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**LifeTime and improving European healthcare through cell-based interceptive medicine**

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97

98 **LifeTime aims to track, understand and target human cells during the onset and progression**  
99 **of complex diseases and their response to therapy at single-cell resolution. This mission will**  
100 **be implemented through the development and integration of single-cell multi-omics and**  
101 **imaging, artificial intelligence and patient-derived experimental disease models during**  
102 **progression from health to disease. Analysis of such large molecular and clinical datasets**  
103 **will discover molecular mechanisms, create predictive computational models of disease**  
104 **progression, reveal new drug targets and therapies. Timely detection and interception of**  
105 **disease embedded in an ethical and patient-centered vision will be achieved through**  
106 **interactions across academia, hospitals, patient-associations, health data management**  
107 **systems and industry. Applying this strategy to key medical challenges in cancer,**  
108 **neurological, infectious, chronic inflammatory and cardiovascular diseases at the single-cell**  
109 **level will usher in cell-based interceptive medicine in Europe over the next decade.**  
110

111 While advances in medicine have led to spectacular progress in certain disease areas, most  
112 chronic disorders still partially or totally escape cure. This is mainly because most diseases are  
113 only detected late once gross physiological symptoms manifest themselves, when tissues and  
114 organs have often undergone extensive or irreversible changes. At this stage, the choice of  
115 interventions is typically quite limited. It is difficult to predict if a patient will respond to a  
116 particular treatment, which often involve invasive or aggressive therapies that can be of  
117 modest benefit, or if therapy resistance emerges leading to relapse. The reason for this is that  
118 despite technology-driven revolutions that enable a patient's physiology to be investigated at  
119 the level of molecules <sup>1,2</sup> and placed in the context of tissues <sup>3,4</sup> in most cases our detection  
120 and predictive power is limited by our incomplete mechanistic understanding of disease at  
121 the cellular level.

122 Cells develop and differentiate along specific lineage trajectories forming functionally distinct  
123 cell types and states <sup>5</sup>, which together with their neighbouring cells underlie and control  
124 normal physiology (Fig 1). However, we have not been able to systematically detect and  
125 understand the molecular changes that propel an individual cell along these trajectories  
126 during normal development or ageing nor the molecular causes that trigger deviations from  
127 healthy trajectories and drive cells and tissues towards disease (Fig 1). Timely detection and  
128 successful treatment of disease will depend crucially on our ability to understand and identify  
129 when, why, and how cells deviate from their normal trajectory. More accurate cellular and  
130 molecular diagnostics will enable us to intercept disease sufficiently early to prevent  
131 irreparable damage. To achieve this interceptive medicine (Fig 1), we need to invest in  
132 approaches that provide a detailed molecular understanding of the basis of disease  
133 heterogeneity in tissues, with sufficient molecular, cellular and temporal resolution.

134 Several challenges need to be overcome to reveal the complex disease landscapes comprised  
135 of vast numbers of potential cellular states (Fig 1). Firstly, we need to resolve normal cellular  
136 heterogeneity across space and time to begin to determine the cell types, states and cell-cell  
137 interactions in the body. This is a main goal of the Human Cell Atlas consortium <sup>6</sup>. However,  
138 to discover the cellular basis of diseases requires that we track cellular heterogeneity and  
139 molecular composition of cell trajectories in health and during disease progression  
140 *longitudinally* - throughout a patient's lifetime ("LifeTime"). Secondly, we need to understand  
141 the molecular mechanisms and complex networks that define a cell's state, and control its  
142 function, fate and trajectory over time to be able to reconstruct a cell's history and predict its  
143 future. This is essential for selecting the optimal intervention for an individual patient. Thus  
144 systematic and longitudinal profiling of samples from many patients is required. Third,

145 computational frameworks for integrating temporal data as well as patient profiles with large  
146 cohorts to identify regulatory changes and to dissect the causes and manifestations of disease  
147 remain elusive. Current attempts to model human disease have not succeeded in integrating  
148 the thousands of molecular phenotypes that are acquired from patients. Finally, we are  
149 limited by our lack of knowledge of the underlying causes of disease. Any given patient's  
150 response to a specific therapy may require testing or modifying cells from the patient in an  
151 experimental system, a challenge yet to be routinely implemented.

152 To address these challenges experts from different disciplines came together in 2018 to form  
153 the LifeTime Initiative (<https://lifetime-fetflagship.eu>). It has since grown to be a pan-  
154 European community consisting of over 90 research institutions with the support from 80  
155 companies, several funding agencies and national science academies. In 2019 the initiative  
156 was awarded a Coordination and Support Action by the European Commission to develop a  
157 Strategic Research Agenda (SRA) <sup>7</sup> for a large-scale long-term initiative with a roadmap for  
158 implementing cell-based and interceptive medicine in Europe in the next decade. The  
159 ambitious goal is the early detection and interception of complex diseases as well as being  
160 able to select the most effective therapeutic strategy for a patient. Between March 2019 to  
161 June 2020 the initiative established several multi-disciplinary working groups (listed in  
162 supplementary information), organised numerous workshops, meetings and surveys (and  
163 thus engaged the wider community) and commissioned stakeholder interviews and an impact  
164 study. The European Commission will use LifeTime's SRA during the planning of the next  
165 research and innovation framework programme - Horizon Europe. Here, we outline LifeTime's  
166 vision and key aspects of the SRA towards establishing cell-based interceptive medicine.

167 Central to LifeTime's vision and approach is the development and integration of novel  
168 technologies, such as single-cell multi-omics and high-content imaging, artificial intelligence  
169 (AI) and patient-derived experimental disease models. Applying these integrated approaches  
170 to address medical challenges and incorporating them in both experimental and clinical  
171 workflows is expected to directly benefit patients. For example, appropriate single-cell based  
172 biomarkers will precociously alert physicians that a cell or tissue is entering a disease  
173 trajectory. Understanding disease heterogeneity at the cellular level and knowing the  
174 molecular aetiology of a disease will allow the systematic identification of drug targets,  
175 resistance mechanisms or define therapeutic approaches, based on a given disease's  
176 molecular or cellular vulnerability. This strategy differs significantly from the classical  
177 approaches in drug discovery <sup>8</sup>. The stratification of patients based on underlying disease  
178 mechanisms, assessed *in situ* within single cells, will help physicians select the most  
179 appropriate treatment(s) or employ combination therapies that are tailored to the individual.  
180 These will be used first to identify cells that are deviating from the healthy trajectory, to steer  
181 them away from disease, and later to reduce the threat of relapse (Fig 1). This transformative  
182 single-cell data-driven approach has the potential to increase the success rates of clinical trials  
183 as well as the efficiency of novel therapeutic interventions in clinics over the next decade.  
184 Overall, the LifeTime strategy is likely to impact both diagnosis and treatment, improve health  
185 and quality of life dramatically and alleviate the societal burden of human diseases such as  
186 cancer, neurological disorders, infectious diseases, chronic inflammatory and cardiovascular  
187 diseases.

188 Below, we outline the technology development and implementation at the heart of LifeTime's  
189 approach, describe LifeTime's mechanism to identify medical priorities, discuss required  
190 infrastructures in Europe, interactions with industry and innovation, ethical and legal issues,  
191 LifeTime's education and training vision, and estimate the expected impact of the LifeTime

192 approach on medicine and healthcare. LifeTime builds on and will collaborate with related  
193 international initiatives that are paving the way by producing reference maps of healthy  
194 tissues in the body, such as the Human Cell Atlas (HCA) <sup>6</sup> and the NIH Human Biomolecular  
195 Atlas Program (HuBMAP) <sup>9</sup>.

196

## 197 **Technology development and integration**

198 Single-cell technologies, particularly transcriptomics, are generating the first reference cell  
199 atlases of healthy tissues and organs, revealing a previously hidden diversity of cell subtypes  
200 and functionally distinct cell states <sup>6</sup>. Single-cell analyses of patient samples are beginning to  
201 provide snap-shots of the changes in cell composition and pathways associated with diseases  
202 including cancer <sup>10-15</sup>, chronic inflammatory diseases <sup>16,17</sup>, Alzheimer's disease <sup>18-20</sup> heart  
203 failure <sup>21</sup>, and sepsis <sup>22</sup>. Since pathophysiological processes within individual cells involve  
204 different molecular levels, understanding the underlying mechanisms requires the integration  
205 of current single-cell approaches. LifeTime proposes the integration of several approaches <sup>7</sup>.  
206 This includes combining transcriptomics (Fig. 2) with methodologies that provide additional  
207 information on chromatin accessibility, DNA methylation, histone modifications, 3D genome  
208 organisation, and genomic mutations <sup>23-25</sup>. Future developments will enable the incorporation  
209 of single-cell proteomes, lipidomes, and metabolomes, adding crucial insight into different  
210 cellular states and their roles in health and disease. In addition to specific cell subtypes and  
211 the role of cellular heterogeneity, investigating the surrounding tissue context and organ  
212 environment is crucial. New spatial -omic approaches, particularly spatial transcriptomics,  
213 include information on the location of diseased cells, their molecular makeup and aberrant  
214 cell-cell communication within the tissue <sup>26-32</sup>. Novel advanced imaging approaches also now  
215 enable systematic spatial mapping of molecular components, *in situ*, within cells and cells  
216 within tissues <sup>28,33-37</sup>. The cellular context with respect to different immune and stromal cell  
217 types, extracellular components and signalling molecules that contribute to disease  
218 progression will help identify the roles of specific cell types and interactions in diseases <sup>32,38-</sup>  
219 <sup>40</sup>. The implementation of cell lineage tracing approaches <sup>41</sup>, which link cellular genealogies  
220 with phenotypic information of the same cells, may help us understand how populations of  
221 cells develop dynamically to form the specific architecture of a healthy or a diseased tissue.

222 LifeTime proposes to develop necessary single-cell methodologies and end-to-end pipelines  
223 (Fig 2) that will be integrated into robust, standardised multi-omics and imaging approaches,  
224 and scaled to profile hundreds of thousands of patients' cells <sup>7</sup>. This will require an in-depth  
225 analysis of longitudinal human samples obtained from patients and cohorts, including  
226 European and national clinical trial groups as well as initiatives collecting longitudinal  
227 biological material connected to well-annotated clinical information (Fig 3). Linking these data  
228 to clinical outcomes will identify the cellular parameters that are permissive to a therapeutic  
229 response, for example during checkpoint blockade immunotherapy <sup>12,42,43</sup> or treatment of  
230 multiple myeloma <sup>11</sup>. By detecting rare drug resistant cells that are present prior to <sup>11,44</sup> or that  
231 emerge during treatment <sup>45</sup>, therapeutic regimens and combinatorial treatments can be  
232 adapted to improve outcome.

233 Handling these large molecular datasets will require sophisticated and distributed  
234 computational and bioinformatics infrastructures, (see Implementation and Infrastructure),  
235 as well as the development of tools to integrate and ensure interoperability of different data  
236 types, including single-cell multi-omics, medical information and electronic health records.  
237 LifeTime will work with ongoing European and national efforts for integrating molecular data

238 into electronic health records and to establish standards and interoperable formats to address  
239 specific disease challenges. This will promote the development of advanced personalised  
240 models of disease. To be able to implement routine longitudinal sampling of patients  
241 approaches need to be developed for sampling small biopsies, including liquid biopsies, that  
242 will detect individual cells or cell-free DNA released from pathological cells before and during  
243 therapy <sup>46</sup>. Multi-dimensional descriptors of cell states from patients taken from different  
244 stages of disease or therapy will be used to derive new biomarker sets or enhance current  
245 panels. Collaboration with ongoing atlas projects, industrial partners and regulatory  
246 authorities, will be key for benchmarking and deriving the new standards that will enable us  
247 to deploy these new methods in the clinic. This will hopefully achieve earlier disease detection  
248 and guide the appropriate selection of drug targets and therapies (Fig 3).

249 Unlocking the potential of unprecedented amounts of integrated digital information  
250 (including molecular data describing how individual cells make decisions) requires AI, in  
251 particular machine learning approaches that can identify meaningful molecular patterns and  
252 dependencies in the datasets <sup>47,48</sup>. Although such approaches have proven very useful when  
253 applied to medical imaging data and have enabled the identification of subtle disease-  
254 associated changes <sup>49</sup>, medical imaging cannot capture the full complexity of human  
255 physiology nor the status of the disease at the single-cell level. High-content imaging, together  
256 with gene expression profiling, chromatin states, protein and metabolic parameters will  
257 contribute to the stratification of disease phenotypes. Machine learning and advanced  
258 modelling approaches will be used to integrate and analyse the different layers of cellular  
259 activity, and can generate multi-scale and potentially even causal models that will allow us to  
260 infer regulatory networks and predict present and future disease phenotypes at the cellular  
261 level <sup>47,50-52</sup> (Fig 2).

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

275 Understanding the cellular origin and aetiology of disease from a patient-centered perspective  
276 requires systems that faithfully recapitulate key aspects of a patient's pathophysiology, and  
277 render them experimentally tractable to test mechanistic hypotheses and predictions.  
278 Organoids are an emerging experimental system that allow modelling aspects of organ  
279 development, regeneration and pathophysiology <sup>3,4,53</sup> (Fig 2). Derived from adult or  
280 pluripotent human stem cells, organoids can capture individual features that are unique to  
281 each patient and can be interrogated molecularly in space and time. Importantly, by  
282 comparing organoid models from diseased and healthy individuals, unique disease features  
283 can be extracted even without knowing the specific genetic cause of the disease. Therefore,  
284 organoid models offer a unique tool for achieving some of the main goals of LifeTime,

285 especially in cases where repeated access to patient tissues is limited or impossible, for  
286 instance for neurological disorders.

287 Despite their promise organoids still require significant development to harness their full  
288 potential for disease modelling (Fig. 2). LifeTime proposes to advance the models to capture  
289 the full degree of cellular heterogeneity, tissue-specific structural and metabolic conditions<sup>54</sup>,  
290 incorporation of key physiological aspects, such as immune response, vascularisation or  
291 innervation. Because complex interactions between multiple tissues and organs are involved  
292 in many diseases, it will be necessary to develop novel tissue engineering principles that  
293 combine multiple organoids in pathophysiologically relevant crosstalk (organoid-on-a-chip).  
294 To optimise translational potential, LifeTime will engage in standardising, automating and  
295 scaling organoid approaches, allowing for systematic derivation, propagation and banking.  
296 Such industrialisation is also needed for large scale chemical or genetic perturbations (e.g.  
297 CRISPR-Cas screens), and for elucidating the genetic basis for disease variability and drug  
298 response at population-relevant scales, in both the preclinical and clinical context (Fig 3). The  
299 resulting mechanistic dissection enabled by large-scale perturbations will be used to validate  
300 corresponding AI models of disease interception and progression.

301 In addition to organoids, *in vivo* model systems are necessary to translate the science from  
302 bench to humans. A complex biological system is required to study the myriad of host-disease  
303 and pathogen interactions associated with complex diseases, such as infectious diseases,  
304 cancer or Alzheimer's disease. The use of animal models is important for understanding the  
305 very complex temporal relationships that occur in disease such as those involving the  
306 vasculature, immune system and pathogens as well as neuronal networks in the brain.  
307 LifeTime will therefore improve their clinical relevance and make use of models in which  
308 patient-derived tissues can be integrated into *in vivo* models<sup>55-59</sup> to study dynamics of cellular  
309 heterogeneity in space and time.

310 LifeTime, as a community, has the capacity to develop and integrate these technologies, that  
311 often require expertise and specialised instrumentation located in distinct laboratories. A  
312 coordinated effort can achieve the required benchmarking and standardisation of  
313 technologies, workflows and pipelines. This will also ensure that the data, software and  
314 models generated adhere to Findable, Accessible, Interoperable, and Reusable (FAIR)  
315 principles<sup>60</sup> (see infrastructure below), are available across national borders, and are in full  
316 compliance with international legislations such as the European General Data Protection  
317 Regulation (GDPR). Moreover, LifeTime will ensure that technologies, including AI and  
318 organoids, will be developed in an ethically responsible way in collaboration with patients,  
319 putting the patient at the centre. (see Ethical and Legal Issues).

320

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

322 LifeTime has initiated a mechanism, called Launchpad, to systematically identify medical  
323 challenges that can be addressed through LifeTime's approach and have a direct impact on  
324 patient care. Initially, the focus has been on five disease areas that are a significant burden to  
325 society: cancer, neurological disorders, infectious diseases, chronic inflammatory diseases as  
326 well as cardiovascular diseases. Importantly, other disease areas will be continuously  
327 monitored, for example rare Mendelian diseases and metabolic diseases, and research  
328 programmes initiated as technologies and infrastructures develop. The LifeTime Launchpad  
329 has defined several criteria to identify the medical challenges. These include: societal impact



330 (including incidence and prevalence, disease severity, economic impact and the pressing need  
331 for new and more efficient clinical treatments and early detection), evidence for cellular  
332 heterogeneity that limits current clinical avenues, availability of samples from biobanks,  
333 relevant preclinical models, existence of patient cohorts including those enabling longitudinal  
334 studies, clinical feasibility and ethical considerations, as well as alignment with national and  
335 EU funding priorities. Subsequently, multidisciplinary working groups, including clinicians, in  
336 each disease area have used these criteria to define the following disease challenges and  
337 develop ten-year roadmaps to address them in the LifeTime Strategic Research Agenda <sup>7</sup>.

338 Despite cancer broadly covering hundreds of individual tumour types, there are critical  
339 knowledge gaps that are common for all cancer entities, including early dissemination and  
340 therapy resistance. Metastatic dissemination of a subpopulation of cancer cells is a leading  
341 cause of death in almost all cancer types. Successful treatment of advanced and metastasised  
342 forms of cancer remains difficult, despite the development of targeted therapies and  
343 immunotherapies, due to the emergence of drug or therapy resistance. To address these  
344 medical priorities LifeTime recommends focusing on understanding the cell types and states -  
345 malignant cells and their microenvironment - involved in early stages of cancer dissemination  
346 and the reprogramming of cellular states during disease and their impact on therapy  
347 resistance.

348 For neurological disorders a major challenge is a lack of understanding of the early events in  
349 disease onset to enable the development of disease modifying therapies. The lack of access  
350 to longitudinal samples from patients requires the establishment of cohorts of patient-derived  
351 disease models to understand the cellular heterogeneity associated with disease. Discovering  
352 pathways and biomarkers for the stratification of patients based on the cellular mechanisms  
353 driving the disease will enable new design of clinical trials to reevaluate drugs previously  
354 tested without such stratification and broaden the drug target portfolio.

355 As seen during the COVID-19 pandemic it is important to be able to understand infection  
356 mechanisms and the host response to rapidly identify the most likely effective treatment. At  
357 the same time the continuous rise of antimicrobial resistance requires the discovery of novel  
358 therapeutic strategies. A key medical challenge for infectious diseases is to understand the  
359 cellular response to infections and develop novel precision immune-based therapeutic  
360 strategies to combat infections.

361 The high burden of chronic inflammatory diseases is due to long-term debilitating  
362 consequences resulting from structural destruction of affected organs or tissue. Current  
363 therapies only treat the symptoms and do not cure or fully control the chronic inflammatory  
364 pathophysiology. While many different targeted therapies exist, they are expensive and are  
365 limited by high rates of non-response to treatment. Consequently, there is an urgent need to  
366 explore and understand how cellular heterogeneity contributes to the pathology of  
367 inflammatory diseases <sup>61,62</sup> and how this relates to the predicted course of disease and  
368 response of a patient to one of the numerous available therapies.

369 Many cardiovascular and metabolic diseases lack effective therapies due to a lack of  
370 knowledge of the underlying causes and the link between abnormal cardiac cell  
371 structure/function and pathophysiology. The identified medical priority is to understand  
372 cellular and molecular mechanisms involved to enable early diagnosis and to design new  
373 mechanism-based therapies for precise clinical treatment.

374 The LifeTime disease roadmaps can be divided broadly into three phases <sup>7</sup>: firstly, immediate  
375 research into the identified medical challenges using established, scaled single-cell  
376 technologies, computational tools and disease models; secondly, the development of new  
377 technologies required to address specific medical challenges, including the development of  
378 spatial- multi-omics and imaging approaches and advanced patient-derived model systems for  
379 longitudinal analyses; finally, applying these next-generation technologies for longitudinal  
380 analyses of patient samples, or patient-derived models, combined with machine learning to  
381 generate patient trajectories and predictive models of disease. Resulting predictions and  
382 biomarkers would be validated in prospectively collected patient cohorts within clinical trials  
383 also including longitudinal liquid biopsies. The routine clinical use of predictors and  
384 biomarkers for risk stratification of patients and resulting interventions - where feasible - is  
385 the pre-final step. The final step is the extension of predictors and biomarkers to the analysis  
386 of large longitudinal patient cohorts such as national cohorts for developing secondary and  
387 tertiary prevention approaches based on the new biomarkers.

388 During implementation of these roadmaps the initiative will establish an experimental design  
389 working group to develop systematic procedures to ensure that the research samples  
390 acquired cover diverse subjects including age, sex-and-gender-in-research dimension and  
391 ethnicity. This will require the development of strict criteria for the inclusion of samples and  
392 ensure appropriate coverage of critical metadata. They will also define standardised  
393 procedures for acquiring and processing of samples from different pathology sites (depending  
394 on the disease area). It is envisaged that during disease challenge pilot projects an  
395 experimental design oversight body will determine, based on early data, the number of  
396 diseases that should be studied as the initiative develops with recommendations on  
397 appropriate sample sizes required to obtain sufficient statistical power.

398

## 399 **Implementation and Infrastructure**

400 The scale of the data that will be generated and analysed, the cross-disciplinary and  
401 international structure combined with the ambition of LifeTime to pioneer novel analytics  
402 using AI, places LifeTime in an excellent position to shape the next generation of European  
403 medical and biological data computational infrastructure. This will require close interaction  
404 with and evolution of the established European infrastructure (Fig 4), such as the European  
405 Open Science Cloud (EOSC) and high-performance computing infrastructures through  
406 EuroHPC. LifeTime will also interact with related European Life Sciences Research  
407 Infrastructures <sup>63</sup> to create added value and to avoid duplication of efforts in strategies and  
408 tools for sharing and accessing data, development and application of standards. As medicine  
409 is inherently decentralised, LifeTime will also contribute to connecting EU medical systems  
410 and large centralised European data infrastructures.

411 Fragmentation of research across borders, disciplines and timeframes needs to be overcome.  
412 LifeTime data generation and technology development will be harmonised across expert  
413 groups and centres, allowing results to be quickly applied in the clinic. Thus, a coordinated  
414 approach is required that integrates the multidisciplinary expertise of single-cell technologies,  
415 data science, and organoids/*in-vivo* models across Europe. It must also engage clinicians and  
416 patients to achieve medical impact. To address these challenges, LifeTime proposes a  
417 multidisciplinary network of LifeTime Centres (Fig 4) with different complementary thematic  
418 clusters across Europe, each working in close association with hospitals. These connected,  
419 flexible innovation nodes will share resources, gather the necessary critical mass for global

420 competitiveness, and be open for collaboration with the entire scientific community.  
421 Importantly, LifeTime Centres should deliver a number of key functions:

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

439 LifeTime aims to analyse data which is inherently distributed across different clinical centres  
440 in different countries, which is a significant challenge. These data are usually not accessible  
441 outside a national, regional clinical care system or specified data 'safe havens', when they are  
442 accessible accredited systems are often required for storing the data and information  
443 governance may be at the hospital, federal or international level. This means that a federated  
444 approach is the only way to access and integrate information from various European  
445 healthcare systems. Thus, the LifeTime data and computational network building on cloud  
446 technologies will provide the necessary capacities to enable federated analytics across the  
447 LifeTime centres and will provide a technical and legal framework for integrating core  
448 information structures, multi-omics assays, imaging, AI/machine learning technologies and  
449 health records (Fig 4). A joint Data Coordination Centre following a multi-level approach will  
450 ensure transparent data access control, compatibility and standardisation. Within this  
451 framework LifeTime will also coordinate and pioneer open data sharing and reuse and  
452 collaboration, including access models prior to publication of data.

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

464

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

466 Collaborations with the private sector will be key for rapid translation and delivery of  
467 technologies, instrumentation, diagnostics and therapies (Fig 4). Currently over 80 companies  
468 support LifeTime's vision. These span multiple sectors as well as industrial associations and  
469 networks such as the European Federation of Pharmaceutical Industries (EFPIA), and the Euro-  
470 Biomedicine Industry Board (EBIB).

471 Transforming breakthrough discoveries into solutions to improve the health of European  
472 citizens involve several crucial steps. These include creating a unifying framework that fosters  
473 and streamlines pre-competitive interactions between academia and industry at the interface  
474 of computer science, single-cell biology, -omics, imaging, patient-derived disease modelling  
475 and precision medicine. A large-scale collaboration platform across Europe should be  
476 developed that provides umbrella agreements, regular physical meetings, dual training of  
477 early-career scientists in academia and industry, as well as exchange programmes. This will  
478 enable joint projects between public and private sectors spanning the entire biomedical  
479 innovation cycle from discovery research, technology development and implementation in  
480 hospitals and the healthcare industry.

481 Cross-sectoral collaborations between small, medium-size and large companies with different  
482 development timelines and distinct business models is crucial to stimulate innovation. To  
483 expedite the identification of, and investment in the emerging technologies developed in  
484 academic and industry laboratories, successful local initiatives such as tech watch and  
485 accelerator programmes (e.g. the VIB Single-cell Accelerator) should be scaled and  
486 coordinated at the EU level. LifeTime aims to create a networking/match-making platform for  
487 individuals, academic and industry organisations that share the goal of developing and  
488 integrating breakthrough technologies and applying them in the clinic to benefit patients.  
489 Further measures could foster innovation and entrepreneurship. For example, a pre-seed,  
490 pre-incubator funding scheme based on competitive calls to support start-up or tech transfer  
491 ideas.

492 Creating a dedicated European ecosystem is also essential. Achieving this requires additional  
493 key measures such as the development of enabling digital environments, promotion of early  
494 disease interception with all necessary stakeholders (patients, regulators, payers, etc.) as  
495 described in the LifeTime call for action launched in December 2019 ([https://lifetime-  
496 fetflagship.eu/index.php/make-eu-health-research-count/](https://lifetime-fetflagship.eu/index.php/make-eu-health-research-count/)).

497

## 498 **Ethical and Legal Issues**

499 The implementation of LifeTime's vision triggers relevant ethical questions from all societal  
500 groups directly impacted by the project (patients, clinicians and scientists), and society in  
501 general. LifeTime aims to pioneer a real-time or parallel ELSI programme that will predict,  
502 identify, monitor and manage the ethical impact of the biomedical innovations that arise from  
503 research and technology development, ensuring that implementation follows ethical  
504 guidelines. LifeTime's ELSI programme can be used as a testing ground for other international  
505 interdisciplinary initiatives (Fig 4). Ethical issues will be identified and managed as early as  
506 possible and ensure that ethical and research integrity guidance is implemented throughout  
507 the entire research process to stimulate positive effects and mitigate negative ones <sup>64</sup>.

508 Specialists in bioethics, public engagement, ethics of technology and lawyers have identified  
509 LifeTime’s ethical and societal priority areas. These include questions related to the  
510 derivation, storage and use of organoids, the use of AI, data ownership and management,  
511 anonymisation of data, equity of access to such revolutionary medical care, the definition of  
512 health and illness, and transparent science communication to society <sup>65</sup>. Initiating a  
513 relationship of trust with citizens will include diverse modes of communication and  
514 engagement, for example through art, citizen science and public dialogue, contributing to  
515 scientific literacy, and promoting individual critical thinking and public participation in  
516 decision-making processes.

517

## 518 **Education and Training**

519 Introducing interceptive medicine into clinical practice in parallel with a multidisciplinary  
520 research programme will require capacity building in health and research systems, and  
521 significant technology deployment in the clinic. This will lead to a collaborative, fast-  
522 developing and interdisciplinary environment in research and in the clinic, requiring new  
523 training inputs. To respond to these needs, LifeTime will create an Education and Training  
524 Programme, ensuring the sustainable application of new technologies and implementation of  
525 new medical and scientific approaches (Fig 4). Importantly, this will be done in an integrative  
526 scheme, intersecting the multiple LifeTime disciplines and areas of actions: disruptive  
527 technologies applied to medical challenges, technology transfer and innovation, research  
528 integrity, data management and stewardship, ethical and societal issues, communication and  
529 emotional skills, or management of medico-scientific and collaborative projects.

530 Each LifeTime training activity will be based on multi-lateral education: basic researchers will  
531 teach other researchers and clinicians about the potential of the technological solutions, while  
532 clinicians will teach researchers about clinical needs and biological challenges of the diseases  
533 in focus. This will strictly follow the idea of bench to bedside and back. The programme will  
534 have an inclusive philosophy to ensure that it can provide training to the wide community,  
535 including researchers, clinicians, technical operators, managers and staff of technology  
536 platforms, as well as administrators, patients and the lay public.

537 LifeTime envisions the organization of cycles of colloquia and outreach activities to inform the  
538 public, the formulation of short-term courses compatible with a culture of lifelong learning  
539 and adaptability, as well as interdisciplinary Masters and PhD programmes. Through  
540 education and training, LifeTime will engage and inform society, will develop new professional  
541 curricula and will train a new generation of highly skilled medical scientists and support staff,  
542 in order to foster scientific and medical excellence in an ethical, responsible and inclusive  
543 framework.

544

## 545 **Impact on Medicine and Healthcare.**

546 Medicine and healthcare are rapidly expanding pillars of our economy. EU countries  
547 collectively spend more than €1,400 billion per year on healthcare for their 500 million  
548 citizens. Given the dimensions and spiralling healthcare costs associated with an ageing  
549 population, these numbers will continue to increase unless we can mitigate the damaging  
550 effects of ageing. We expect that coupling the current health monitoring with early detection  
551 and disease interception, will have a major economic impact. In Europe, 20% of the population  
552 will soon be over 65, with an age distribution that will continue to change until 12% are over

553 80 in 2080<sup>66</sup>. Given the prevalence and cost of caring for people with degenerative conditions  
554 and the increase in chronic lifestyle-induced diseases, the knowledge and technologies  
555 developed by LifeTime will allow us to detect them earlier, and avoid their worst  
556 manifestations. LifeTime would also have an impact in the era of unexpected pandemics such  
557 as COVID-19 by rapidly determining the cellular and molecular basis of the disease. This would  
558 identify potential therapeutic strategies for patient subgroups as well as starting point for the  
559 development of new efficient therapies.

560 One of healthcare's largest outstanding issues is that many patients do not respond to  
561 commonly prescribed treatments. Whereas well-controlled randomised clinical trials provide  
562 evidence for statistical utility of a given therapy, in actual practice often many patients must  
563 be treated before a single patient will show a measurable benefit. Other patients may not  
564 benefit at all or even be harmed<sup>67</sup> leading to an economic loss that is estimated to be in the  
565 hundreds of billions €/year. The variable therapeutic responses originating from the cellular  
566 and genetic heterogeneity that exists in cancer and other complex diseases, contributes not  
567 only to the failure of treatments, but also to the rising cost of drug development, which is  
568 currently estimated at ~€1-2 billion per drug. *In silico* models for disease trajectories  
569 generated by LifeTime will enable the integration of personal genetic and lifestyle information  
570 into predictive models of disease course. This will allow physicians to determine and  
571 implement optimal therapeutic strategies tailored to the individual (precision medicine) with  
572 sophisticated timing of disease interception. The knowledge gained will also contribute to a  
573 more appropriate selection of patients for clinical trials.

574

## 575 **Outlook Summary**

576 Recent advances in key single-cell technologies, AI and patient-based experimental systems,  
577 such as iPS and organoids, have set the stage for their integration and deployment to improve  
578 mechanistic molecular understanding, prediction, and treatment of disease onset and  
579 progression. Patients will benefit from cell-based medicine though the earlier detection of  
580 diseases at a stage where they can be effectively intercepted. The novel, integrated  
581 technologies will enable the selection, monitoring and, if necessary, modification of  
582 therapeutic strategies for an individual to improve clinical outcomes based on high-resolution  
583 cellular information. Within the next decade, the obtained molecular mechanistic information  
584 has the potential to revolutionise drug discovery processes, clinical trial design, and eventually  
585 be incorporated into clinicians' daily decision-making processes. As the LifeTime community  
586 continues to grow, new individuals, institutions and companies are encouraged to join and  
587 contribute to establishing a European platform to implement single-cell and data-driven  
588 medicine to address the growing burden of complex and chronic diseases.

589

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596

## 597 **Author Contributions**

598

599 All authors contributed to the writing of the article and provided comments and feedback.  
600 They all approved submission of the article for publication.

601

## 602 **Competing Interests**

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

612

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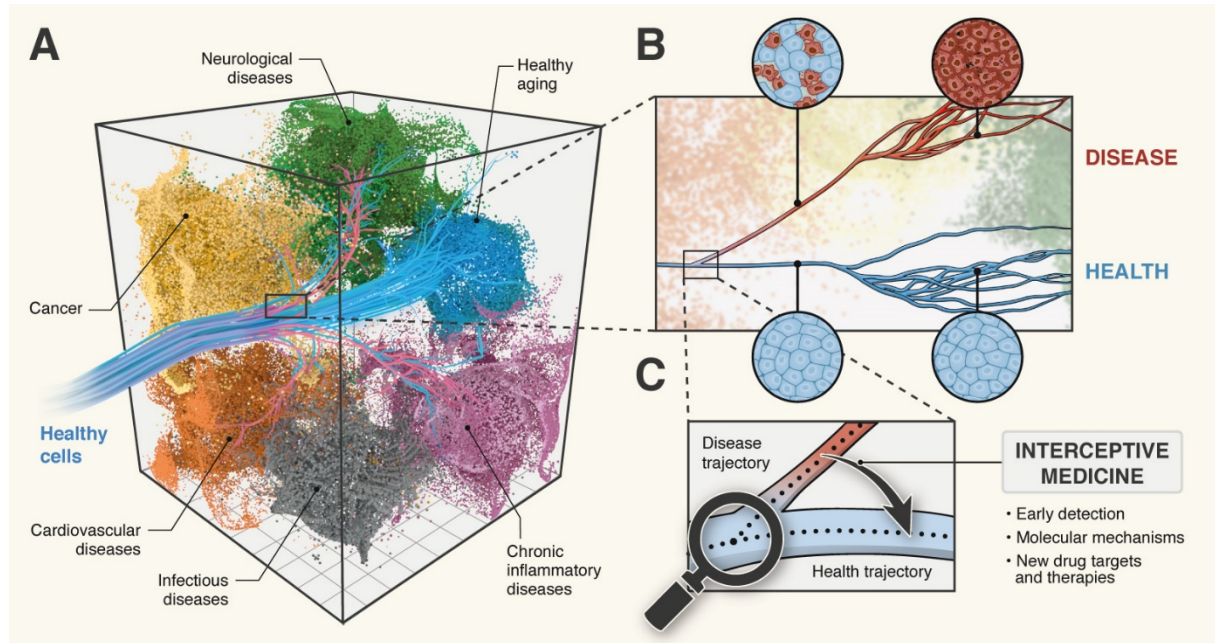
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**Figure 1. Early disease detection and interception by understanding and targeting cellular trajectories through time.**

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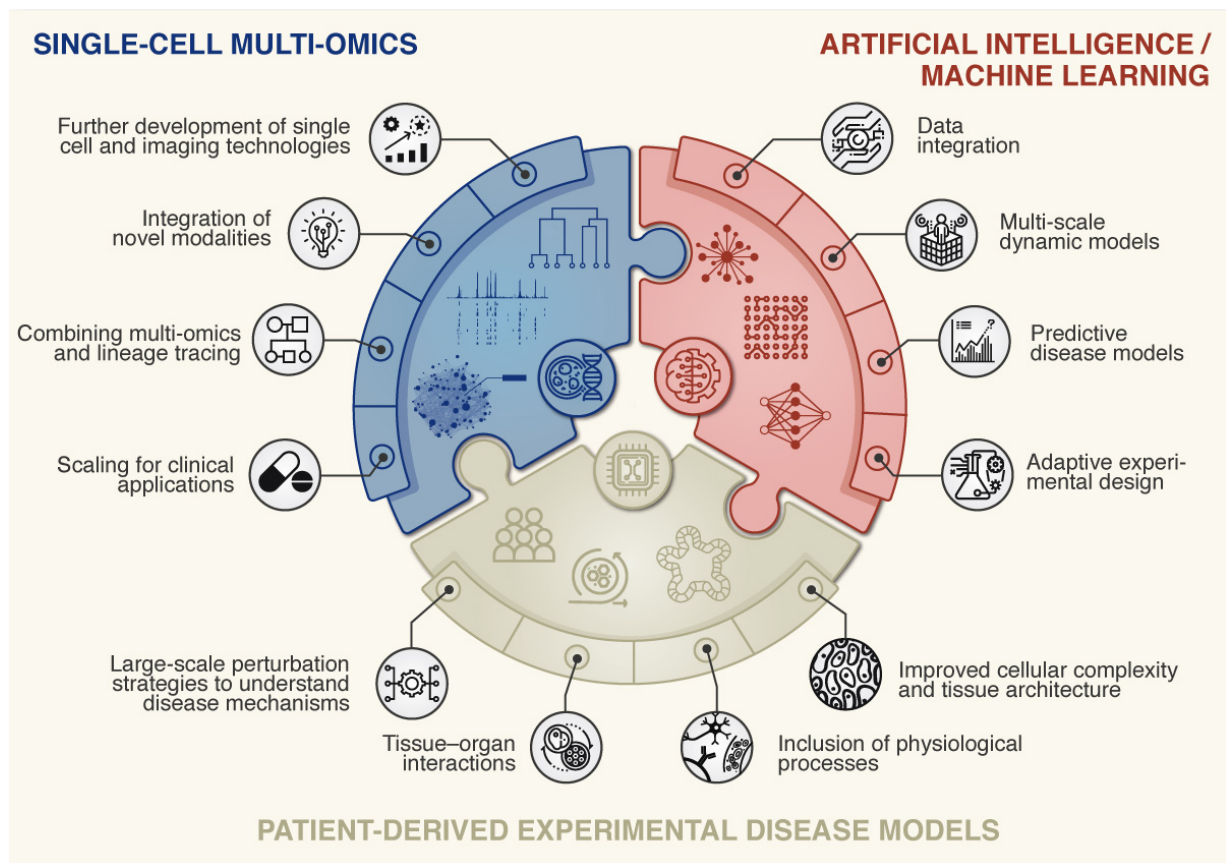
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(A) Cells are programmed to develop and differentiate along many different specific lineage trajectories (blue trajectories) to finally reach their functional state. When these normal lineage processes go awry, it can cause a cell to deviate from a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

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

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



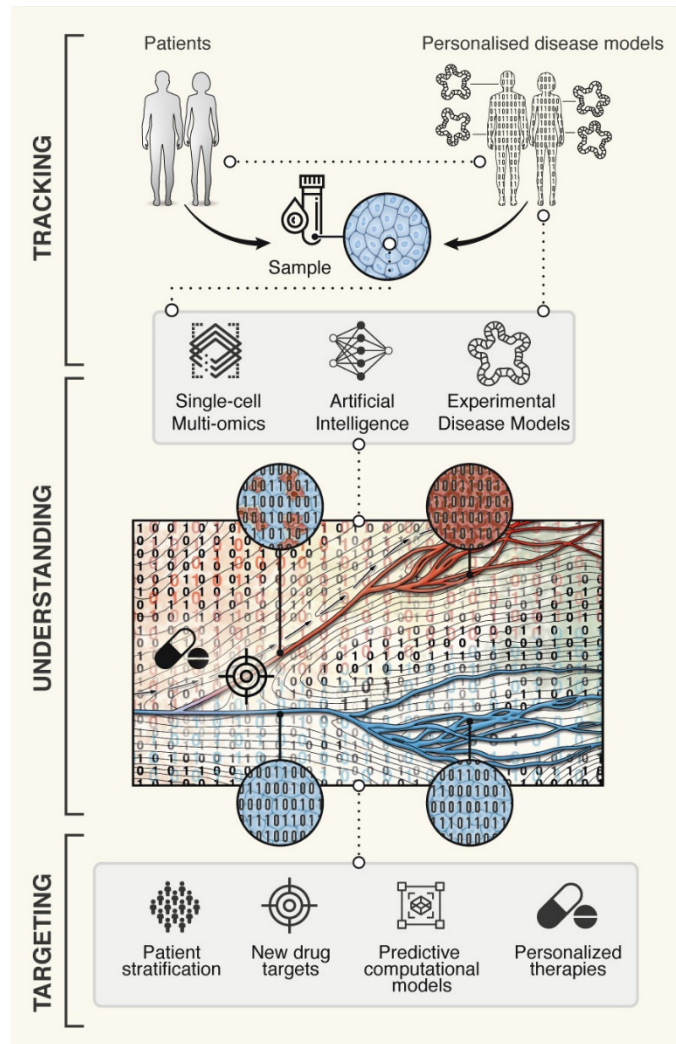
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**Figure 2. Hallmarks of the LifeTime approach to disease interception and treatment.**

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

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

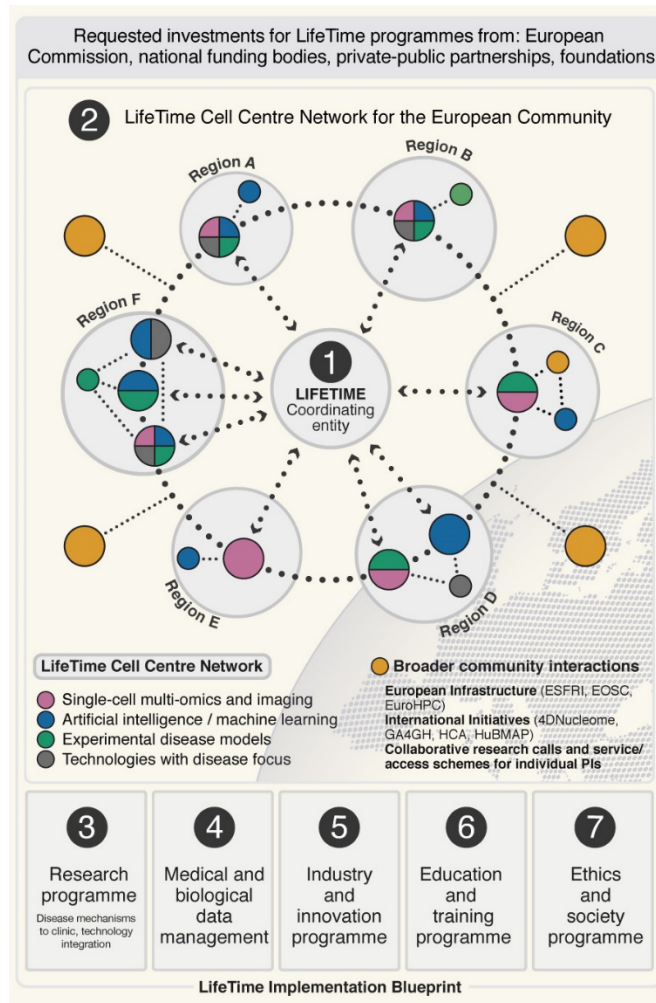
Patient-derived disease models such as organoids will be further developed to improve tissue architecture, incorporation of physiological processes, such as vasculature, nerve innervation and immune system to provide models that more faithfully recapitulate disease processes. Improved knowledge of disease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



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

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



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

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