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LifeTime and improving European healthcare through cell-based interceptive medicine

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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 ^{1,2} and placed in the context of tissues ^{3,4} 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 ⁵, 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 ⁶. 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) ⁷ 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 ⁸. 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) ⁶ and the NIH Human Biomolecular
195 Atlas Program (HuBMAP) ⁹.

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 ⁶. 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 ¹⁰⁻¹⁵, chronic inflammatory diseases ^{16,17}, Alzheimer's disease ¹⁸⁻²⁰ heart
203 failure ²¹, and sepsis ²². 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 ⁷.
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 ²³⁻²⁵. 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 ²⁶⁻³². Novel advanced imaging approaches also now
215 enable systematic spatial mapping of molecular components, *in situ*, within cells and cells
216 within tissues ^{28,33-37}. 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 ^{32,38-}
219 ⁴⁰. The implementation of cell lineage tracing approaches ⁴¹, 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 ⁷. 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 ^{12,42,43} or treatment of
230 multiple myeloma ¹¹. By detecting rare drug resistant cells that are present prior to ^{11,44} or that
231 emerge during treatment ⁴⁵, 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 ⁴⁶. 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 ^{47,48}. 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 ⁴⁹, 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 ^{47,50-52} (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 ^{3,4,53} (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 conditions⁵⁴,
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* models⁵⁵⁻⁵⁹ 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 principles⁶⁰ (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 ⁷.

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 ^{61,62} 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 ⁷: 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 ⁶³ 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 BiImaging 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 ⁶⁴.

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 ⁶⁵. 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 2080⁶⁶. 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 harmed⁶⁷ 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

613 **References**

614 1 Claussnitzer, M. *et al.* A brief history of human disease genetics. *Nature* **577**, 179-189,
615 doi:10.1038/s41586-019-1879-7 (2020).

616 2 Karczewski, K. J. & Snyder, M. P. Integrative omics for health and disease. *Nat Rev Genet* **19**,
617 299-310, doi:10.1038/nrg.2018.4 (2018).

618 3 Clevers, H. Modeling Development and Disease with Organoids. *Cell* **165**, 1586-1597,
619 doi:10.1016/j.cell.2016.05.082 (2016).

620 4 Lancaster, M. A. & Knoblich, J. A. Organogenesis in a dish: modeling development and disease
621 using organoid technologies. *Science* **345**, 1247125, doi:10.1126/science.1247125 (2014).

622 5 Tanay, A. & Regev, A. Scaling single-cell genomics from phenomenology to mechanism. *Nature*
623 **541**, 331-338, doi:10.1038/nature21350 (2017).

624 6 Regev, A. *et al.* The Human Cell Atlas. *Elife* **6**, doi:10.7554/eLife.27041 (2017).

625 7 The LifeTime Initiative. LifeTime Strategic Research Agenda. (2020).

626 8 Yofe, I., Dahan, R. & Amit, I. Single-cell genomic approaches for developing the next generation
627 of immunotherapies. *Nat Med* **26**, 171-177, doi:10.1038/s41591-019-0736-4 (2020).

628 9 HuBmapConsortium. The human body at cellular resolution: the NIH Human Biomolecular
629 Atlas Program. *Nature* **574**, 187-192, doi:10.1038/s41586-019-1629-x (2019).

630 10 Guo, X. *et al.* Global characterization of T cells in non-small-cell lung cancer by single-cell
631 sequencing. *Nat Med* **24**, 978-985, doi:10.1038/s41591-018-0045-3 (2018).

632 11 Ledergor, G. *et al.* Single cell dissection of plasma cell heterogeneity in symptomatic and
633 asymptomatic myeloma. *Nat Med* **24**, 1867-1876, doi:10.1038/s41591-018-0269-2 (2018).

634 12 Li, H. *et al.* Dysfunctional CD8 T Cells Form a Proliferative, Dynamically Regulated
635 Compartment within Human Melanoma. *Cell* **176**, 775-789 e718,
636 doi:10.1016/j.cell.2018.11.043 (2019).

637 13 Puram, S. V. *et al.* Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor
638 Ecosystems in Head and Neck Cancer. *Cell* **171**, 1611-1624 e1624,
639 doi:10.1016/j.cell.2017.10.044 (2017).

- 640 14 Tirosh, I. *et al.* Dissecting the multicellular ecosystem of metastatic melanoma by single-cell
641 RNA-seq. *Science* **352**, 189-196, doi:10.1126/science.aad0501 (2016).
- 642 15 van Galen, P. *et al.* Single-Cell RNA-Seq Reveals AML Hierarchies Relevant to Disease
643 Progression and Immunity. *Cell* **176**, 1265-1281 e1224, doi:10.1016/j.cell.2019.01.031 (2019).
- 644 16 Der, E. *et al.* Tubular cell and keratinocyte single-cell transcriptomics applied to lupus nephritis
645 reveal type I IFN and fibrosis relevant pathways. *Nat Immunol* **20**, 915-927,
646 doi:10.1038/s41590-019-0386-1 (2019).
- 647 17 Zhang, F. *et al.* Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues
648 by integrating single-cell transcriptomics and mass cytometry. *Nat Immunol* **20**, 928-942,
649 doi:10.1038/s41590-019-0378-1 (2019).
- 650 18 Grubman, A. *et al.* A single-cell atlas of entorhinal cortex from individuals with Alzheimer's
651 disease reveals cell-type-specific gene expression regulation. *Nat Neurosci* **22**, 2087-2097,
652 doi:10.1038/s41593-019-0539-4 (2019).
- 653 19 Keren-Shaul, H. *et al.* A Unique Microglia Type Associated with Restricting Development of
654 Alzheimer's Disease. *Cell* **169**, 1276-1290 e1217, doi:10.1016/j.cell.2017.05.018 (2017).
- 655 20 Mathys, H. *et al.* Single-cell transcriptomic analysis of Alzheimer's disease. *Nature* **570**, 332-
656 337, doi:10.1038/s41586-019-1195-2 (2019).
- 657 21 Wang, L. *et al.* Single-cell reconstruction of the adult human heart during heart failure and
658 recovery reveals the cellular landscape underlying cardiac function. *Nat Cell Biol* **22**, 108-119,
659 doi:10.1038/s41556-019-0446-7 (2020).
- 660 22 Reyes, M. *et al.* An immune-cell signature of bacterial sepsis. *Nat Med*, doi:10.1038/s41591-
661 020-0752-4 (2020).
- 662 23 Argelaguet, R. *et al.* Multi-omics profiling of mouse gastrulation at single-cell resolution.
663 *Nature* **576**, 487-491, doi:10.1038/s41586-019-1825-8 (2019).
- 664 24 Clark, S. J. *et al.* scNMT-seq enables joint profiling of chromatin accessibility DNA methylation
665 and transcription in single cells. *Nat Commun* **9**, 781, doi:10.1038/s41467-018-03149-4 (2018).
- 666 25 Rooijers, K. *et al.* Simultaneous quantification of protein-DNA contacts and transcriptomes in
667 single cells. *Nat Biotechnol* **37**, 766-772, doi:10.1038/s41587-019-0150-y (2019).
- 668 26 Chen, W. T. *et al.* Spatial transcriptomics and in situ sequencing to study Alzheimer's Disease.
669 *Cell in press*, doi:10.1016/j.cell.2020.06.038 (2020).
- 670 27 Giladi, A. *et al.* Dissecting cellular crosstalk by sequencing physically interacting cells. *Nat*
671 *Biotechnol*, doi:10.1038/s41587-020-0442-2 (2020).
- 672 28 Moffitt, J. R. *et al.* Molecular, spatial, and functional single-cell profiling of the hypothalamic
673 preoptic region. *Science* **362**, doi:10.1126/science.aau5324 (2018).
- 674 29 Nitzan, M., Karaikos, N., Friedman, N. & Rajewsky, N. Gene expression cartography. *Nature*
675 **576**, 132-137, doi:10.1038/s41586-019-1773-3 (2019).
- 676 30 Stahl, P. L. *et al.* Visualization and analysis of gene expression in tissue sections by spatial
677 transcriptomics. *Science* **353**, 78-82, doi:10.1126/science.aaf2403 (2016).
- 678 31 van den Brink, S. C. *et al.* Single-cell and spatial transcriptomics reveal somitogenesis in
679 gastruloids. *Nature*, doi:10.1038/s41586-020-2024-3 (2020).
- 680 32 Vickovic, S. *et al.* High-definition spatial transcriptomics for in situ tissue profiling. *Nat Methods*
681 **16**, 987-990, doi:10.1038/s41592-019-0548-y (2019).
- 682 33 Bintu, B. *et al.* Super-resolution chromatin tracing reveals domains and cooperative
683 interactions in single cells. *Science* **362**, doi:10.1126/science.aau1783 (2018).

- 684 34 Cardozo Gizzi, A. M. *et al.* Microscopy-Based Chromosome Conformation Capture Enables
685 Simultaneous Visualization of Genome Organization and Transcription in Intact Organisms.
686 *Mol Cell* **74**, 212-222 e215, doi:10.1016/j.molcel.2019.01.011 (2019).
- 687 35 Chen, K. H., Boettiger, A. N., Moffitt, J. R., Wang, S. & Zhuang, X. RNA imaging. Spatially
688 resolved, highly multiplexed RNA profiling in single cells. *Science* **348**, aaa6090,
689 doi:10.1126/science.aaa6090 (2015).
- 690 36 Mateo, L. J. *et al.* Visualizing DNA folding and RNA in embryos at single-cell resolution. *Nature*
691 **568**, 49-54, doi:10.1038/s41586-019-1035-4 (2019).
- 692 37 Medaglia, C. *et al.* Spatial reconstruction of immune niches by combining photoactivatable
693 reporters and scRNA-seq. *Science* **358**, 1622-1626, doi:10.1126/science.aao4277 (2017).
- 694 38 Jackson, H. W. *et al.* The single-cell pathology landscape of breast cancer. *Nature*,
695 doi:10.1038/s41586-019-1876-x (2020).
- 696 39 Keren, L. *et al.* A Structured Tumor-Immune Microenvironment in Triple Negative Breast
697 Cancer Revealed by Multiplexed Ion Beam Imaging. *Cell* **174**, 1373-1387 e1319,
698 doi:10.1016/j.cell.2018.08.039 (2018).
- 699 40 Maniatis, S. *et al.* Spatiotemporal dynamics of molecular pathology in amyotrophic lateral
700 sclerosis. *Science* **364**, 89-93, doi:10.1126/science.aav9776 (2019).
- 701 41 Baron, C. S. & van Oudenaarden, A. Unravelling cellular relationships during development and
702 regeneration using genetic lineage tracing. *Nat Rev Mol Cell Biol* **20**, 753-765,
703 doi:10.1038/s41580-019-0186-3 (2019).
- 704 42 Helmink, B. A. *et al.* B cells and tertiary lymphoid structures promote immunotherapy
705 response. *Nature* **577**, 549-555, doi:10.1038/s41586-019-1922-8 (2020).
- 706 43 Krieg, C. *et al.* High-dimensional single-cell analysis predicts response to anti-PD-1
707 immunotherapy. *Nat Med* **24**, 144-153, doi:10.1038/nm.4466 (2018).
- 708 44 Kim, C. *et al.* Chemoresistance Evolution in Triple-Negative Breast Cancer Delineated by Single-
709 Cell Sequencing. *Cell* **173**, 879-893 e813, doi:10.1016/j.cell.2018.03.041 (2018).
- 710 45 Rambow, F. *et al.* Toward Minimal Residual Disease-Directed Therapy in Melanoma. *Cell* **174**,
711 843-855 e819, doi:10.1016/j.cell.2018.06.025 (2018).
- 712 46 Corcoran, R. B. & Chabner, B. A. Application of Cell-free DNA Analysis to Cancer Treatment. *N*
713 *Engl J Med* **379**, 1754-1765, doi:10.1056/NEJMra1706174 (2018).
- 714 47 Eraslan, G., Avsec, Z., Gagneur, J. & Theis, F. J. Deep learning: new computational modelling
715 techniques for genomics. *Nat Rev Genet* **20**, 389-403, doi:10.1038/s41576-019-0122-6 (2019).
- 716 48 Lahnemann, D. *et al.* Eleven grand challenges in single-cell data science. *Genome Biol* **21**, 31,
717 doi:10.1186/s13059-020-1926-6 (2020).
- 718 49 Topol, E. J. High-performance medicine: the convergence of human and artificial intelligence.
719 *Nat Med* **25**, 44-56, doi:10.1038/s41591-018-0300-7 (2019).
- 720 50 Argelaguet, R. *et al.* Multi-Omics Factor Analysis-a framework for unsupervised integration of
721 multi-omics data sets. *Mol Syst Biol* **14**, e8124, doi:10.15252/msb.20178124 (2018).
- 722 51 Efremova, M. & Teichmann, S. A. Computational methods for single-cell omics across
723 modalities. *Nat Methods* **17**, 14-17, doi:10.1038/s41592-019-0692-4 (2020).
- 724 52 Pearl, J. & Mackenzie, D. *The Book of Why: The New Science of Cause and Effect.* (Penguin,
725 2019).
- 726 53 Amin, N. D. & Pasca, S. P. Building Models of Brain Disorders with Three-Dimensional
727 Organoids. *Neuron* **100**, 389-405, doi:10.1016/j.neuron.2018.10.007 (2018).

728 54 Knoblich, J. A. Lab-Built Brains. *Sci Am* **316**, 26-31, doi:10.1038/scientificamerican0117-26
729 (2016).

730 55 Bleijs, M., van de Wetering, M., Clevers, H. & Drost, J. Xenograft and organoid model systems
731 in cancer research. *EMBO J* **38**, e101654, doi:10.15252/embj.2019101654 (2019).

732 56 Byrne, A. T. *et al.* Interrogating open issues in cancer precision medicine with patient-derived
733 xenografts. *Nat Rev Cancer* **17**, 254-268, doi:10.1038/nrc.2016.140 (2017).

734 57 Espuny-Camacho, I. *et al.* Hallmarks of Alzheimer's Disease in Stem-Cell-Derived Human
735 Neurons Transplanted into Mouse Brain. *Neuron* **93**, 1066-1081 e1068,
736 doi:10.1016/j.neuron.2017.02.001 (2017).

737 58 Hasselmann, J. *et al.* Development of a Chimeric Model to Study and Manipulate Human
738 Microglia In Vivo. *Neuron* **103**, 1016-1033 e1010, doi:10.1016/j.neuron.2019.07.002 (2019).

739 59 Mancuso, R. *et al.* Stem-cell-derived human microglia transplanted in mouse brain to study
740 human disease. *Nat Neurosci* **22**, 2111-2116, doi:10.1038/s41593-019-0525-x (2019).

741 60 Wilkinson, M. D. *et al.* The FAIR Guiding Principles for scientific data management and
742 stewardship. *Sci Data* **3**, 160018, doi:10.1038/sdata.2016.18 (2016).

743 61 Alizadeh, A. A. *et al.* Toward understanding and exploiting tumor heterogeneity. *Nat Med* **21**,
744 846-853, doi:10.1038/nm.3915 (2015).

745 62 Schultze, J. L., consortium, S. & Rosenstiel, P. Systems Medicine in Chronic Inflammatory
746 Diseases. *Immunity* **48**, 608-613, doi:10.1016/j.immuni.2018.03.022 (2018).

747 63 European Life Science Research Infrastructures. <> (

748 64 Sugarman, J. & Bredenoord, A. L. Real-time ethics engagement in biomedical research: Ethics
749 from bench to bedside. *EMBO Rep* **21**, e49919, doi:10.15252/embr.201949919 (2020).

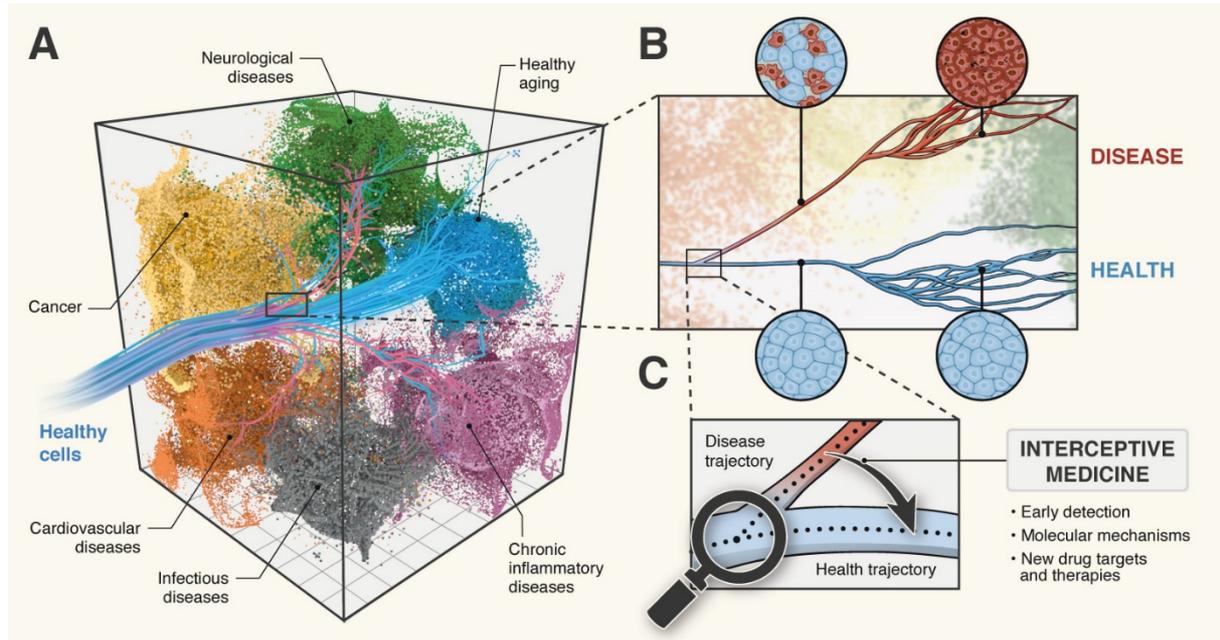
750 65 Torres-Padilla, M. E. *et al.* Thinking 'ethical' when designing a new biomedical research
751 consortium. *EMBO J*, doi:10.15252/embj.2020105725|TheEMBOJournal.(2020) :e105725
752 (2020).

753 66 European Commission. People in the EU: who are we and how do we live? , (2015).

754 67 What happened to personalized medicine? *Nat Biotechnol* **30**, 1, doi:10.1038/nbt.2096 (2012).

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

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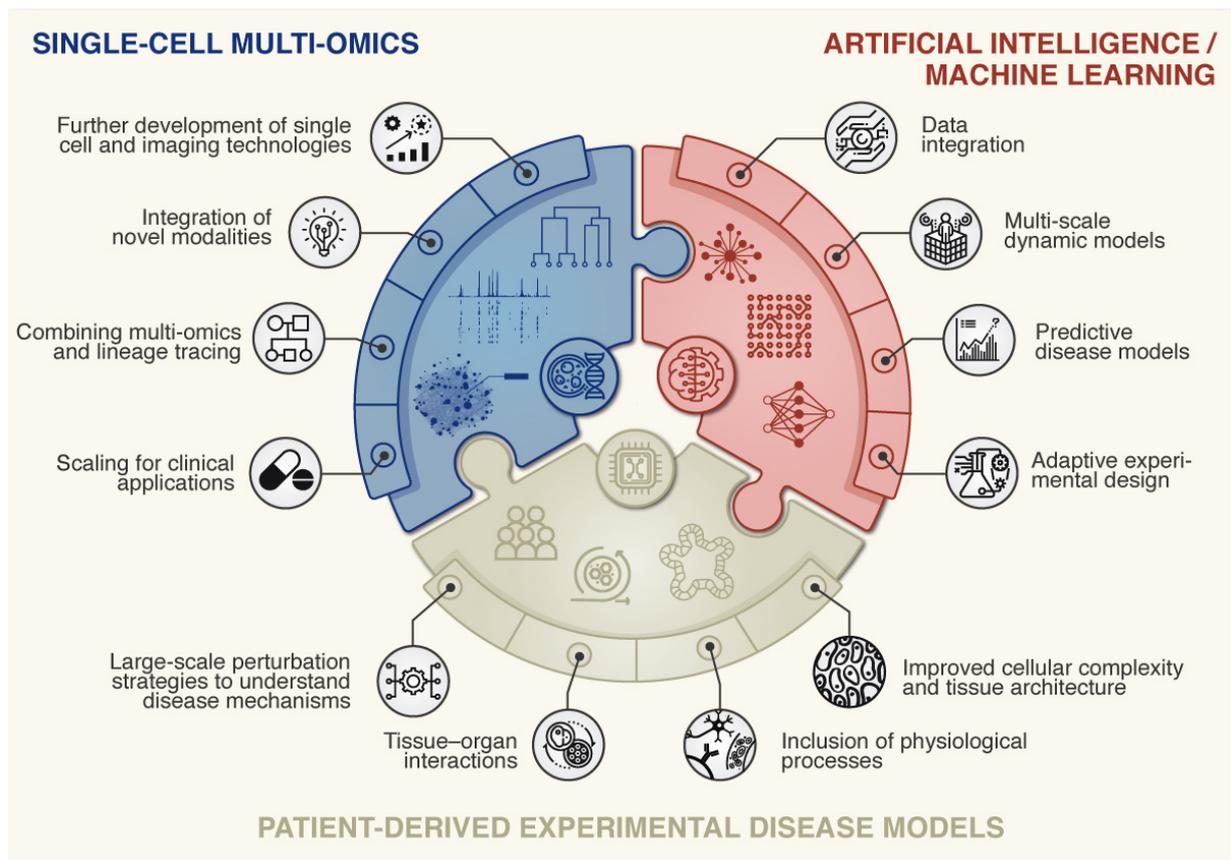
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(A) Cells are programmed to develop and differentiate along many different specific lineage trajectories (blue trajectories) to finally reach their functional state. When these normal lineage processes go awry, it can cause a cell to deviate from a 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.

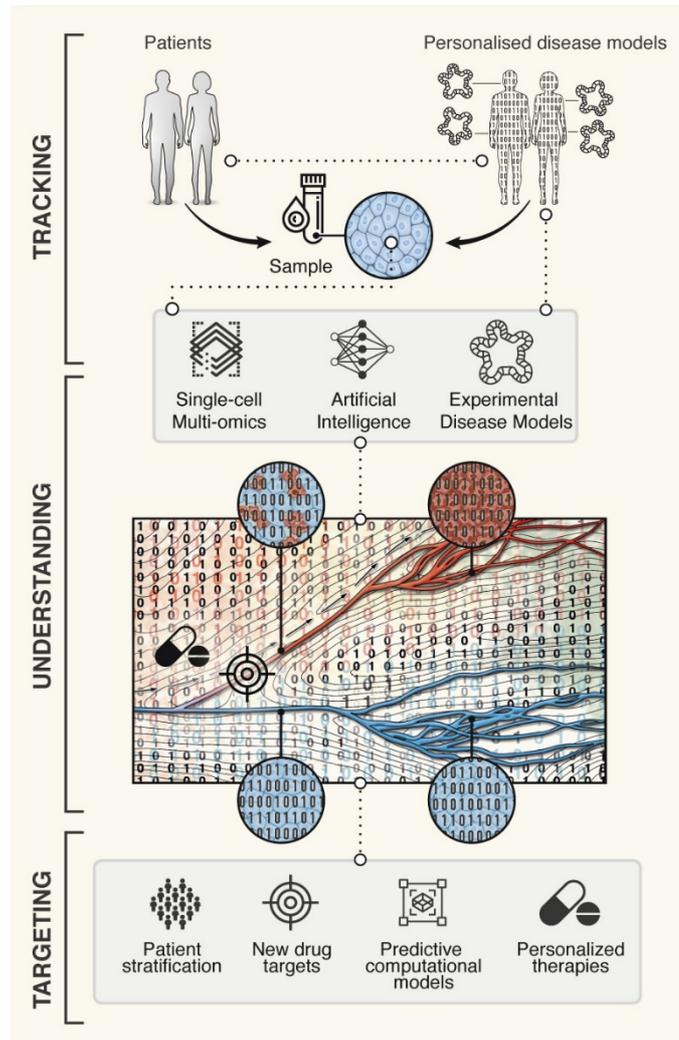
(C) Understanding the early molecular mechanisms that cause cells to deviate from a healthy to a disease trajectory will provide biomarkers for early detection of disease and new drug targets and innovative therapies to intercept diseases before onset of pathophysiology and manifestation of symptoms.



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

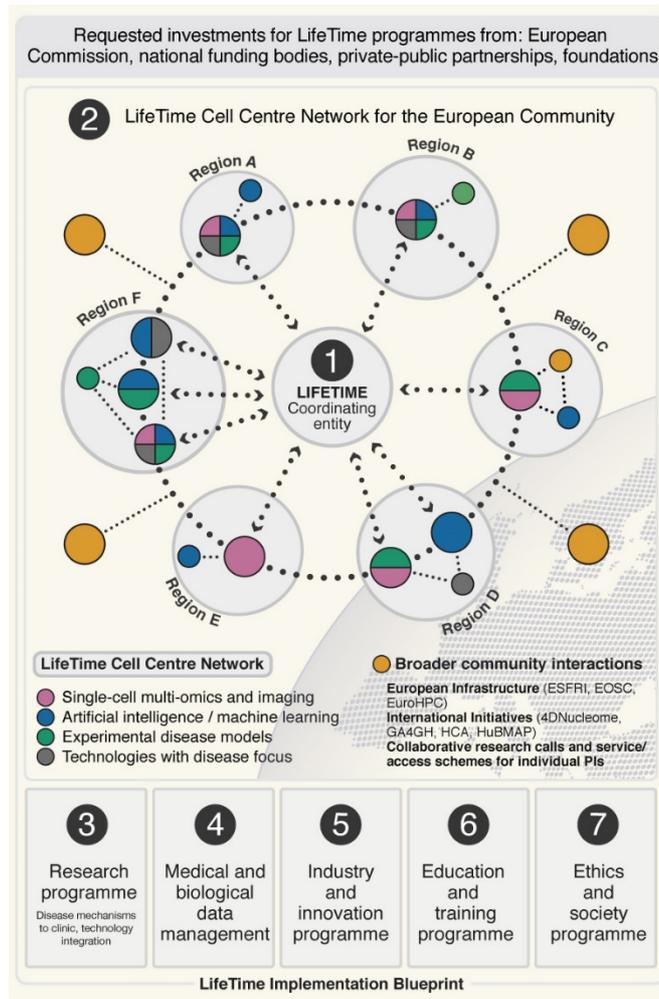
The scheme represents the development and integration of key technologies for investigating human diseases as envisioned by the LifeTime initiative. Single-cell multi-omics and imaging technologies will be developed for high throughput applications. Different modalities are combined to provide insight 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.