalised treatment and advance early-stage technologies such as molecularly empowered predictive machine learning. This not only requires intensive collaboration between academia and industry partners from the following areas but also strong interactions with the finance industry to improve overall framework conditions for innovation, including access to finance (risk capital and other alternative sources of financing):

- // **Single-cell technologies:** sample isolation/preparation, microfluidics, sequencing, epigenomics, proteomics/metabolomics, etc.
- // **Pharmaceuticals:** target identification, drug development, new therapies, translational medicine, etc
- // **Medical diagnostics:** biomarkers, assays, devices, point of care testing, etc.
- // **Biotechnologies:** CRISPR-Cas, organoids, subcellular analyses, etc.
- // **Imaging technologies:** advanced microscopy, live imaging, deep imaging, etc.
- // **IT & Data sciences:** infrastructure, high performance and cloud computing, secure data management, bioinformatics, analytics, AI & machine learning, etc.

To maximise the impact of this SRA, LifeTime has developed an Industry Strategy addressing the following major bottlenecks:

- // **Absence of a comprehensive platform driving multi-sector collaboration and enabling all stakeholders to participate in creating transformative healthcare solutions**
- // **Insufficient engagement of industry in lower TRL Research and Innovation (R&I) projects**
- // **Lack of awareness of the latest advances and available solutions across sectors and too high threshold for implementing emerging technologies limiting technology diffusion across Europe**
- // **Cultural barriers limiting exchange between sectors, insufficient knowledge and data flows between disciplines and actors**
- // **Complex environment of health innovation, highly regulated industry and very cost-intensive Research and Development (R&D) not offering quick returns on investment**
- // **Low access to risk capital, bottlenecks in providing financing to new companies, risk averse European investors**



LifeTime Industry Strategy and Innovation Framework

In addition to the implementation of the five proposed platforms, LifeTime recommends creating an innovation framework for innovative ways of interacting and sharing risk between stakeholders, supporting public/private partnerships and business creation. The ultimate goal is to organise a highly dynamic and attractive market space for accessing early-stage innovations from LifeTime. The IP policy should ensure the incentives are aligned towards maximising the probability of translation into product and service development trajectories with add-on investment from the private market.

4.1 Accelerating Technology Adoption and Development

Technological innovation has always been a major driver for breakthrough discoveries. Therefore, LifeTime proposes to develop a technology adoption and development platform across Europe, in collaboration with industrial technology providers with the aim to lower the threshold for scientists in both industry and academia to implement emerging technologies in their pre-clinical and clinical research. It would create a win-win situation whereby users can test innovative or disruptive technologies for applications in their research much earlier and developers can feed these experiences back into their developmental pipelines. This will ensure that future products deliver what researchers require to accomplish their goals. We have identified the following key elements:

- /// **Scouting and early-access programmes** for new, emerging technologies developed by industry or academia. A screening system should enable the earlier discovery of innovative technologies that can potentially impact LifeTime research and promote start-ups. This will form a basis for a long term and interactive matching process with the goals of the LifeTime community. Early-access programmes should accelerate the adoption of the scouted technologies at various development stages in academic or industry laboratories. Based on competitive calls, LifeTime recommends to provide grants to scientists working on the proposed disease roadmaps ([section 3.2](#)) to support implementation of these new technologies in their research. Different funding rates could apply for different categories from non-commercialised technologies in the prototype phase to recent commercialisation (e.g. < 3 years). Moreover, commercial agreements with technology providers offering competitive product pricing would be in the interest of both companies and research institutions.
- /// **Open technology innovation laboratories** to create a bridge between external early-access prototypes and commercial ready to use technologies by enabling direct expertise and knowledge exchanges between technology developers and researchers. There should be dedicated laboratory space with technology specialists working alongside interested researchers to launch the technologies, perform troubleshooting, train scientists, manage the collaboration with companies and help LifeTime researchers make strategic implementation decisions after careful technology evaluation. Industrial partners (e.g. biotech and pharma companies) could also be granted access to these innovation lab platforms under well-defined conditions that appropriately cover commercial aspects. Open laboratories can lead to joint new developments of future commercial value that should be protected by appropriate agreements.
- /// **Technology co-development projects:** The technological developments proposed in [section 3.1](#) can only be realised in collaboration between the public and private sector. Technology companies from the fields of single-cell analysis, imaging and IT/data science are very interested in LifeTime's vision and eager to co-develop technologies with academia. For them it is crucial to see current and future directions in their respective fields, determine priorities and requirements for scaling up and

integrating new technologies. Many single-cell technology companies (liquid handling platforms, single-cell transcriptomics, proteomics, epigenomics & multi-omics, RNA-protein interactions, etc.) welcome the co-development of pipelines, instruments, protocols and novel applications in joint projects. They are also willing to support the commercialisation of technologies coming from academia. Some also offer their infrastructure to scale up/further develop (e.g. to create diagnostics based on multi-omics analysis of liquid biopsies) technologies and concepts from academic labs (e.g. providing a platform to multiplex assays). Focused, multi-stakeholder consortia across industry sectors in partnership with academia can leverage new opportunities and help to bring down cost, and increase efficiency.

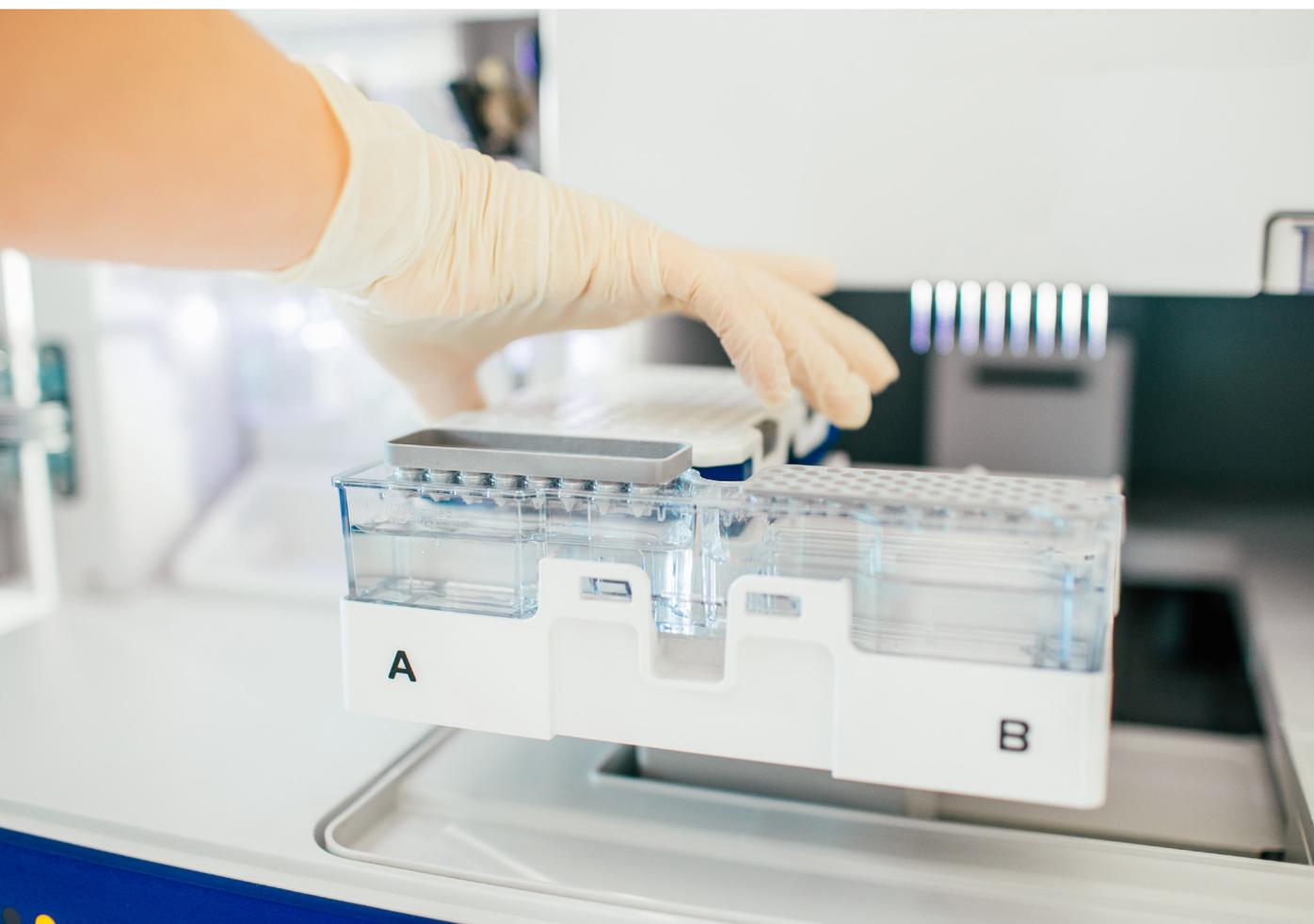
The proposed technology adoption & development programme offers attractive benefits for many industry supporters of LifeTime. It provides them with an early indication of what is needed to take the technologies to market or into the clinic. Moreover it enables testing and evaluation of new technologies from different sectors or academic developers in their own R&D efforts. Different companies could also synergise more between each other, with such a platform - combined with the network support ([section 4.3](#)) - serving as a catalyst. This would also be beneficial for technology developed by academic groups which would be identified, tested, and presented to collaborating companies earlier in their development pipeline.



4.2 Fostering Successful Transition from Lab to Market

LifeTime recognises the importance of strategic partnerships between public and private sectors. These should involve all relevant stakeholders in the value chain and span the entire biomedical innovation cycle from discovery research, technology development, and implementation into hospitals and the healthcare industry. Building on the success of the Innovative Medicine Initiative (IMI) and seizing opportunities arising from the newly developing EU public private partnership - European Partnership for Health Innovation or EU health PPP - joint projects between academia and industry from different sectors should be supported. Covering the cycle of innovation from high-risk research to higher TRLs as well as bridge and integrate the different sectors of pharma, biotech, imaging and data sciences would bring strategic innovation potential. Significant support is required for basic single-cell biology, for multi-omics research and imaging, for organoid-based disease models and for the translation of novel computational approaches to single-cell biology data as well as their integration into clinical studies. We recommend that public-private partnerships deal with the following aspects in a collaborative effort:

/// Benchmarking, standardisation: Multi-centre, multi-site studies and benchmarking initiatives for instrumentation, as well as experimental approaches, are crucial for industry. Common standards will facilitate the technology development and its scalability following the identified priorities outlined in [section 3.1](#) for each of the technology areas. Through shared procedures and goals, common standards will boost research outcomes and market uptake of innovation. Among different technology areas, companies are calling in particular for standardisation of data format, transfer, storage and analytic software.



-
- Translational research:** The proposed disease roadmaps ([section 3.2](#)) including the generation of advanced patient-derived disease models, identification of biomarkers and novel drug targets should be implemented by inter-sector collaborations ensuring that new insights in basic biomedical research are translated rapidly and efficiently, to maximise impact on patients' lives. Improving collaboration among all actors from the translational research value chain, including patients, scientists, clinicians, physicians, regulators and industry is therefore essential.

 - Sharing of samples:** Creating “cohorts” of patient-derived disease models for longitudinal analysis requires access to patients from whom cell samples are available and which can be linked to functional medical imaging, genetic and clinical data. The availability of relevant human biological material is often a bottleneck for both academia and industry, especially for longitudinal analyses and the development of advanced personalised disease models. To accelerate research, biotech and pharma companies as well as academic researchers absolutely need high quality human samples. This requires the development of unified, controlled access systems.

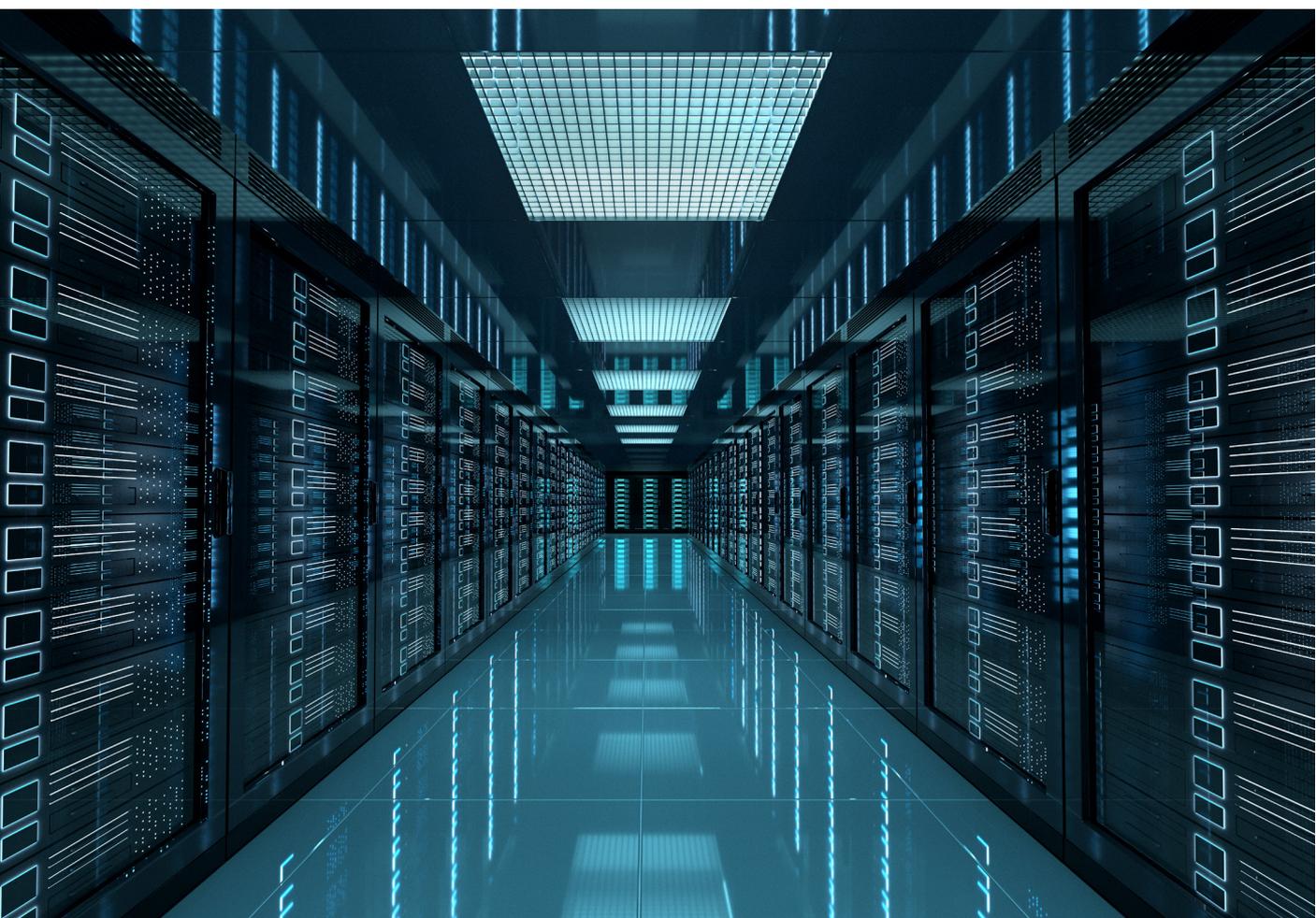
 - Large scale cohorts and clinical trials:** Longitudinal studies of disease onset and progression will lead to improved understanding of disease mechanisms. This will enable rational stratification of patients on the basis of biomarkers empirically linked to pathogenic mechanisms, the systematic identification of key molecules/pathways for drug targeting and/or repurposing and early disease detection and better prediction of disease prognosis. Together, these insights are poised to transform the design of clinical trials. Academia and industry should collaborate to bridge clinical with molecular/cellular endpoints and therapeutic approaches on the basis of validated patient-specific disease mechanisms.

 - Raw data repositories:** Joint industry/academia efforts should also focus on building repositories of data including raw data (single-cell, imaging), pre-clinical model treatment and/or clinical treatment outcome data. These data should, as much as possible, aim to comply with European Open Science and Innovation standards and the Findable, Accessible, Interoperable and Reproducible (FAIR) data principles. Data access needs to support quality control and data queries in line with agreed intellectual property rights. Beyond project-based collaborations, partners need to plan the sustainability of controlled FAIR data access and wherever patient data is generated or used, it should be integrated across studies in a legally and ethically compliant way, including requirements of the European General Data Protection Regulation (GDPR).

 - Secure data management:** Highly sensitive personalised data (e.g. genetic information, clinical data and medical imaging data) are collected and stored locally at hospitals and institutes, but derivatives of these data need to be made available in a secure and GDPR compliant way to all relevant stakeholders. Only a consolidation of data from multiple sites can leverage the power of subsequent AI-based analytics and therefore a secure data management concept is most important for the success of LifeTime. It needs to address, amongst others, different levels of data sensitivity and user-permissions (e.g. for clinicians, researchers and industrial partners), FAIR data, and an intuitive access platform.

Here, a European decision on how to handle clinical and omics data will be critical. Several companies in Europe as well as some EU-initiatives are working on solutions for this complex problem and should be supported as much as possible to scale their solutions to international level. The development of secure data management for LifeTime has the potential to be a cornerstone of European efforts towards ethical AI and a prime example for successful AI applications of clinical data worldwide.

- /// **Computing infrastructure:** Public-private partnerships should foster pioneering technologies (e.g. faster processing, in memory computation, AI-specialised hardware, etc.) to shape the next generation of the European medical and biodata compute infrastructure. The scale of the data that will be generated by the programmes proposed by LifeTime, the cross-disciplinary and international organisation combined with the ambition to pioneer novel analytics using AI, requires joint efforts across sectors and to connect and to build on existing European infrastructures and initiatives as much as possible (e.g. EMBL-EBI, ELIXIR, EOSC).
- /// **Data analytics and AI:** A priority should be to transfer algorithms, pipelines and processes from academic centred research in Europe to foster a strong private European sector in this discipline with a particular emphasis on supporting precision medicine efforts. It will also be critical for academia to develop new avenues to enable this sector to flourish and to become part of the required analytical ecosystem. To reduce the dependencies on the Big Seven in AI and to foster European efforts, developing a culture that integrates the private sector in data analytics into initiatives such as LifeTime will be key. This would also provide this sector sufficient space to develop commercially successful products, even if these seem to compete with efforts currently centred around academic institutions.



4.3 Enabling Exchange Between Industry and Academia and Across Different Industry Sectors

Identification and engagement of the most appropriate industrial and translational partners from the private and public sectors is crucial for implementing the potential strategic partnerships introduced above. Moreover, new collaboration opportunities that have not initially been anticipated will and should arise. Therefore, LifeTime recommends creating a networking brokerage platform for individuals, academic and industry organisations that share the goal of developing and integrating breakthrough technologies and applying them in the clinic for the benefit of patients. This platform would also support the technology adoption platform ([section 4.1](#)) and could include the following engagement activities:

- /// **Regular cross sectoral meetings:** LifeTime supporting companies would strongly welcome more opportunities for networking and knowledge exchange forums between partners from different fields that share the same vision and the continuation of the dialogue/exchange process initiated by LifeTime. To share experiences and ideas with all sectors interested in specific clinical or biological topics, we recommend the organisation of more focused cross-sectoral meetings (e.g. histopathology of cancer samples that would bring together single-cell and imaging-associated academics with diverse companies also working in the field of AI). Biohackatons where contributors work on specific challenges proposed by some participants could also be organised.
- /// **Exchange programmes:** In addition to meetings, LifeTime also put forward the need for programmes supporting cross sectoral exchanges of individuals not only between academia and industry but also between fields, for instance between IT and pharma. It is clear that optimising interactions requires a better understanding of different development timelines and distinct business models that exist in various industries.
- /// **Training/education:** Besides staff exchanges and more other activities, LifeTime Education and Training Programme ([section 6](#)) should engage industry partners. High-quality training courses and materials provided by Europe's leading experts in technology, innovation and entrepreneurship will be both developed with and accessible to industry partners.
- /// **Open innovation community:** Clear guidelines for an open innovation framework should enable the open sharing of well defined non-competitive results and data to foster new ideas and accelerate research progress.
- /// **Communication forum:** LifeTime communication channels that are tailored to industry needs will enable smooth information exchange between all members of the open innovation community (vacancies, latest technology offers, funding calls for academia/industry collaboration, etc.).

Public funding consulting: Industry sectors that are not or are less involved in IMI so far welcome new opportunities for public/private collaboration funded by the EU and other research funding organisations. However, access to such programmes is often a challenge for many companies lacking experience and resources. To foster public/private collaborations and support their funding competitiveness, dedicated support staff could facilitate this process: help identify partners, prepare grant applications, etc.

Interaction with regulators: LifeTime expects market entry of new products and services in precision medicine to follow a more complex path compared to previous procedures. To bring such products and services faster to market, we will promote interactions between regulators and academic partners (e.g. regarding medical device regulation, which will affect many technology developers) as an integral part of the application for market approval in a regulated market. LifeTime recommends the development of a framework for such fruitful collaborations between academia and industry when it comes to interactions with regulators.



4.4 Stimulating the Creation of Successful and Sustainable Spin-offs

LifeTime is committed to stimulate the creation of successful and sustainable spin-offs based on technologies invented/developed by the initiative's partners and beyond. In addition, LifeTime will continue to engage with investors such as venture capital funds as well as private equity specialised in the healthcare and life science sector to enable them to participate in the various industry engagement platforms. It proposes the following activities:

- /// **Nurturing entrepreneurial culture:** The diverse activities of the LifeTime Education and Training Programme ([section 6](#)) as well as of the other industry engagement platforms will contribute to develop an entrepreneurial culture. Academic partners will benefit from a supportive environment with multiple opportunities to obtain real-life business world experience.
- /// **Pre-seed/pre-incubation fund:** Given the high need to support innovation projects across high-risk fields, LifeTime recommends to engage with different funders, including venture capital funds, business angels, private equity, corporate ventures and public sources such as the European Investment Bank (EIB) to create a specialised LifeTime innovation fund. This would fund few, well-chosen innovation projects per year especially fostering technology bundling and enabling proof of concept studies before the founding of a new company.
- /// **Support for founders:** LifeTime will assist entrepreneurs with evaluating and developing the company concept and fundraising. The LifeTime industry engagement platforms will help founding projects to find appropriate management and infrastructure, and support the early phases after the company creation.

4.5 Reciprocal Expert Advising

From the start, LifeTime has interacted with and sought feedback and advice from key stakeholders in various industry sectors. Reciprocally, LifeTime research and clinical experts can inform and advise industry partners about the latest technology developments in their field, key challenges and most promising applications. LifeTime has an opportunity to function at the intersection of academic and industrial research, mediate closer interactions between the two sectors while advising in both directions:

/// **Industry advisory board:** Collecting strategic feedback and understanding the specific needs as well as challenges of various industry sectors is key to ensure that LifeTime strategy and operations are relevant for industry partners. We recommend that the Industry Advisory Board LifeTime has started to establish should regularly issue recommendations during LifeTime's further development ([section 7.3](#)). It includes experts from single-cell and imaging technology providers, the biotech, diagnostics and pharmaceutical industry, as well as the IT and data science sector.

/// **LifeTime expertise:** LifeTime experts can contribute to defining strategic Science & Technology agendas and help to identify critical priorities for the development and applications of breakthrough technologies (e.g. EU Health PPP planning and future topics definition).

Beyond this expert advising platform, LifeTime stakeholders from industry and academia can form an advocacy group acting as a strong body able to influence healthcare transformation in the next years by shaping national and international R&I policies.



4.6 Creating a Globally Competitive Innovation Framework for Companies in Europe

The successor of the Innovative Medicine Initiative, the next EU public private partnership - or EU Health PPP - could offer a framework for some joint projects between industry and academia ([section 7.4](#)) The increased involvement of other health industry sectors in the cross-sectoral private consortium compared to IMI is a very good starting point. Furthermore, the disease interception objective of LifeTime aligns closely with the EU health PPP strategic aims. Both initiatives have identified the better understanding of disease mechanisms as a major societal challenge. As of now, the new EU health PPP seems to be less focused on more fundamental research and early development/integration which is vital for emerging technologies as proposed by LifeTime. However, numerous representatives from the private sector have expressed interest in participating in these activities. It is also widely acknowledged that early industrial involvement is critical for a successful transition from the laboratory to the market and early development of industry standards with international partners ([section 1.5](#)).

Therefore, we are facing an unparalleled opportunity to expand the ecosystem of players related to the scientific objectives of LifeTime in particular with participation of small and medium-sized (bio)tech companies and new start-ups. To include the European computational, data, and software industry better is another important aspect. The open source policy in the academic biomedical field can often generate a difficult environment for commercial products to flourish. Yet, data analysis is one of the most promising growth areas for the coming decades, which will require a strong European private sector with sufficient start-ups, small and medium-size enterprises (SMEs) to provide data analytics and AI to users in the biomedical field.

Legal aspects and in particular IPR regulations should be adapted to the operational and business models as well as research and development timelines of companies not involved in IMI so far in order to define the best co-development pathways. For example, data science and analytics companies still experience the biomedical sector - in comparison to other sectors - as a high-risk area, which is a clear barrier for engagement of many IT and data science companies in Europe, particularly for start-ups and SMEs. Yet, this area might be one of the most promising growth markets in the 21st century for Europe. Therefore, to develop a European precision medicine sector, the ultimate goal should be to link the development cycle of pharma, imaging, biotech, diagnostic, digital and single-cell technology companies. To incentivise tech companies compared to pharma organisations, there could be a shift from the previously shared use of any discovery in IMI projects. An adapted legal framework established between the academic and industry partners could allow for some inventions to be protected and used for commercial applications. This should provide the opportunity for players in the industrial ecosystem to acquire IP, even on an exclusive basis, enabling companies to justify the investment needed for development and commercialisation.

Some industry sectors will also need support mechanisms to understand better the opportunities offered by public funding programmes such as the EU Health PPP. Companies from the non-medical imaging, ICT and AI industry interested in working in the health sector but not organised in European trade associations such as EFPIA or COCIR would for instance welcome dedicated staff to facilitate their engagement. This is specifically true for SMEs which do not have the resources to invest into call watch, partner search and proposal preparation ([section 4.3](#)).



05

Implementing an Ethically Responsible Strategic Research Agenda

As a pan-European programme that will develop and apply breakthrough research technologies to improve health, LifeTime will inevitably face and continually raise important ethical questions that are relevant not only to the medical and research communities, but also to citizens, including patients. While several of the ethical issues relevant to LifeTime have been addressed in earlier genomics projects, they should be revisited in light of LifeTime's European scale. This also applies to the continuous evolution of LifeTime's research plan to use and share patients' samples, ethical issues associated with the technologies as well as the application of technologies that will be developed in the future.

In this Strategic Research Agenda (SRA), we recommend the adoption of an Ethics Mechanism to continuously co-produce the ethical impact of LifeTime's biomedical innovations and ensure a socially and ethically responsible implementation. This concerns multiple risk areas: i) research on patients' samples and data, and the sharing of human samples and sensitive data within institutions; ii) the development and application of innovative technologies in research and healthcare, such as artificial intelligence (AI) and personalised disease models; iii) emerging issues in healthcare regarding citizens' perceptions of health and disease, and what priorities should be set in addressing them.

5.1 A LifeTime Ethics Mechanism

It is paramount that ethical and societal issues are evaluated and considered from the initial stages of the project, ensuring that LifeTime's strategy is founded on the principles of societal responsibility. LifeTime recommends implementing a strategy of constant ethics engagement at the core of its mission, overseen by a task force. Given the current rapid speed of technological advances, as well as LifeTime's objectives to promote technology diffusion throughout Europe and accelerate take up of emerging technologies ([section 4.1](#)), ethical issues will likewise continuously evolve and therefore require a dedicated mechanism to monitor, identify and address them. We thus propose a continuous monitoring of LifeTime's ethical issues, through the implementation of a real time ethics parallel research strategy. This will ensure that scientific developments, research choices and their clinical application will be used for human benefit. The real-time ethics engagement approach combines the following key points:

- /// Unraveling complex societal questions**
- /// Introducing ethics research as early as possible**
- /// Co-production of ethics research together with the development of scientific and clinical programmes**
- /// Involvement of empirical research**
- /// Involvement of public participation**
- /// Focus on societal impacts**

Through its Ethics Mechanism, LifeTime recommends close collaboration with ethics committees of other initiatives. To ensure we are equipped with all the necessary expertise, we will secure interactions with advisory groups of various areas of expertise including philosophers, lawyers, human rights experts, sociologists, patient representatives and regulatory ethics committees across Europe, and consultations with different stakeholder groups.

LifeTime has initiated such a mechanism to identify ethical and societal opportunities and risks, in light of LifeTime's three technology pillars. These issues can and will be dealt with the "real-time ethics engagement mechanism" proposed, as briefly described below and are mainly centred around i) maintaining the individual and his/her priorities at the centre of the research, including its design, ii) working with clinicians to make the consent a workable and humane instrument and iii) comprehend the potential risks of technology through analyses with different stakeholders.

5.2 Mitigating Ethical and Societal Risks

5.2.1 Research on Patients' Material and Sharing of Data and Samples

Performing medical testing and research on patients' material raises various ethical concerns related to material ownership and consent. Patients are indisputably the owners of their own material and data, and its use requires consent forms that are still complex and heterogeneous in different countries. LifeTime recommends harmonisation and higher flexibility of consent protocols, reducing psychological burden on patients and their relatives, and ensuring measures that are more inclusive and adapted to specific cases. Additionally, LifeTime's proposed research programmes addressing medical challenges ([sections 3.2.1-3.2.5](#)) raise ethical issues related to incidental findings, the involvement of industry or patients' privacy. Below we list the identified risk areas and recommend strategies to ensure that LifeTime's innovative vision reflects societal needs.

/// **Biobanks.** The use of samples from biobanks will be an extremely valuable resource for LifeTime. However, biobanks follow various national guidelines, creating difficulties in a pan-European research strategy. As LifeTime will also contribute to the growth of biobanks, biobanking guidelines might need to be reevaluated and adapted to ensure more agile but always consented access to patient material in the future. LifeTime's Ethics Mechanism will need to engage with biobank organisations, such as BBMRI-ERIC, and work with them to develop broad and in-depth consent strategies. LifeTime recommends the adoption of new consent concepts described below, including the option for individuals to change their will and participation. Importantly, patients should have the choice to be updated on the course of research performed using their samples.

/// **Consent Forms.** Due to the nature and rapid development of research, it is currently difficult to predict the duration, purpose and conditions for the use of patients' data and samples. This uncertainty exposes the limitations of the traditional consent forms. LifeTime proposes the establishment of a task force together with heads of hospitals, and recommends the creation of "dynamic consent" or a "consent for governance". While the former is kept as a dynamic process, relying on a constant dialogue between participants and researchers and/or clinicians, the latter proposes consenting to contribute to an infrastructure subjected to certain governance conditions, instead of consenting to a range of biomedical research purposes. Another important recommendation is the creation of uniform consent forms in Europe, that could settle regional differences and contribute to equitable implementation of LifeTime. The adoption of more agile consent protocols would facilitate the application of LifeTime's Science and Technology Roadmap, while reducing the psychological burden of patients.

/// **Incidental Findings.** The diagnostic and research technologies recommended in this SRA can easily lead to incidental findings, which are seen as a highly problematic ethical and philosophical issue. As such findings can profoundly impact a person's self-perception and decisions on future life projects, patients will have to be asked whether they want to be informed of additional findings in their records.

Important aspects include whether the incidental findings concern treatable or untreatable conditions, whether the outcome depends on tackling the disease earlier, or whether the disease can impact family members and their decision to be screened or treated when possible¹. As it might be impossible to find a single way to proceed, LifeTime recommends to develop an adequate disclosure policy for returning clinically relevant findings to patients and donors, with the flexibility to deal with incidental findings. In addition, establishing a reference system covering all possible scenarios, will provide guidance to appropriately deal with each possible outcome.

Industry Involvement. With citizens often feeling limited trust towards private companies, and with the potential commercial value of patients' data and samples, the involvement of industry in LifeTime ([section 4](#)) has to be clearly discussed for each project. LifeTime recommends fair benefit sharing as a leading principle in this collaboration. Benefit sharing will ensure the equal distribution of monetary and non-monetary benefits among all participants, and it can be translated into negotiation of reimbursements and fair pricing of drugs, sustainable infrastructures for banking of publicly available data, contributing to a balance between public and private interests.

Privacy. Patients' privacy and data protection will require constant surveillance. We recommend the creation of a portal dedicated to releasing and sharing information in formats that comply with the principles of patients' privacy, and the formation of a body who oversees the use of data and their purpose. Such a body will work in close contact with the Data Management working groups and committees ([section 7.2](#)).

Data Ownership. Data policies will need a specific task force dedicated to consent and data ownership. It is of utmost importance to always consider who is the owner and who is the controller of the data, and respect that the ownership of the data will always and unconditionally remain with the patient or donor. As it is the consent that allows the use of data, LifeTime recommends working towards a unified consent form that can ensure sharing of the data while complying to the European General Data Protection Regulation (GDPR), national legislations and, most importantly, protecting patients' privacy. Within LifeTime, this responsibility will be coordinated with the data management working groups and committees.

¹ Knowledge & Innovation (2020): Report on the social implications of LifeTime technologies – Contribution to the development of the LifeTime Roadmap

5.2.2 Innovative Technologies in Research and Healthcare

The use of patients' material naturally raises ethical questions, especially when we consider the novelty and level of information provided by the LifeTime technologies. While some of the concerns raised by single-cell technologies are equivalent to concerns previously raised by genomics testing¹, LifeTime recommends close consideration of issues related to the use of technologies that are more novel in healthcare and biomedical research such as the establishment of personalised disease models and the use of artificial intelligence (AI).

/// **Personalised Disease Models.** The use of complex human tissue disease models raises ethical concerns related to the ambiguous relationship patients can develop with material derived from their own tissues, and with the fact that this material can be banked. Here, LifeTime recommends the development of adequate governance of organoids, including among others the use of accurate language when describing these complex cellular structures, instead of defining them as mini-organs, which can impact general perception and acceptance of these tools. We also recommend specific sections in consent forms, ensuring the ethical provenance of human material and agreement to the establishment of laboratory-made human tissue models.

/// **Artificial Intelligence.** AI will have a central role in LifeTime's clinical and research approaches. To ensure ethically sound applications of AI in LifeTime, it is vital that the system remains unconditionally under human control, and scientists and clinicians should be informed clearly about the applications of responsible AI. Moreover, the Ethics Mechanism has defined the imperative recommendations for the use of AI in LifeTime's patient-centered approach: i) use exclusively excellent data sets and ii) develop inclusive AI tools that exclude any bias related to sex and gender, communities or ethnicities. LifeTime recommends the exclusive use of representative and inclusive datasets obtained from high-quality research, and the application of research funds specifically dedicated to implementation of AI.



5.2.3 Emerging Issues in Healthcare

Besides the issues related to technological approaches, LifeTime's vision also raises questions relating to healthcare, policy making or people's life projects. While these issues are not directly related to samples, technologies or data sharing, they need to be identified and addressed so they can impact how citizens at large perceive LifeTime.

/// New Perceptions in Health and Disease. With the shift in focus to intercepting diseases before the onset of symptoms, the implementation of LifeTime will lead to new concepts and new boundaries between what it means to be ill or healthy, and affect one's self-perception. It also needs to be considered that early disease detection and diagnosis can affect personal life choices such as engaging in certain career paths, acquiring property or planning a family. Moreover, LifeTime will ultimately lead to the acquisition of new habits: disease interception or pre-symptomatic diagnosis will require a proactive attitude from citizens when approaching their practitioners. LifeTime recommends close evaluation of these questions by its Ethics Mechanism, which should work towards the prevention of social stigma and discrimination, or feelings of responsibility for having a certain disease.

/// Promise-making and Expectations. Implementation of ambitious and innovative solutions can be accompanied with over-statements of their impact or the necessary time to implement them in society. This can be particularly concerning in clinical applications, as it impacts an individual's emotional response. To address this issue, LifeTime recommends to constantly evaluate benefits, risks and limitations and to balance expectations with ambitious objectives and realistic promise-making. We also recommend to carefully and constantly evaluate the time needed to achieve our different goals and impact areas, which is of particular relevance for the new technologies that will be developed.

/// Equity of Access to Care. The use of LifeTime's technologies in patient care and the development of personalised therapies might not be equally accessible to all because of their cost but also because of the patient's country of residence. While cost will likely decrease over time and such issues reflect broader societal issues, we recommend LifeTime takes an active role in aspects such as the differences in healthcare and reimbursement systems across Europe. Even though responsibility for reimbursement currently rests with national authorities and varies between countries^{2,3}, the establishment of a pan-European healthcare plan requires more uniform policies. To overcome unequal access due to country of residence, LifeTime recommends the free flow of patients' data between European countries, to promote the right of access to the best technologies independent of the country of residence.

2 EIT Health, McKinsey & Company (2020): [Transforming healthcare with AI, the impact on the workforce and organisations](#)
3 WHO (2018): [Medicines reimbursement policies in Europe](#)

5.3 Engaging Citizens

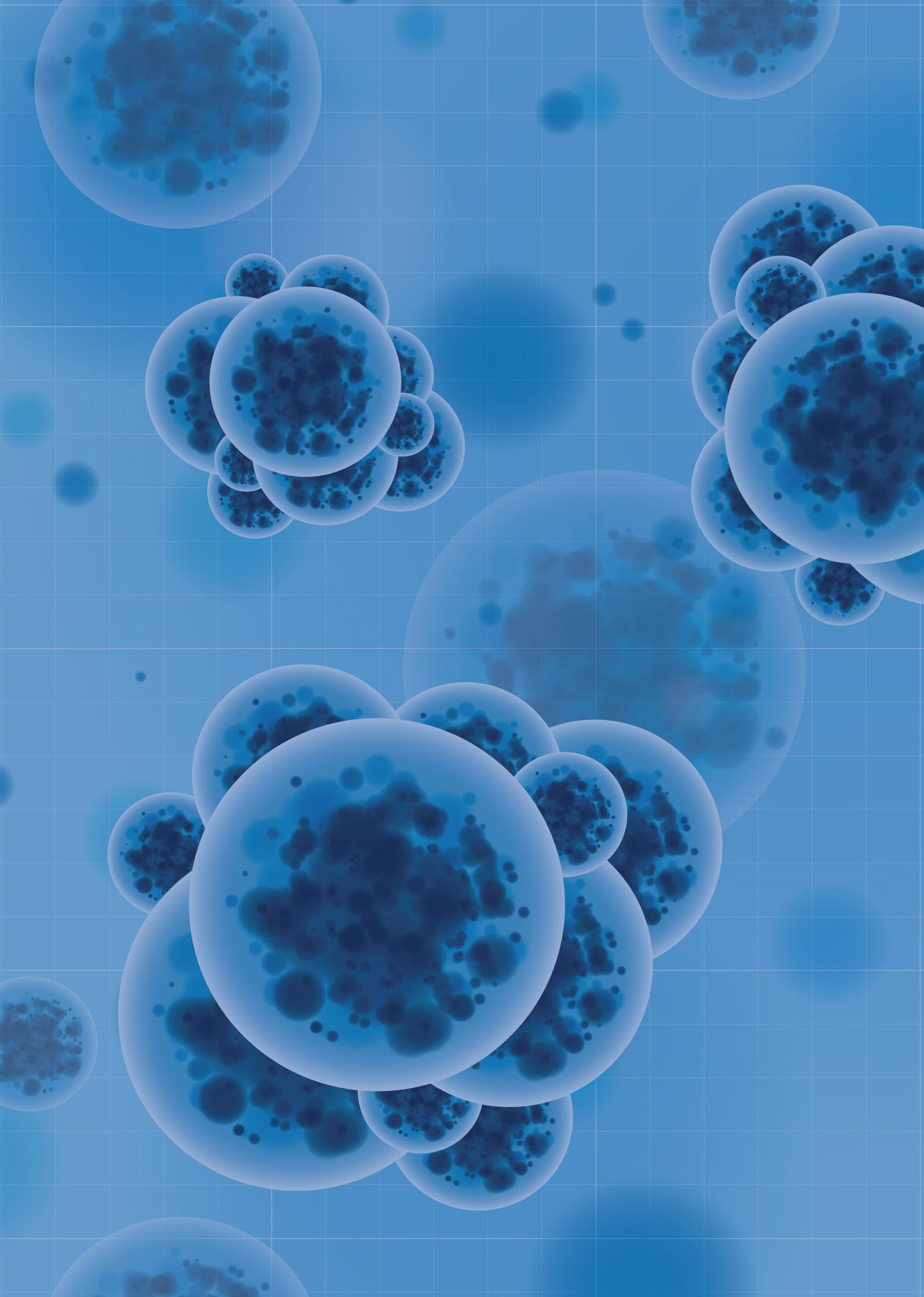
Besides the above-mentioned risk areas and recommendations, we suggest a wide communication and engagement strategy to reach the broad community impacted by the implementation of LifeTime's Science and Technology Roadmap. Open, transparent and inclusive communication with the public will help identify new risk areas, promote an attitude of trust among stakeholders, help decrease the spread of mistrust and misinformation and contribute to general scientific literacy in Europe. Such strategies should not only inform the public, but also promote individual critical thinking and ensure citizen representation as part of LifeTime's governance and in the decision-making process.

A previously used and successful strategy is the creation of public engagement activities that challenge both scientists and the public, such as exhibitions or performances at the crossroads of art and science (Science Gallery International). Additionally, we will encourage scientists and clinicians in our community to reach out to the public and participate in science outreach activities, podcasts and interviews. All these activities should be organised in parallel with LifeTime's technological developments and implementation of its research and innovation programmes, allowing a truly public dialogue and considering public opinion throughout⁴. To understand the public's opinion, fears and expectations regarding LifeTime's vision, we recommend the organisation of public consultations, where we can assess public awareness on LifeTime's technologies, or citizen's attitudes towards the societal and ethical implications of LifeTime. These activities should always be organised timely, so that public opinion can influence strategic decisions.

An additional key recommendation is the access to bioethics training to the new generation of scientists and clinicians, making them aware of the societal implications of their research and medical activities, and of the use of technology. Training activities will be organised in collaboration with the LifeTime Education and Training Programme ([section 6.3](#)).

4 ScienceWise (2018): [The Government's approach to public dialogue on science and technology](#)





06

Preparing Europe for Cell-based Medicine

Implementing LifeTime's research-orientated medical and healthcare plan will require that scientists and clinicians from various fields work in close collaboration and think beyond their current expertise to find the best solutions for their patients. Clinicians will work closely together with biologists, computational scientists, physicists, chemists or mathematicians, and will deal with new types of medical examinations and patient information. Interdisciplinary interactions between scientists will increase, as will their exchange with industry partners, clinicians and the entire hospital workforce. This will lead to a redefinition of professional and organisational arrangements, requiring new training inputs. To respond to these demands, this Strategic Research Agenda (SRA) recommends creating a pan-European and interdisciplinary Education and Training Programme, based on a culture of lifelong learning and high adaptability to the constantly expanding medical challenges and technology development, and citizen literacy and empowerment for an open society trusting science and innovation.

While technological progress has been accompanied by the prompt creation of training modules for early-career scientists, such as PhD students or postdoctoral researchers, these modules still lack interdisciplinarity and its approaches to thinking and operating. Due to various factors such as limited training opportunities, shortage of required local expertise or the current lack of clear career paths, interdisciplinarity has been identified as one of the most vulnerable areas or skills in the European training landscape¹. With most higher-education institutions in Europe not planning or being largely unprepared to include interdisciplinary training in medical² or scientific curricula, these skills should rather be acquired in short- or long-term courses, as well as higher education postgraduate programmes.

With the creation of its Education and Training Programme, LifeTime will sustainably contribute to strengthen its own interdisciplinary workforce, to European scientific and medical excellence, to European innovation with highly-skilled and adaptable professionals, and to increased citizen literacy in LifeTime's core disciplines but also more generally in fields such as epigenetics, genomics, or ethical considerations of science.

¹ [BBSRC and MRC review of vulnerable skills and capabilities](#)
² EIT Health, McKinsey & Company (2020): [Transforming healthcare with AI, the impact on the workforce and organisations](#)

To reach society and the wide professional community concerned by LifeTime, we recommend an inclusive education and training strategy based on three main pillars including postgraduate university education, short-term training to strengthen skills and ensure lifelong learning, and a citizen empowerment programme to increase general scientific literacy. Additionally, LifeTime proposes an appropriate framework to ensure coordination and quality standards of the proposed strategies.

6.1 Promoting Interdisciplinary University Education

As the new skills required by LifeTime are currently not covered by university curricula, and it is challenging to do so in the near future², LifeTime recommends the creation of postgraduate education programmes: Masters and PhDs. Besides the above-mentioned interdisciplinary requirements, students should be exposed to non-academic science sectors, such as industry or healthcare. The University Education will be complemented with short-term learning throughout its term. Students will be highly encouraged to enroll in training in transferable skills, entrepreneurship, bioethics or project management in cross-sectoral settings and in translational collaborative research. The University Education Programme will put in place the necessary instruments ensuring guidance and supervision, as well as mentorship schemes that will provide support and counselling on professional development.

The target audience includes scientists, clinicians and managers of technology platforms. Graduates from LifeTime's education programme will finish their training with a new set of skills that will foster scientific and medical excellence, interdisciplinary and cross-sectoral mindset, creativity and innovative spirit. LifeTime will train new Masters, PhDs and MD-PhDs in fields such as entrepreneurship in biotech, interception clinician-scientists or interceptional medicine technologies.



6.2 Encouraging Lifelong Workforce Training

LifeTime highly encourages every member of its workforce and the wider community to acquire training and strengthen skills that are relevant for the correct functioning of the research and medical programmes. Workforce training sessions will be organised in short- (two to five days) and longer-term courses (up to one month), providing a more flexible framework where lifelong learning can be easily combined with professional activity. This programme will target the widest community, including scientists, clinicians and managers of technology platforms, similarly to the University Education Programme, but also industry partners, medical and scientific technical staff, and administrators that might need training in handling of patients' samples and data. Besides training in various scientific and technological areas, LifeTime recommends training on project management in interdisciplinary or translation research, in technological intersections or even training in entrepreneurship in research and innovation. To raise awareness and train scientists to face the societal implications of research, we recommend training in bioethics as well as Open Science and citizen engagement practices.

Scientists and clinicians will more than ever work together in medical examination, research and therapeutic design, which requires a collaborative mindset³. To face and adapt to the new work culture, they will be encouraged to enroll on specific training sessions on cross-sectoral collaborations. With a big part of the information processing done by machines, clinicians will need to spend more time communicating with the patients, which requires skills such as social and emotional intelligence, compassion, empathy and judgement² that will be valued and covered in LifeTime's Education and Training Programme.

The workforce training programme will contribute to strengthening clinical and scientific skills, keep professionals up to date with new trends and breakthroughs, and highlight the importance of soft skills in medical care.

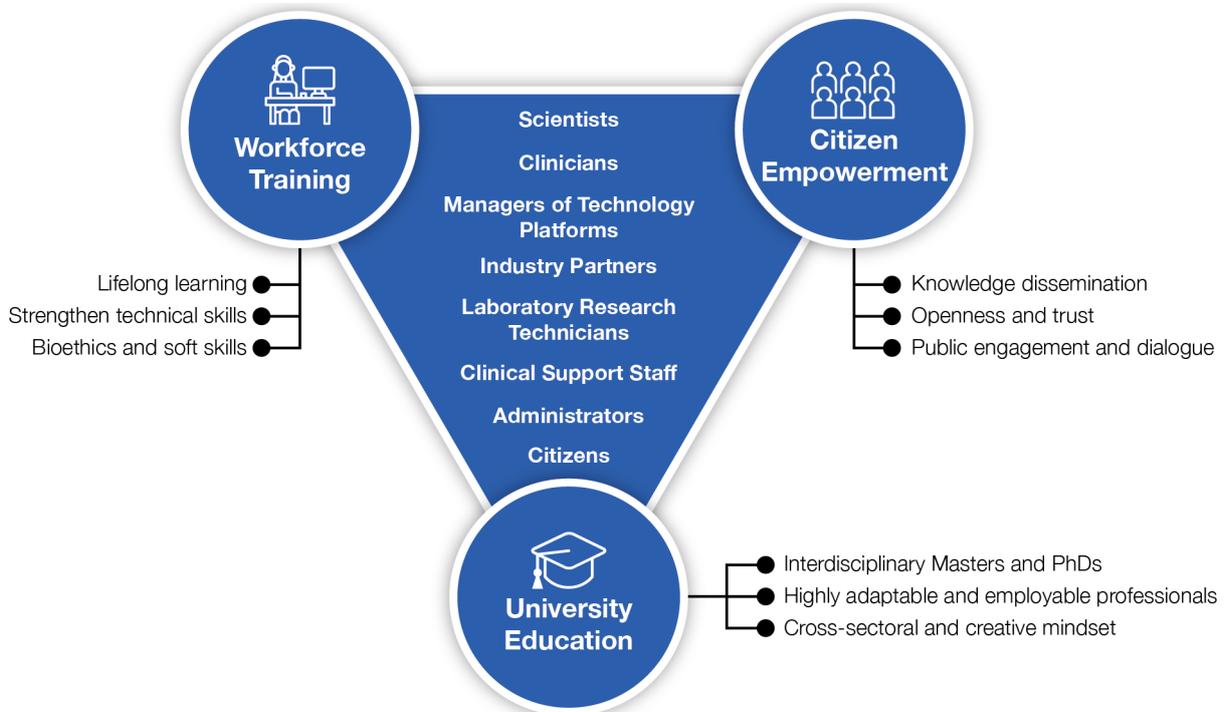
3 The Topol Review [“Preparing the healthcare workforce to deliver the digital future”](#) (2019)

6.3 Empowering Citizens and Disseminating Knowledge

Scientific literacy is still a challenge, and even more so with recent and fast-developing technologies. Since LifeTime aims to apply breakthrough technologies in patient care, it is of utmost importance to overcome this challenge. Teaming up with our Ethics Mechanism ([section 5.3](#)), LifeTime proposes an educational programme to inform and empower citizens, with the organisation of outreach activities such as cycles of colloquia with scientists, as well as exhibitions and dissemination of informative and accessible documentation. This programme will contribute to creating awareness and disseminating knowledge about LifeTime's innovative projects, and will represent an important first step for citizen participation in the decision-making processes.

The recommended public consultations to evaluate public opinion about LifeTime technologies and their implications ([section 5.3](#)), will also help create awareness and disseminate knowledge.

This joint programme of the education and training and Ethics Mechanism teams will contribute to a literate society, more open and empowered to discuss the implementation of new technologies, and encouraging citizens to act proactively together with clinicians and researchers defining the best therapeutic strategies and becoming active members of the research implementation process.



Preparing Europe for cell-based medicine through education and training

6.4 Harmonising the LifeTime Education and Training Programme

LifeTime will create a training framework currently nonexistent in Europe. Not only will we need to train LifeTime's workforce in the various technologies and fields of knowledge, but these will also need to be integrated and applied in combination to the different health challenges. To optimise efforts and ensure synergies between LifeTime's programmes and the available opportunities presently provided by various European institutions, we will collaborate with the training departments of the EMBL, the CRG or the VIB, among many others. To create and support our own solid and coherent Education and Training Programme across Europe, we recommend a framework that will harmonise and coordinate LifeTime's newly proposed activities.

We propose that LifeTime institutions should have their own training departments or conduct some of the training activities. While LifeTime institutions will generally share a common vision, each of them will naturally have its own distinctive strengths. We recommend that the training offered by the individual LifeTime institutions should be based on their local expertise, but highly complementary to other institutes. Complementarity with the global goals of LifeTime education and training should be achieved by a coordination platform connecting all local education and training departments or initiatives. The LifeTime education and training network will be fully based on LifeTime's strong network of university partners, research institutions, research infrastructures, businesses, SMEs, and other socio-economic actors, providing joint research training opportunities. The expansion of the LifeTime network of institutions will be fully accompanied by the expansion of education and training opportunities, contributing to an equitable distribution of excellent education throughout Europe. We recommend that funding of education and training activities should result from a combination of investments in LifeTime, subsidies from the member states and alignment with the currently available European training resources fostering exchange, interdisciplinarity and multi-sectoral research ([section 7.3](#)).

LifeTime trainees will be encouraged to visit other academic and non-academic organisations to get exposed to a variety of environments. In parallel the local training units should provide a learning infrastructure allowing the combination of the training programme with the exercise of the respective professional activities, which can be of particular importance to clinicians.

With networking performing a key role in today's professional interactions, we recommend to organise international networking sessions where students and alumni can connect with professionals from various employment sectors. An alumni network and a career-tracking system should also be put in place to promote exchange of experience and collect information about students' professional developments, helping our teams identify new needs and gaps in European education and training.

To provide correct functioning and conformity with the necessary quality standards, LifeTime recommends significant investments to ensure the space, resources and professionals dedicated to the conception of educational materials and courses, organised in teams composed of training experts with scientific and managerial experience.



07

Implementing the LifeTime Strategic Research Agenda

The LifeTime vision is based on the successful development and integration of its three technology pillars, bringing together expertise currently scattered across Europe to support a more data-driven and patient-centred European healthcare. To propel European science and medicine into a position of global leadership, the LifeTime Strategic Research Agenda (SRA) proposes a long-term collaborative effort. It is sustained by an open and interactive European community based on cooperation among a range of disciplines and programmes. This requires a consolidated pan-European action plan, as no individual EU member state can provide the necessary resources and offer comprehensive expertise in all the technological and scientific fields implicated in delivering the impact of the SRA.

This SRA proposes an implementation plan drawing on imaginative organisation of existing infrastructure, investment in new infrastructure and opportunities for innovative collaborative research centred around connected infrastructure hubs, the multidisciplinary LifeTime Cell Centres. This framework includes a shared biomedical data management programme, a medico-scientific research and technology integration programme, programmes for training and bioethics as well as an open innovation framework accelerating the translation of knowledge into clinical use.

Europe has for many years invested in better development and use of large research infrastructures through the strategy-led approach of the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap; a wide range of technologies and their further development are supported by ESFRI Projects and ESFRI Landmarks. Many of the Life Sciences European Research Infrastructure Consortium (ERICs) will be strong collaboration partners for the proposed initiative, but there is a need for an additional, more flexible approach to take LifeTime's fast-developing pioneer technologies to the user and novel applications to the clinic. The LifeTime concept rests on upgrading, extending and connecting small and medium sized infrastructures and R&D units with different specialisations, funded partly by national initiatives. Establishing a network of these infrastructures and R&D units with focus on their interoperability, complementarity and access would not only enable the progress of technology development per se, but provide cost-effective access of researchers and innovators and talent to the LifeTime technologies everywhere in Europe. It would deliver essential, cutting-edge technological support, develop and implement new technologies and train the next generation of scientists. These multidisciplinary LifeTime Cell Centres should operate in close association with hospitals and be linked by a shared data infrastructure ([section 7.2](#)), innovation strategy ([section 4](#) and [section 7.4](#)) and education programme ([section 6](#) and [section 7.4](#)). The founding set of interdisciplinary infrastructure nodes should complement each other's strengths and expertise in the three LifeTime technology areas and function as vantage points for a growing network. This offers the advantage of accelerating the generation of data standards for science and the clinics as well as promoting scientific excellence across Europe, without the complex set-up of a dedicated pan-European infrastructure. New centres should be allowed to join this open network, thereby fostering its agility and the capability to react quickly to technological progress and emerging challenges.

Building on but not dependent on this network, LifeTime puts forward a comprehensive research and technology integration programme encompassing the three key technology areas ([section 3.1](#)) applied to solving critical medical challenges in major therapeutic areas ([section 3.2](#)). The LifeTime Launchpad, a key mechanism employed for the identification of the medical challenges presented in this SRA will allow to continually survey upcoming technologies and clinical developments, promising great future impact for patients. LifeTime promotes an open discussion with stakeholders, foreseeing a citizen engagement programme and continual exchange with experts in bioethics, which can be a model for collaborative medical and research programmes in Europe. To safeguard successful implementation and deliver the envisioned impact, an optimal fit of these interlacing elements has to be assured. Hence we strongly recommend to create a central coordination body to optimise collaboration and increase coherence and effectiveness ([section 7.3](#)) of the LifeTime Cell Centre network and the proposed programmes.

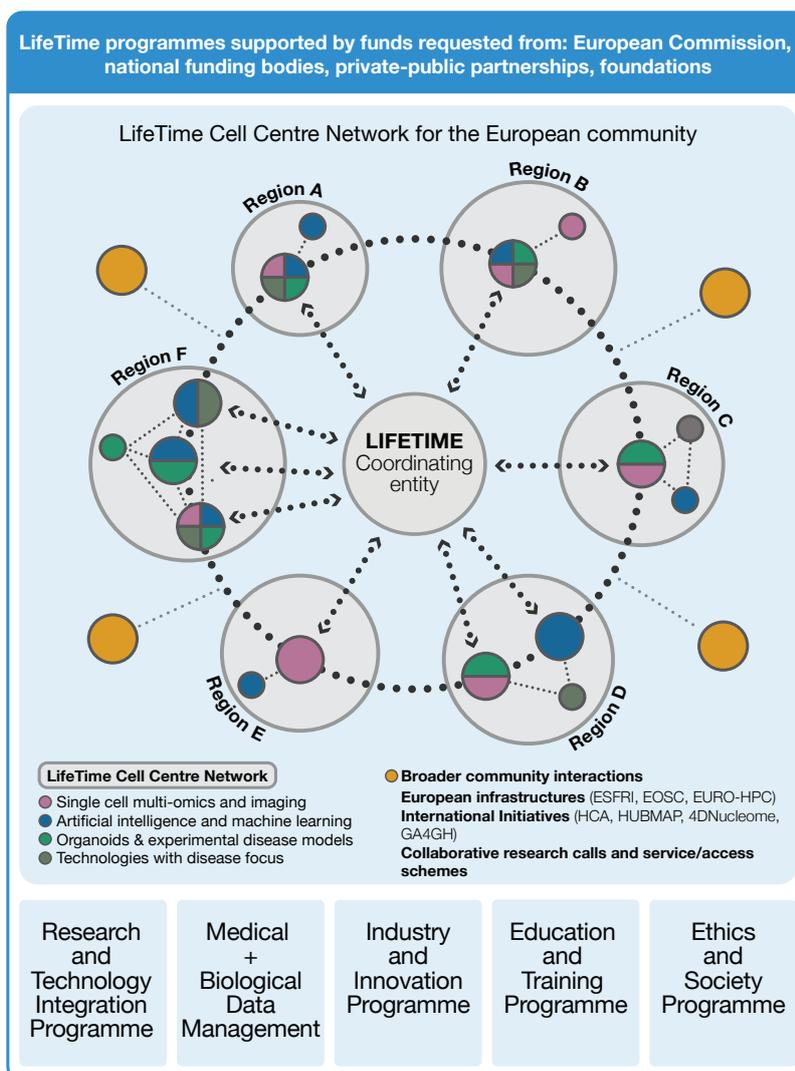
The concept of consolidating breakthrough technologies in a synergistic manner will complement and strongly cooperate with projects of the ESFRI Roadmap and other existing national, European and international efforts, especially the Human Cell Atlas, which can be foreseen to be a strong and complementary partner.

7.1 The LifeTime Cell Centre Network

The LifeTime concept is based on the successful integration of several breakthrough technologies to achieve the envisioned major medical impact, which requires multidisciplinary action on a European level. The sum of individual efforts cannot compare with the strong potential and synergies of a coordinated approach, especially with regard to interoperability of procedures, standards, quality control or avoiding duplication of efforts. The LifeTime technology pillars are fast moving, pioneering R&D areas, their consolidation requires both a stabilising framework as well as a maximum of flexibility in order to flourish. To deliver the necessary coherence and coordination while maintaining the capability to react quickly to new challenges, LifeTime proposes to set up a network of European Cell Centres.

The Cell Centres will typically be small or medium sized infrastructures or research & technology units attached to already existing research institutions, universities or larger infrastructures (although setting up new centres is not excluded). The Cell Centres are planned to be operating synergistically but independently from each other, functioning as pivotal points for open collaboration and the advancement and integration of state-of-the-art technologies. They will share resources, gather the necessary critical mass for global

competitiveness and form a powerful network stimulating the development of novel approaches in the national context and on the European stage. Close interaction between the centres is expected to expedite progress of research and technology development and facilitate common data standards and operating procedures, leading to the effective exchange, comparison and exploitation of data and research results. Additionally the network would fulfill the role of providing world class services to users both from the LifeTime research & technology integration programme and the wider community, local and (inter) national as well as to academia- and industry-based researchers and innovators. An example for this is the organoid field, which would strongly profit from new protocols, standardisation, automation and benchmarking.



LifeTime implementation Blueprint

The European Cell Centre concept requires the centres to operate in tight association with hospitals and to actively integrate technology development with clinical practice, also ensuring access to bio-samples and clinical data. To optimise interactions, the Cell Centres should be located in close proximity to a hospital and, if applicable, include a strong thematic focus on the specific diseases dealt with at the clinic. This close alliance will allow research results to be quickly turned into solutions and applied in day-to-day clinical work. The connected but geographically distributed nodes will serve as innovation hubs with strong links to industry, aiming to replace individual cooperation agreements with a joint collaboration framework for business and academia. The objective is to create an open innovation ecosystem accelerating research, technology transfer and eventually the introduction of new products and services in the market, for instance sensitive diagnostic and progression biomarkers and promising new combination therapies for major aggressive cancers.

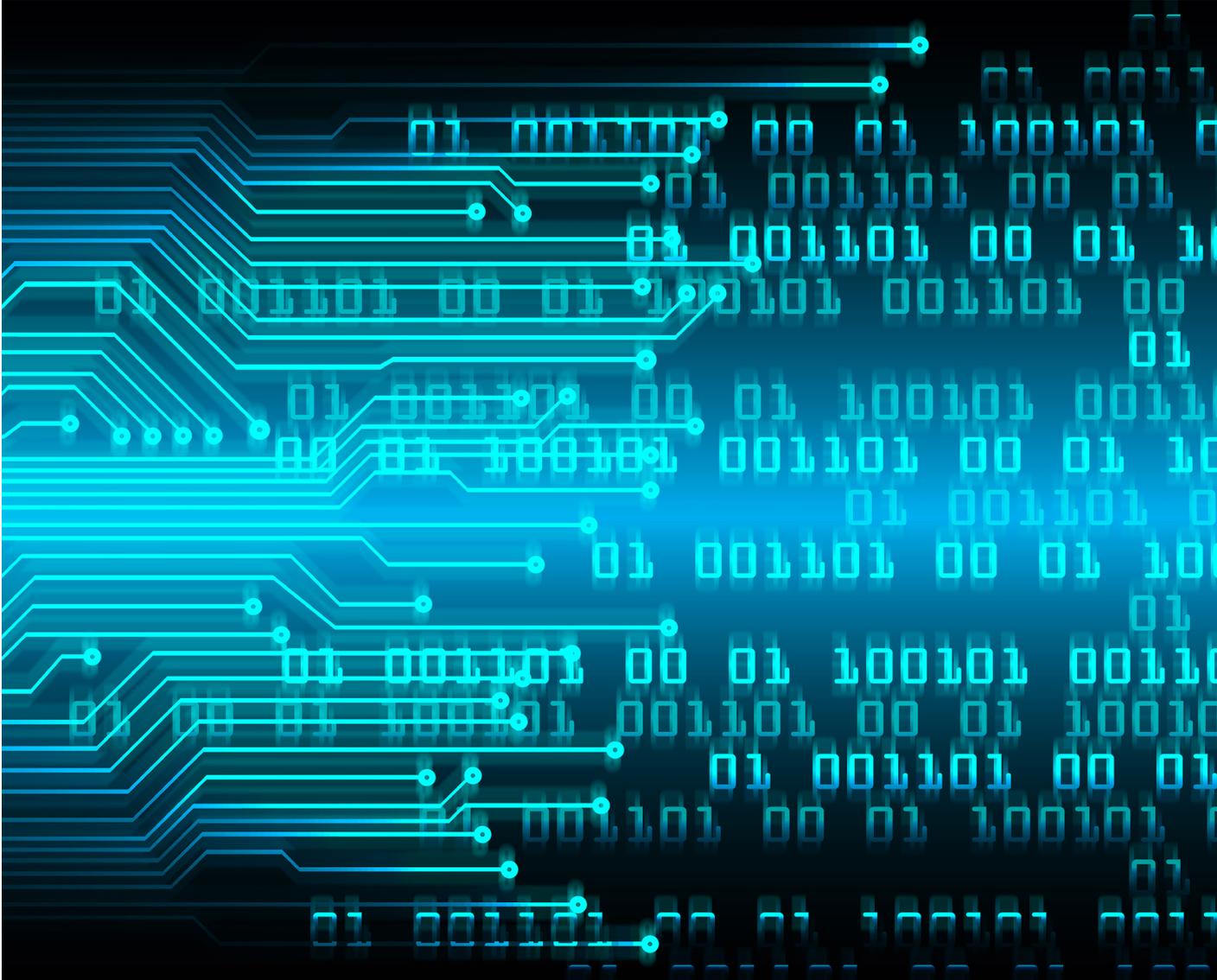
Key functions of the LifeTime Cell Centres:

- // Serve as platforms for the development and advancement of breakthrough technologies for single-cell research, machine learning/artificial intelligence and experimental disease models**
- // Closely and actively collaborate with hospitals and clinicians, in some cases with a specific disease focus**
- // Set standards in data generation, standardisation and management supporting the FAIR principles**
- // Offer opportunities to collaborate, test and benchmark new analysis methods**
- // Offer unique opportunities to industry to translate recent knowledge and novel technologies from the laboratory to the market**
- // Provide an early technology adoption platform across Europe**
- // 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**
- // Offer opportunities for methods developers to access benchmarked datasets and to deliver new methodologies**

Training and education occupy a prime position for supporting sustainable innovation and raising scientific excellence across Europe. Easy access and widespread dissemination of the new LifeTime technologies and approaches will play a crucial role in creating open and accessible knowledge flows. The initiative's comprehensive education and training programme ([section 6](#)), will be nourished by the daily work at the LifeTime Cell Centres, which will act as education and training centres serving the whole scientific community as well as offering information and opportunities for European patients and citizens to engage.

The integrated R&D perspective of the Cell Centre network is expected to provide the necessary cohesion but also allows to accommodate different systems, funding models, as well as the different approaches to research infrastructures in a Europe-wide context. It could constitute an engine and vehicle for excellence and innovation by linking priorities and funding instruments on the institutional, regional, national and European levels. An increasing number of countries, including Italy¹, Germany² or Poland³, have started to invest into programmes that closely align with the LifeTime vision. Several of these nationally funded efforts could together build the core of the Cell Centre network and specific activities be scaled up across the network. An example is the Single-Cell Accelerator Programme⁴ successfully executed at the VIB in Belgium. Since the network would offer services accessible to the whole scientific community, hospitals and industry, its activities would not exclusively benefit the institutions and countries involved but provide stimulation and impetus for research, technology development and transfer across Europe and beyond. While it is foreseen that the basis of Cell Centre funding should stem from national sources, in order to maximise impact of the LifeTime SRA we explicitly stress that further pan-European investment in the network is required to reach full operability and scalability. This applies especially to the proposed bio-medical computational infrastructure. Additional funding will greatly expedite the collaborative approaches between Research Performing Organisations (RPO), universities, hospitals, business and industry, patients and society at large.

1 Human Organoid Models Integrative Center (HOMIC) - University of Milan
2 Berlin single cell research focus - Berlin single cell hospital; MDC, BIH & Charité
3 LifeTime Single Cell Center; IBCH PAS & NIEB PAS
4 [VIB Single Cell Accelerator](#)



Criteria for a LifeTime Cell Centre

Owing to their different national contexts, thematic specialisations and backgrounds, the LifeTime Cell Centres will operate following their own organisational models. A set of principles will create a conducive environment for delivering LifeTime Research and Technology Integration. It will also provide the required cohesion, set quality standards and create the optimal conditions to carry out benchmarking exercises and perform evaluations ensuring scientific excellence of the individual centres and the network as a whole. These principles will also ease effective collaboration between the Cell Centres and support long-term sustainability of the network.

A centre will have to comply with defining criteria and follow requirements concerning implementation and operation to qualify as a LifeTime Cell Centre. In order to be considered as a Cell Centre, a unit/ infrastructure needs a funding plan with a view to long-term sustainability, clearly expressed support from the (national) government/funders as well as institutional support from the superordinate entity (if applicable). It will have to follow an overall strategy with defined objectives compatible with network objectives and introduce an access policy based on the European Charter for Access to Research Infrastructures as well as a reliable and a normalised reference framework for impact assessment (key performance indicators - KPI). Its governance structure has to be in line with the network governance structure including clear responsibilities and reporting lines. It is expected to comply with network policies on user support structure, data management, audits/reviews/evaluation, and a quality management programme with inter-laboratory analyses to ensure accreditation and quality.

Cell Centre defining criteria:

- // Closely collaborate with hospitals to enable the transfer of solutions to the clinic;**
- // Integrate the three LifeTime technology pillars**
- // Build on different priorities and strengths**
- // Be complementary (particularly at the beginning of the network)**
- // Participate in the development of shared standards**
- // Educate young scientists and clinicians**
- // Establish a technology transfer programme**
- // Provide services to the community**

7.2 Medical and Biological Data Management Platform

The initiatives proposed in this SRA, and scientific and technological advancements in related fields, will create an unprecedented amount of data. The scale of data brought about by new technologies, close collaboration across Europe and beyond and novel analytics using artificial intelligence (AI) ([section 3.1.2](#)) requires upgrading of the European biodata compute infrastructure. Unlocking the potential of big data in medicine through high-quality, standardised data and predictive and interpretive AI-driven computational models will require considerable infrastructure investment on the European level. We propose a data management platform resting on federated cloud computing solutions and connected to high-performance computing centres, which will fit into and be a valuable contribution to the Digital Europe strategy. It will coordinate standardisation, ensure quality management and benchmarking and will benefit multiple stakeholders including scientists, clinicians and industry.

The LifeTime Data Infrastructure in the Context of Existing European Initiatives

The LifeTime Science and Technology Roadmap will foster new ways of using high-volume leading-edge omics and imaging technologies to address pertinent questions in human health. The scale of the data being generated, the cross-disciplinary and international structure combined with the ambition of LifeTime to pioneer novel analytics using AI, mean that an implementation of the proposed SRA will require but also shape the next generation of the European biodata compute infrastructure. As a result of this, substantial and sustained investments into computational infrastructure are essential and will benefit multiple stakeholders including scientists, clinicians and industry.



We recommend that the core data infrastructure of LifeTime should build on a federated compute and data model, borrowing and extending concepts from the existing federation model of the European Genome-Phenome Archive (EGA), which is also the preferred technology to realise the European '1+ Million Genomes' Initiative. While the first national implementations of federated EGA nodes are already underway, for example the Nordic ELIXIR Nodes (DK, FI, NO, SE) and the German Human Genome-Phenome Archive, LifeTime poses unique additional challenges and requirements that go beyond sharing of genome and omics data. These future hurdles include the deep integration of multi-omics assays, imaging and critically also health records. Consequently, LifeTime is uniquely positioned to pioneer technologies and a biodata infrastructure to enable the deep integration of data across domains, linking up currently disconnected biodata infrastructures.

Key Requirements and Needs for a LifeTime Data Infrastructure

The LifeTime vision includes the establishment of Cell Centres across Europe, which provide expertise and training in the three technological pillars, single-cell analytics, AI and machine learning and personalised experimental disease models. Connected to these data generation hubs, we envision a federated compute network, leveraging national investment, providing substantial capacity for computational processing, disk space as well as fast networks to enable federated analytics across the LifeTime Cell Centres. The following points outline the design requirements & guide capacity estimates:

- /// **Large-scale data centres with a compute and storage capacity that is comparable to current existing European data infrastructures (e.g. EMBL-EBI, CERN). The proposed programmes will generate sequencing and imaging data on the scale of multiple petabyte per year, and this rate is expected to accelerate rapidly as research and technology development progress**
- /// **Multi-tier encrypted storage systems, supplying high-performance I/O for data processing and analysis but also long-term archival, including geo redundant archival mechanisms across centres**
- /// **Versatile and flexible computing setup, equipped to both supply high-volume I/O-intensive data processing tasks, but also to address the computing requirements of machine learning and AI algorithms and methods. The strong integration of AI technologies in particular will require new designs that are not realised in classical biodata infrastructures**
- /// **Mechanisms and incentives for public-private partnerships, for example to foster pioneering technologies (e.g. faster processing, in memory computation, etc.)**
- /// **Upgrading and extending network data infrastructure, including fast data links between centres, thereby enabling seamless data integration and facilitating distributed analytics (to bring algorithms to data)**

- /// The biodata infrastructure realised as a federated network, built on cloud computing technologies, connected to and strongly integrated with the European Open Science Cloud (EOSC), owing to technical, financial but also ethico-legal constraints. Strong requirements on certification, data protection and privacy measures are required given the nature of the data.
- /// Strong networks of expertise and training to enable a new generation of scientists to maximally leverage novel compute and data strategies, including federated and distributed computation
- /// Points of contact with biobank and national clinical infrastructures and a standards approach to support federated clinical data discovery, access, harmonisation and analysis



7.3 Community Coordination and Governance

The LifeTime SRA puts forward a multi-layered research and innovation programme whose complementary and comprehensive approach promises to be flexible and capable of rapid responses as well as providing a stable framework encouraging the setting of standards for the sharing of medical data across Europe and beyond. A crucial challenge is the effective and efficient coordination across all proposed efforts to deliver on evolving and transforming disease detection and treatment and facilitate the transition to a more data-driven and patient-centred European healthcare. We need to integrate the key technologies: single-cell technologies and imaging, AI and machine learning, and personalised disease models. We need to build the required data infrastructure capable of supporting the sharing of biomedical data and standardisation of data and operating protocols. We need to explore and identify answers to essential medical questions, their translation into new solutions and clinical applications including transfer to the market; and we need to educate and train a new generation of researchers and clinicians and engage with patients and society as a whole. This bold vision relies on both an underlying infrastructure network providing the necessary conditions for excellent technology development as well a flexible programme of research and innovation projects, which act independently but are also jointly coordinated and steered for maximal impact. For this purpose, and to help avoid parallel and fragmented efforts, we propose to establish a central coordinating body across all LifeTime activities, which requires dedicated European cohesion funding with mid to long-term sustainability. This potentially virtual central hub would ensure coherence of the implemented activities and should list the coordination of the Cell Centre network, the LifeTime Education and Training Programme, the Ethics Mechanism and Launchpad Mechanism among its principal tasks. Further functions should include overseeing the continual Launchpad mechanism as well as a review board to evaluate the contribution of independently funded projects towards realising LifeTime's full impact ([section 2](#)).

The governance model of a LifeTime central hub should be built on dedicated governing bodies, with an assembly of all members having full decision making power. Individual institutes should formally join the LifeTime network, the assembly representatives being designated by the member organisations. An executive board with an executive director and team to handle the day-to-day management of the initiative should be nominated. A variety of working groups and committees handling different aspects would provide the necessary input and support the assembly in its decision making. Such groups will include a medico-scientific board with separate committees for the technology pillars and disease areas, data management, training, ethics and public engagement. We would like to particularly mention the Launchpad Mechanism, which should follow the procedures adopted to identify the medical challenges for this SRA to scout for novel technologies and monitor new disease challenges. Each key industry sector should be represented in a strategic advisory innovation board, which should provide input to the SRA in general and particularly the Industry and Innovation Programme. The governance scheme has to determine clear responsibilities and reporting lines, as well as international supervisory and relevant external advisory bodies.

7.4 Research and Technology Integration and Training

The multi-level approach put forward in this SRA comprises, along with the Cell Centre concept, programmes in research and technology integration, education and training as well as ethics and society. These separate elements act synergistically, are mutually beneficial and strongly benefit from a cross-pollination of ideas but are not strictly dependent on each other for implementation, even if quality and impact would be substantially curtailed through a patchwork policy. Whilst it is possible to focus on selected elements of the global SRA and achieve partial success, only substantial adoption of the agenda promises major output.

We believe that a dedicated large-scale initiative would provide the best conditions to achieve the envisioned impact but we are committed to exploring alternative routes. The proposed programmes require an imaginative and creative use of existing funding instruments, as well as new investment to deliver novel solutions for Europe. Projects should preferentially involve but not exclusively require the LifeTime Cell Centres. We propose funding through a portfolio of research opportunities, stemming from projects both on the national as well as European level. Existing project funds from European programmes could be bundled to feature topics relevant to LifeTime research or projects belonging to Pillar II of Horizon Europe, such as projects in the framework of the Mission on Cancer or the European Commission (EC) Roadmap on Europe's Beating Cancer Plan. Even ERC single investigator and synergy grants could if thematically within the framework of LifeTime contribute towards the goals of this Strategic Research Agenda. Funding of LifeTime's education and training programmes could benefit from available European resources such as the Innovative Training Networks, the European Joint Doctorates or COFUND initiatives for PhD candidates and post-docs, the Erasmus Mundus Joint Masters Degrees for master's students, or the Research and Innovation Staff Exchange initiative. The Pathfinder and Accelerator programme of the European Innovation Council (EIC) as well as projects associated to the European Innovation Ecosystem as part of Pillar III could add important contributions for collaboration with industry. We propose to set up a pre-seed pre-incubation fund for innovation projects, in particular for technology bundling, and proof of concept calls could be earmarked for LifeTime. IMI/EU Health PPP calls or calls from thematically related partnerships will also offer opportunities for LifeTime projects. National as well as private funding will provide additional opportunities.



This heterogeneous landscape of funding sources with projects being reviewed independently of the LifeTime SRA and according to their own programme logic may make it challenging in some cases to assess the potential contribution of a funded project to the overall LifeTime strategy and to align the different projects. Initiatives that have received funding and have registered interest to be part of the LifeTime canon, should be reviewed by a dedicated board of the coordinating body ([section 7.3](#)) to determine if they are in line with LifeTime's objectives, standards and operating procedures. Potential criteria include: relevance to the LifeTime objectives, contribution to the envisioned LifeTime impact ([section 2](#)), strategy concerning data sharing, standards and quality control. It is conceivable to introduce a tier system including LifeTime core and associate projects.

It is expected that the programme will interact with, benefit and take inspiration from existing key European programmes such as the biological and medical research infrastructures from the ESFRI Roadmap, the Digital Europe strategy through the European Open Science Cloud or the European High- Performance Computing Joint Undertaking. A special relationship with projects related to the Human Cell Atlas is foreseen, especially with regard to metadata analysis, data sharing, standards and quality control, as already started with the joint task force on COVID-19.

7.5 Ethics and Society Programme

The proposed LifeTime Ethics Mechanism ([section 5.1](#)) will continually monitor the ethical implications raised by the fast development of technology and the resulting new way of delivering medicine. "Ethics parallel research" will ensure that scientific developments, research choices and their clinical application will be used for the benefit of the patient. We recommend that all research projects and programmes put forward by this SRA should make sure that linked ethical considerations are practically considered and implemented in the research. A dedicated project, such as a "Science with and for Society"-type project, would be important to develop such a mechanism and explore the wider implications.

The possibility to make early and detailed diagnoses will trigger positive reactions in the sense of prevention and empower patients to better manage their own health. However, it will also ask for a more proactive role of patients and raise a number of concerns relating to trust in science and questions of self-perception, which will impact acceptance of interceptive medicine. We propose a shared decision-making process through engaging citizens in LifeTime's governance and an activating citizen programme.

The LifeTime initiative is strongly committed to clear, effective and knowledge-based external and internal communications. The programmes proposed in this SRA will encourage participation and contribution from political, public and commercial audiences across Europe and world-wide. The communication strategy will aim to place LifeTime at the cutting-edge of communication and engagement practices, including incorporating the Open Science principles, and will actively seek to ensure that the knowledge it generates is freely accessible to the wider scientific community and also both open and comprehensible to the public. In recognition of the breadth of relevant audiences and their differing requirements, LifeTime's engagement approach will be tailored specifically to best meet these needs, performing assessments of each audience type's requirements, the aim of the communications, and the most effective methods of achieving this objective.

7.6 A dedicated Innovation Framework to Implement the LifeTime Industry Strategy

The development and integration of the three technology pillars will require close collaboration between the public and private sectors spanning multiple disciplines. Programmes fostering existing and establishing new links between both sectors will accelerate the translation of discoveries into solutions, contributing to the health of European citizens. In the absence of a long-term and well-defined legal basis provided by a EU subsidy programme such as the Framework Partnership Agreement used for the H2020 FET-Flagship projects or the regulations of the Innovative Medicines Initiative 2 Joint Undertaking, it is complex to create a general framework for innovative ways of interacting and sharing risk between stakeholders, supporting public/private partnerships and business creation and requires a long-term vision.

Several ongoing EU, national or institutional activities in different European countries could help kick-start the innovation activities and serve as blueprints to build LifeTime industry engagement platforms (see [sections 4.1 - 4.5](#)). There are several successful local initiatives fostering new technology adoption and co-development which could be scaled-up and/or coordinated across Europe. In Belgium the VIB has been very active in this area with the tech watch programme and the technology innovation lab and most relevant the innovative VIB single-cell Accelerator rolled out in 2017. Dedicated competitive grants for early technology adoption could not only benefit industry technology providers but also the exploitation of new technology developed by academics and support creation of start-ups in Europe. An adapted legal framework established between academic and industry partners ensuring the protection of inventions and their use for commercial applications could be a way to incentivise technology providers other than pharma companies to develop a European precision medicine sector. Another important step would be to engage regulators and regulatory bodies earlier, in particular to enable early disease interception.



The development of an open innovation ecosystem could be in part aided by a dedicated networking/ brokerage platform, which could take the form of partnering with existing academia/industry event platforms, for instance, collaborating with the ERICs ELIXIR and Euro-BioImaging to co-organise SME events and cover topics around imaging, data analysis and data management. For single-cell technology providers, forming new networks to support community building should be explored by using existing models, e.g. COST actions. Platforms such as the recently launched Open Discovery Innovation Network (ODIN) programme at Aarhus University or the OpenTargets platform, an innovative public-private partnership between pharma and public data providers using human genetics and genomics data for systematic drug target identification, provide an alternative model. A network of the Technology Transfer Offices (TTOs) of institutes engaged in the LifeTime SRA and a shared programme fostering further intersectoral mobility could be developed with template agreements.

In order to facilitate the creation of start-up companies, we propose to establish a dedicated early stage investment fund. Building on EU programmes and networks such as the EIC and the EIT Health, as well as institutional initiatives (e.g. EMBL Ventures), the fund management should have strong early-stage investment experience and offer not only flexible financial support but also expertise, resources, time adapted to each innovation project in order to create lasting value. Funding for a pre-seed, pre-incubation scheme based on competitive calls could be provided by institutional and private investors (VC, business angels, private equity and also corporate investments from industry partners) in Europe.

The EC could also support this effort to foster technology bundling with for instance FET proactive calls earmarked for LifeTime technology integration topics.



7.7 European and International Context and Collaboration

The proposed SRA supports a number of key EU strategies. A new cell-based, data-driven medicine based on breakthrough single-cell/imaging and organoid technologies will require the accelerated uptake of AI and continual upgrading of High Performance Computing (HPC), which are both central points of the Digital Europe strategy. The highly complex challenge of implementing precision medicine concepts requires the free flow of information including electronic health records and genomic information for research, linking it closely to the European Open Science Cloud (EOSC) and European Data programmes such as the 1+Million Genomes Initiative. Pooling, integrating and sharing of high-quality, interoperable data are crucial for a European Health Data space, necessitating questions of standards, definitions and data annotation to be solved at the European level. The proposed research and development concepts will influence personalised interceptive medicine and directly contribute but not be restricted to Europe's Beating Cancer Plan and be closely linked to the Horizon Europe Mission on Cancer. As set out in this SRA, the proposed technological concepts are applicable to a number of other disease areas and will add important approaches to the European One Health Action Plan against Antimicrobial Resistance. Most importantly, they will contribute to a joint European response to the current COVID-19 pandemic and add to the world-wide effort of rapidly identifying mechanisms, new drug targets and ways of containing infections before they can take hold across the globe.

While the Cell Centres are expected to be operating embedded in the national context, performing together as the LifeTime Cell Centre network will add further functions, create synergies and facilitate collaboration. Open access for the European scientific community will constitute a key element to drive European research in the three LifeTime technology pillars and allow to gather the critical mass instrumental for a European lead in these areas.

Cooperation with the European Life Sciences Research Infrastructures

The LifeTime Cell Centre network and the proposed research and technology integration programme will result in opportunities to closely interact with established European research infrastructures, especially in the fields of bioinformatics and data – ELIXIR, in the area of biobanks - BBMRI-ERIC, for imaging - Euro-Biolmaging, and the medical research facilities EATRIS-ERIC and ECRIN-ERIC but also other relevant Life Sciences ERICs. As a basis for collaboration, regular meetings to exchange information about activities in the different areas and to identify opportunities to converge have been put on the agenda. LifeTime and the Life Sciences Research Infrastructures (LSRI) agree that a possible outcome could be to identify suitable funding opportunities that could help establish such a collaboration. Furthermore we see opportunities to align efforts to ensure that LifeTime centres can interface with the emerging European Open Science Cloud (EOSC).

Link to the Human Cell Atlas

The Human Cell Atlas (HCA) and LifeTime share the objective to chart human biology in unprecedented detail by leveraging the recent explosion of single-cell and spatial analysis technologies. Despite many key synergies, the goals of the two initiatives are not congruent. The HCA's objective is to create comprehensive reference maps of all human cells as a basis for both understanding human health and diagnosing, monitoring, and treating disease. In contrast, while sharing many approaches with the HCA, the LifeTime SRA puts forward a comprehensive framework for implementing data-driven medicine in Europe within the next decade. It is based on research and technology development programmes integrating three key technologies to address priority medical challenges, including an innovation framework and the LifeTime Education and Training Programme. Close links between LifeTime and the HCA are expected to be mutually beneficial, establishing a common framework for openly sharing knowledge, tools, data, and other resources. An example is the joint COVID-19 registry, where members of both initiatives and others can contribute their expertise and the scientific and technological power of single-cell analysis and data integration to unravel the interaction of SARS-CoV-2 with the cells and tissues of the human body.

Working with Other Initiatives

The programmes and actions proposed in this SRA will link to other existing efforts, for instance international alliances such as IHEC, or European partnerships such as the IMI/EU Health PPP and help to streamline interaction between national European and international programmes. Internationally, LifeTime will build on multiple research and innovation programmes for single-cell data generation and technology development, such as the NIH common fund programmes in the US e.g. the Human BioMolecular Atlas Programme (HuBMAP). LifeTime will use best practice guidelines from existing large-scale consortium projects, including the Human Genome Project, the Cancer Genome Atlas, the ICGC, the NCI's Genomic Data Commons, and the GA4GH. The LifeTime Cell Centres will work together with EU supercomputing facilities (Partnership for Advanced Computing in Europe (PRACE), Jülich Supercomputing Centre, DE; BSC, ES; CINECA & INFN, IT; ICHB PAN-PCSS, PL) and national distributed grids of university high performance computing centres. A number of potential disease specific interaction partners initiatives can be found in [section 3.2](#).



LifeTime Working Groups

(members listed alphabetically)

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Glossary

AAI	Authorisation, Access and Identification protocols
AI	Artificial intelligence
BBMRI-ERIC	Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium
BSC	Barcelona Supercomputing Center
CERN	European Organization for Nuclear Research
CID	Chronic inflammatory disease
CMD	Cardiovascular and metabolic disease
COCIR	European Trade Association representing the medical imaging, radiotherapy, health ICT and electromedical industries
COST	European Cooperation in Science and Technology
COVID-19	Coronavirus disease 2019
CRG	Centro de Regulación Genómica
CRISPR-Cas	Genetic engineering technique (Clustered regularly interspaced short palindromic repeats-CRISPR-associated)
EATRIS	European Infrastructure for Translational Medicine
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Genome-phenome Archive
EHR	Electronic health records
EIB	European Investment Bank
EIC	European Innovation Council
EIT	European Institute of Innovation and Technology
ELIXIR	European Life-Sciences Infrastructure for Biological Information
ELLIS	European Laboratory for Learning and Intelligent Systems
EMBL-EBI	European Bioinformatics Institute
EOSC	European Open Science Cloud
ERC	European Research Council
ERIC	European Research Infrastructure Consortium
ESFRI	European Strategy Forum on Research Infrastructures
EU health PPP	EU public private partnership - European Partnership for Health Innovation
Euro-Biolmaging	European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences
EuroHPC	European High-Performance Computing
FAIR	Findability, Accessibility, Interoperability and Reusability
FIHR	Fast Healthcare interoperability Resources
GA4GH	Global Alliance for Genomics and Health
GDP	Gross Domestic Product
GDPR	General Data Protection Regulation

HCA	Human Cell Atlas
HCA-DCP	Human Cell Atlas Data Coordination Platform
HF	Heart failure
HL7	Health Level Seven International
HPA	Human Protein Atlas
HPC	High Performance Computing
HTAN	Human Tumor Atlas Network
IBCH PAS	Institute of Bioorganic Chemistry, Polish Academy of Sciences
ICHB PAN-PCSS	Institute of Bioorganic Chemistry Supercomputing Centre
IHEC	International Human Epigenome Consortium
IMI	Innovative Medicines Initiatives
ICGC	International Cancer Genome Consortium
ICGC-ARGO	International Cancer Genome Consortium - Accelerating Research in Genomic Oncology
ICT	Information and Communications Technologies
INFN	National Institute for Nuclear Physics
I/O	Input/Output
IP	Intellectual Property
IPR	Intellectual Property Rights
iPSC	induced Pluripotent Stem Cell
IT	Information Technologies
KPI	Key Performance Indicators
MALDI	Matrix-assisted laser desorption/ionization
ML	Machine Learning
NCI	National Cancer Institute
NIEB PAS	Nencki Institute of Experimental Biology, Polish Academy of Sciences
NHS	National Institutes of Health
OMOP	Observational Medical Outcomes Partnership
PDX	Patient-derived Xenografts
PRACE	Partnership for Advanced Computing in Europe
R&D	Research and Development
R&I	Research and Innovation
RPO	Research Performing Organisation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMEs	Small and Medium-sized Enterprises
SRA	Strategic Research Agenda
TCGA	The Cancer Genome Atlas
TRL	Technology Readiness Level
VC	Venture Capital

