A preliminary study of LifeTime economic impact in Europe

LifeTime

Published by:
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Report based on an independent analysis conducted by PwC in May-June 2020

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Berlin, October 2020

This project has received funding from the European Union's Horizon 2020 research and innovation framework programme under grant agreement 820431.

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1. Executive summary

1.1 Background

LifeTime is a pan-European initiative, coordinated by the Max Delbrück Center for Molecular Medicine in Berlin and the Institut Curie in Paris, which is connecting more than 90 research institutions across Europe, as well as industry partners from the pharmaceutical, medtech, life sciences and IT industry. Overall, the members cover several capabilities, including basic and applied biomedical research, biotechnology, diagnostics, data and analytics, as well as imaging.

LifeTime's goal is to **revolutionise healthcare** by characterising how individual cells change during life and respond to disease. By applying this knowledge in the clinical practice - primarily by intercepting diseases before clinical appearance, but also by improving diagnosis, disease course prediction and response to treatment for each individual patient, based on his/her unique cellular profile – LifeTime aims to bring in the **next generation of precision medicine solutions**. This goal can be optimally achieved via the unique interface provided by the LifeTime initiative to integrate skills, experience, knowledge and perspectives among different scientific disciplines.

LifeTime's research output aims to transform healthcare delivery and have a broader impact on the **European economy**, thanks to the **growth** of the single-cell analysis industry, the push to European **innovation** and **competitiveness**, and the **healthcare cost savings** that will be achieved.

1.2 Current landscape

1.2.1 The growing burden of disease cannot be addressed with today's tools

The rise of chronic diseases is shaping the way health systems worldwide prioritise interventions. First, such conditions involve increasing portions of society – as more people live long lives, and second, disease management poses challenges in terms of long-term safety and costs. Therefore, in recent years an increasing focus has been put on disease prevention and awareness, as well as on personalised medicine which often results in wasted resources and suboptimal patient response. This is also reflected by the high R&D attrition rates, i.e. the number of compounds that fail the clinical phase, considering the limited ability to predict the efficacy of a compound early on.

The Human Genome Project (1990-2003) and the emerging genomic industry were instrumental to achieve today's targeted therapies, i.e. therapies approved for specific patient subpopulations characterised via their genotype. However, looking ahead, scientists need more sophisticated tools to further understand disease physiopathology. In this respect, next-generation sequencing technologies, combined with advanced analytical capabilities and sophisticated in vitro disease models, promise to deliver valuable insights - at much lower cost and higher speed than what could be imagined only a few years ago.

1.2.2 Single-cell multi-omics research will transform healthcare in the years to come

Single-cell research is a less mature field, but investments are growing rapidly worldwide - with large academic consortia already operating on large-scale initiatives aiming to map human cell profiles. The Human Cell Atlas (2016) is a global consortium whose goal is to build a reference multi-omic atlas at single-cell resolution. In the US, multiple NIH-driven cell atlas initiatives are ongoing, most notably the Human BioMolecular Atlas Program (HuBMAP) and the Human Tumor Atlas Network (HTAN). In China, the 10 Million Single-Cell Transcriptome Project (2019) aims to sequence the RNA of 10 million cells by the end of 2021. In the private sector, medtech and life sciences companies are investing in the development of sequencing instruments and consumables, while pharmaceutical companies are watching academic research closely, also recruiting leading single-cell scientists to develop internal expertise. The medtech industry around single-cell analysis is predicted to grow up to USD 5.32 billion globally in the next 5 years (16.2% CAGR 2018-25), similarly to the 3D cell culture market, which will experience a comparable growth (14.3% CAGR 2016-24). Overall, the precision medicine market will reach USD 53 billion in Europe, growing by 10% over the period 2017-28.

In order to create a fertile environment for innovation, a set of conditions that are required to support the success of single-cell analysis research need to be in place, such as **skill training** and availability; **capacity** or computational power to manage the amount of data generated; **infrastructure** where different disciplines meet and reach the "critical mass" to generate innovative ideas; the capital **investments** required to build appropriate facilities and equipment; and the **regulations** around personal data - which must be simultaneously protective of individuals, while also conducive of innovation and commercialisation.

1.3 LifeTime impact

1.3.1 LifeTime has a unique value proposition around disease interception

LifeTime uniquely combines basic and clinical research around cell-based **disease interception** - also by using in vitro disease model validation. In just over one year, LifeTime has built a strong network of scientists, clinicians, computational scientists, engineers, as well as corporate partners, eager to work together to improve **European patient's health**. LifeTime aims to excel in positioning Europe **competitively** in biomedical research, with a positive impact on local **economic growth** around innovation.

1.3.2 LifeTime has the potential to drive innovation and push economic growth in Europe

It has consistently been estimated that translational biomedical research yields returns on investment up to 35-50% annual rate, and significantly contributes to economic growth, especially when considering job creation and foundation of new companies. A pivotal initiative such as the Human Genome Project, which described human genes and paved the way to today's genomic industry, has been shown to have generated USD 141 in tax revenues for each dollar spent by the US government. Notably, single-cell research will explain human gene behavior, bringing disruptive knowledge and innovation, in the wake of what the Human Genome Project achieved. If LifeTime will achieve its research goals, a considerable economic drive can reasonably be expected, even though not quantifiable at present, due to the early research stage (i.e. discovery), and unknown elements around the transformation of the industry in preparation of the future precision medicine revolution, the regulatory landscape, and the time horizon that we are looking at (10+ years).

1.3.3 The next generation of precision medicine will transform healthcare delivery

LifeTime research output aims to create the conditions to design personalised interventions for those in need. The current approach to healthcare is expected to undergo a transformation – for example by focusing on disease interception and screening in healthy individuals, but also later down the pathway, with laboratories and clinics/providers working in close connection at diagnosis, treatment and monitoring to deliver personalised care. Newly conceived infrastructure and healthcare professional profiles will be instrumental to bring innovation to European patients. Indeed, the European precision medicine market, current worth USD 25 billion, is predicted to reach almost USD 53 million in 2028. Globally, China might overtake the US as the world's largest precision medicine market by 2040, driven by recent multi-billionaire public investments.

1.3.4 Novel single-cell based strategies will allow considerable healthcare cost savings compared to today

LifeTime research outcome has the potential to considerably improve European patients' health. Novel -omic biomarkers and targeted therapies will enter the market after 2030, improving health outcomes, and determining considerable direct and indirect healthcare cost savings across Europe.

Today, 25% of global cancers occur in the European region. At the current rates, in 2030 almost 4 million new cases and 1.8 million deaths will occur, representing a total productivity loss of EUR 99 billion. LifeTime scientists expect that their work will improve today's ability to cure cancer. In **breast cancer**, a 11% improvement in the cure rate[1] would grant **EUR 1.3 billion** of productivity gains in 2030 - which is only a small part of the overall benefits related to increased survival for women and their families. The gain across **all cancer cases** could amount to **EUR 6.1 billion** at least.

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

LifeTime research is also intensively focusing on the emerging threat represented by **COVID-19**. Early predictive biomarkers would allow earlier treatment of patients, bringing additional benefit such as, relieving hospitals from excessive intensive care occupancy during epidemics, and also representing savings in the range of **EUR 155-360 million**[2] across Europe for **each day** of shorter ICU stay. Importantly, a better and more rapid patient management would bring an immense benefit to the economy, considering the impact of the pandemic on global productivity.

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

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

From this partial and **preliminary study**, it is evident that, even when just considering specific economic components such as mortality- and morbidity-related productivity losses in few selected disease areas, the potential for industrial economic growth and better use of healthcare resources deriving from LifeTime research output are considerable.

[1] Assumptions on potential future health benefit for all disease areas have been generated by LifeTime experts, based on their expectations and working hypotheses.
[2] Assuming a similar number of cases (2 million) as in spring 2020 in Europe.

1.4 Key recommendations

1.4.1 LifeTime relies on sustained collaboration and cross-cutting resources

LifeTime relies on sustained collaboration to generate synergies, progress rapidly, and achieve a long-term impact. Especially when looking at the dense US ecosystem and extensive infrastructure around public research - also combined with dynamic and conspicuous private investments - it is crucial to support LifeTime with infrastructural investments (including Cell Centres and the crucial data platform), and private investment injections corroborating public funds, especially towards the clinical development phase.

1.4.2 Europe is called to define a patient-centric and competitive model of innovation

Europe needs to uniquely position itself with regards to next-generation precision medicine and big data revolution. Leveraging the European cultural heritage, there is room for Europe to take a humanistic, patient-centered approach to biomedical innovation - generating knowledge which is directly applicable to the clinical practice, but also addressing key challenges related to data protection and/or "data as public good", which will be crucial to protect innovation and maintain a focus around the patient in the future medicine. Europe could also act as a role model on innovation for low-/middle-income countries, building an ecosystem in which small, highly innovative players find a ground to expand.

1.4.3 Europe has an opportunity to remain an attractive location for STEM talents

Single-cell multi-omics research is taking off worldwide and young talented researchers, alongside established group leaders, will understandably seek to develop their research projects in world-class laboratories and innovation clusters. Europe must create spaces where students and scientists from different backgrounds can meet around single-cell analysis research. Such clusters will be one of the key attractions allowing to keep talents in Europe, rather than leaving permanently to conduct their research elsewhere, notably in the US or China.

In summary, LifeTime is a promising Europe-based biomedical research initiative, which could shape the future approach to healthcare and medicine. LifeTime's research outcome could have a tremendous impact on the industrial economy, healthcare budget management, and innovation. Most importantly, LifeTime could allow European patients and potential wider society to benefit from personalised and effective healthcare interventions.

2. The healthcare landscape around single-cell analysis research

2.1 Current landscape

2.1.1 Today's unmet needs

The rise of chronic health conditions has been one of the key factors shaping public health priorities in the past decades. Improved medical care, together with an increasing focus on disease awareness and prevention, are key drivers of human life span extension and quality of life improvement. On the other hand, an increasingly large portion of the adult population faces the burden of chronic health illnesses, which they might deal with for many years.

Further to this, chronic diseases are often diagnosed late, and are not treated efficiently in the long-term, potentially due to toxicity of medications from prolonged administration, reduced efficacy over time, or simply a lack of availability for certain diseases/disease stages. In addition, progressive health deterioration for the elderly population often results in multiple comorbidities, all of which being treated in parallel, with increasing issues around safety, therapy adherence and costs.

The increasing prevalence of chronic conditions is putting a heavy strain on healthcare budget, as suggested by the World Health Organization (WHO)[3] data, showing a global spending on healthcare of USD 7.8 trillion in 2017. Specifically, the public spend in health in Europe in 2018 amounted to EUR 944 billion, or 7.0% of GDP on average (ranging from 4.7% in Romania up to 8.3% in Denmark)[4], for its 445 million citizens. According to the projections, the public expenditure on healthcare and long-term care will rise by 1.7% of GDP by 2045, mostly driven by the European aging population trend[5]. Consequently, healthcare systems seek for approaches that help spend "better" the limited resources, limiting the waste of resources that derives from lengthy diagnoses and ineffective treatments.

The concept of personalised medicine has been around for several decades and has largely been associated to the success of the Human Genome Project, the most ambitious biomedical project of all time. The first "targeted therapies", such as Herceptin (trastuzumab), Erbitux (cetuximab) and Gleevec (imatinib), reached the market more than 20 years ago, and represented the first drugs specifically designed for patient subpopulations featuring a specific genetic profile (see section 2.2.1 for market size and forecast).

Despite the huge medical advancements that have happened over the last two decades, WHO has recently calculated that, globally, 40% of patients are still harmed by medical errors during primary and ambulatory health care, with these errors most frequently happening in relation to diagnosis, prescription and the use

[3] Global spending on health: a world in transition", WHO, 2019
[4] "Government expenditure on health", Eurostat, 2018
[5] Brändle, T, & Colombier, C., "Healthcare expenditure projections up to 2045 (FFA Working Paper No. 21)", Federal Finance Administration, 2016

of medicines. Errors in drug usage are estimated to be worth USD 42 billion annually[6]. While this is partly due to human error and lack of knowledge, there are still limited tools available to predict for each individual patient the speed and severity of disease progression, the most effective and safe treatments among those available. All these challenges can today only be addressed via a trial-and-error approach, with an evident burden on the patient and on healthcare system resources.

It is a common idea across the scientific community that the traditional genomic/bulk sequencing (i.e. Human Genome Project-like) approach has been by now largely exploited, and most clinically relevant discoveries developed and brought to the market (or are on their way); further advancement will require innovative approaches and new ways to look at disease[7]. In particular, novel technologies, including next-generation sequencing and biomarker assays, are being rapidly approved by regulatory bodies including the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), thus expanding the arsenal of tools accessible to support the development and adoption of novel therapies over one-size-fits-all therapies and treatment, and most stakeholders look at discoveries in the field of single-cell analysis as the most promising approach to develop the next generation of precision medicines[8].

2.1.2 Healthcare trends relevant to single-cell analysis approach

At present, the healthcare landscape is characterised by a set of factors and dynamics that call for innovative and personalised approaches in medicine:

- The unreasonable cost of trial-and-error method for the development of conventional drugs as compared to targeted-clinical-trial practice (see Figure 1), considering that a pivotal trial for the approval of a novel agent costs on average around USD 20 million (and up to USD 45- and 157 million for oncology and cardiovascular trials respectively)[9]

- The dramatic decrease in sequencing technology cost triggered by next-generation sequencing methods, computational and analytical capabilities advancement. According to the NIH National Human Genome Research Institute, the cost of sequencing a human genome decreased from USD 100 million in 2001 to USD 1,000 in 2020[10] and will likely further drop

- The research focus on non-invasive biomarkers, companion diagnostic and preventive medicine

- The growing amount of real-world data and advancement in big-data analytics, allowing the observe effectiveness of therapies outside of controlled clinical conditions

- Patient empowerment and increasing awareness around their health, accompanied by rising expectations towards healthcare professionals and providers

[6] WHO calls for urgent action to reduce patient harm in healthcare", WHO, 2019
[7] Experts' opinion (internal research and analysis, May 2020).
[8] Experts' opinion (internal analysis) and peer-reviewed literature, see for example Shalek and Benson (2017). Single-cell analyses to tailor treatment. Science Translational Medicine, 9(408):eaan4730; Chen et al. (2020), Single Cell Omics: From Assay Design to Biomedical Application. Biotechnology Journal, 15(1): e1900262; Olivier et al. (2019). The Need for Multi-Omics Biomarker Signatures in Precision Medicine. Int J Mol Sci, 20(19):4781.
[9] Moore et al. (2018). Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015 – 2016. JAMA Internal Medicine, 178(11): 1451-1457.
[10] The cost of sequencing a human genome", NIH National Human Genome Research Institute [accessed 06 June 2020].

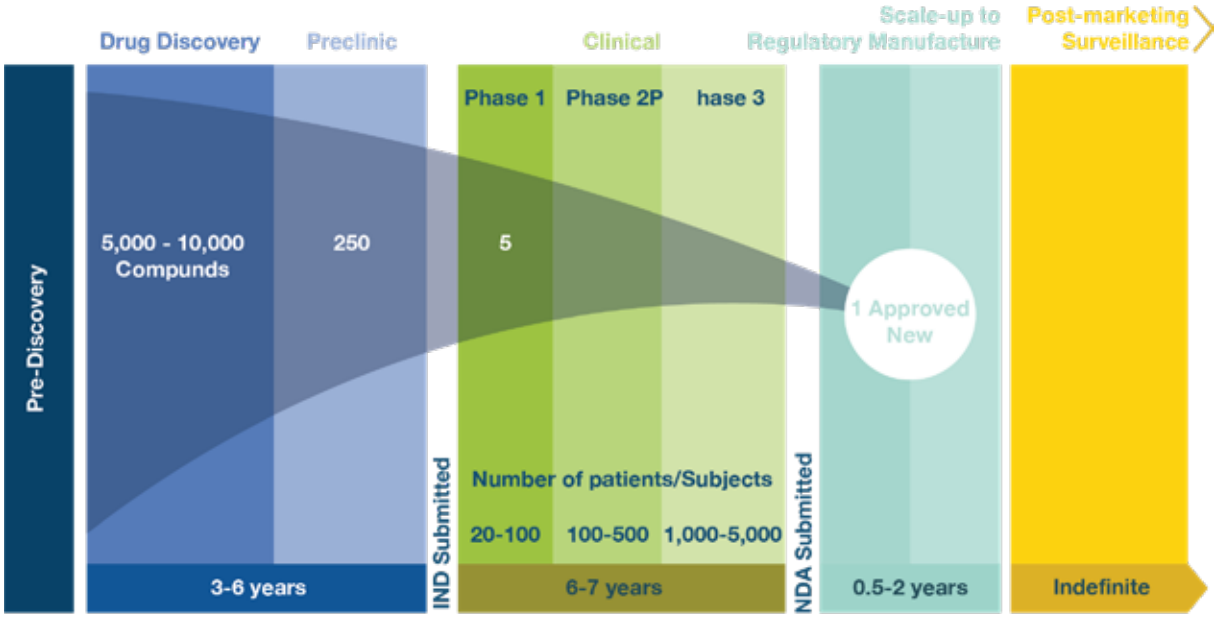


Figure 1 Attrition rates in pharmaceutical R&D

IMI2 Strategic Research Agenda, 2014; CBO, Research and Development in the Pharmaceutical Industry, 2006

2.2 Evolving landscape

2.2.1 The precision medicine market

Precision medicine is an approach to patient management which revolves around patient-specific information to diagnose and characterise the diseases, as opposed to a one-fits-all approach. Currently available precision-medicine treatments are typically tailored to individual's specific genotypes, an example being trastuzumab, which is effective for patients overexpressing the protein HER2/neu. Looking ahead, the precision-medicine approach is expected to lead to individualised treatments for each patient, based on their specific "multi-omics" profiling, but also macro-factors, such as socioeconomic status, environment, and lifestyle.

There has been significant growth in the precision medicine market over the last few years. It was estimated that, in 2017, 35% of all drugs approved by the FDA were "precision medicine drugs", compared to only 5% in 2005[11]. The European market represents roughly 20% of the global market, and will more than double in the next few years. Globally the market is predicted to grow up to USD 217 billion in 2028[12], with North America dominating by size the global market. However, China might overtake the US as the world's largest precision medicine market on the long run, driven by multi-billion dollar state investments[13].

Among disease area applications, oncology will represent almost half of the overall market.

2.2.2 The use of artificial intelligence in healthcare

From a macro-economic perspective, it has been calculated that, in 2030, the incremental application of AI technology will increase the global GDP by 14% compared to current trends, corresponding to USD 15.7 trillion. This growth will be primarily driven by automation of processes, augmentation of current workforce, and demand for higher quality products (see Figure 2). The largest gains are attributed to China (+26.1% GDP) and the US (+14.5% GDP), while Europe is predicted to grow by 9.5 - 11.5%[14]. AI applications in healthcare, education, public service, and recreation industry will lead the transformation.

[11] Kiernan, U. & Naylor, S, "Precision Medicine Drugs - Pleonasm or Reality?, Drug Discovery World, 2018.
[12] "Global Precision Medicine Market - Analysis and Forecast, 2018-2028", BIS Research, 2019.
[13] Experts' opinion (internal research and analysis, May 2020).
[14] "The macroeconomic impact of artificial intelligence", PwC, 2018

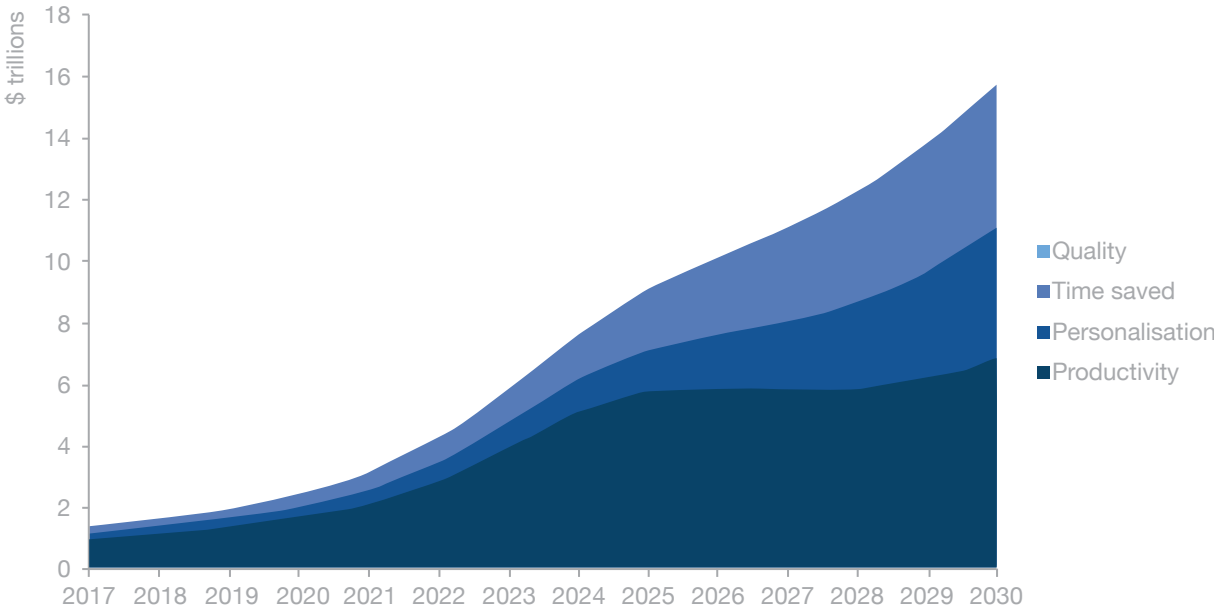


Figure 2 The estimated global GDP impact by effect of AI
Source: PwC (2018).

Indeed, the use of Artificial Intelligence (AI) in healthcare will transform the way innovation is achieved and healthcare is delivered. AI applications will span across the whole value chain, from biomedical research, to drug production and to supply, to service organisation and delivery, to clinical care. Specifically, in biomedical research, AI finds potential applications at all stages of drug discovery/development, as illustrated in Figure 3. In particular, AI will be powered by Big Data, i.e. large volume of patient datasets coming from real-world studies, wearables, connected devices, digitalisation of medical records (electronic health records, EHRs), large-scale -omic initiatives (see sections from 2.3.2 to 2.3.4), etc. The use of AI to extract insights from large volumes of information has the potential to drive real change in clinical practice, from personalised therapy and intelligent drug design to population screening and EHR mining.

The market related to the use of AI in healthcare is growing significantly. Globally, the market was valued USD 2.5 billion in 2018, and is predicted to grow in the next 5 years at the rate of 41.5% (CAGR)[15].

[15] "Artificial Intelligence In Healthcare Market Size, Share & Trends Analysis Report By Component (Hardware, Software, Services), By Application, By Region, Competitive Insights, And Segment Forecasts, 2019 – 2025", Grand View Research, 2019.

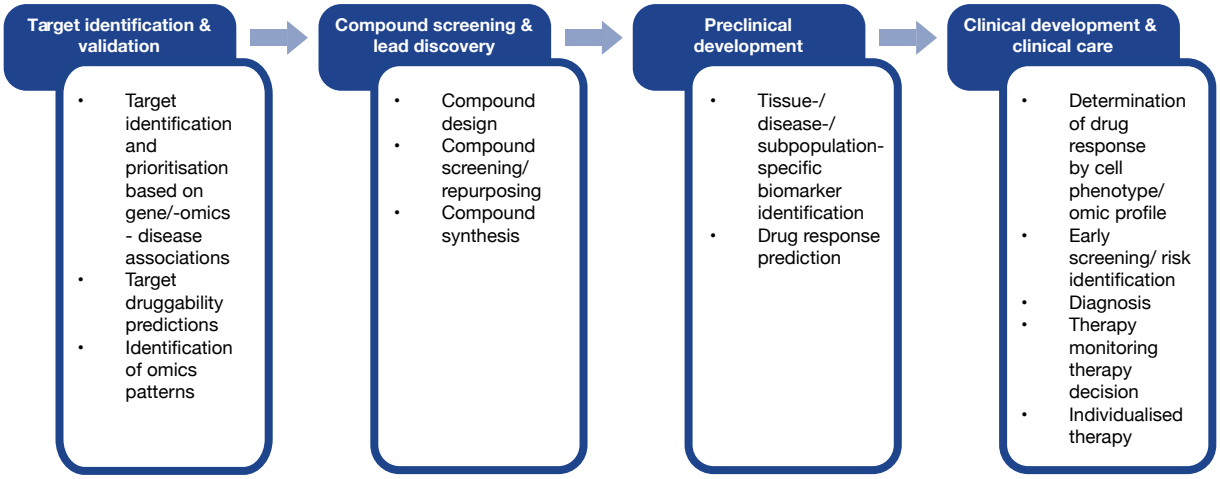


Figure 3 Application of AI in drug development

Adapted from Hofmarcher et al. (2019). Comparator Report on Cancer in Europe 2019 - Disease Burden, Costs and Access to Medicines, IHE Report, 7, 23, IHE: Lund, Sweden.

2.2.3 The single-cell multi-omics market

From a methodological perspective, single-cell multi-omics techniques are predicted to be at the heart of the cutting-edge research that could lead to the novel generation of precise therapeutics and diagnostics. The predicted growth of the market for lab instruments and consumables supporting single-cell multi-omics research is a clear indicator of the field's rising importance: the global market was worth USD 1.83 billion in 2018 and is predicted to grow up to USD 5.32 billion by 2025[16].

The single-cell multi-omics segment growth is attributed mostly to the increasing prevalence of chronic diseases, such as cancer and other degenerative conditions (and consequently, the need for early diagnostics and treatments), the technological advancements, and the growing interest and investments from leading pharmaceutical companies.

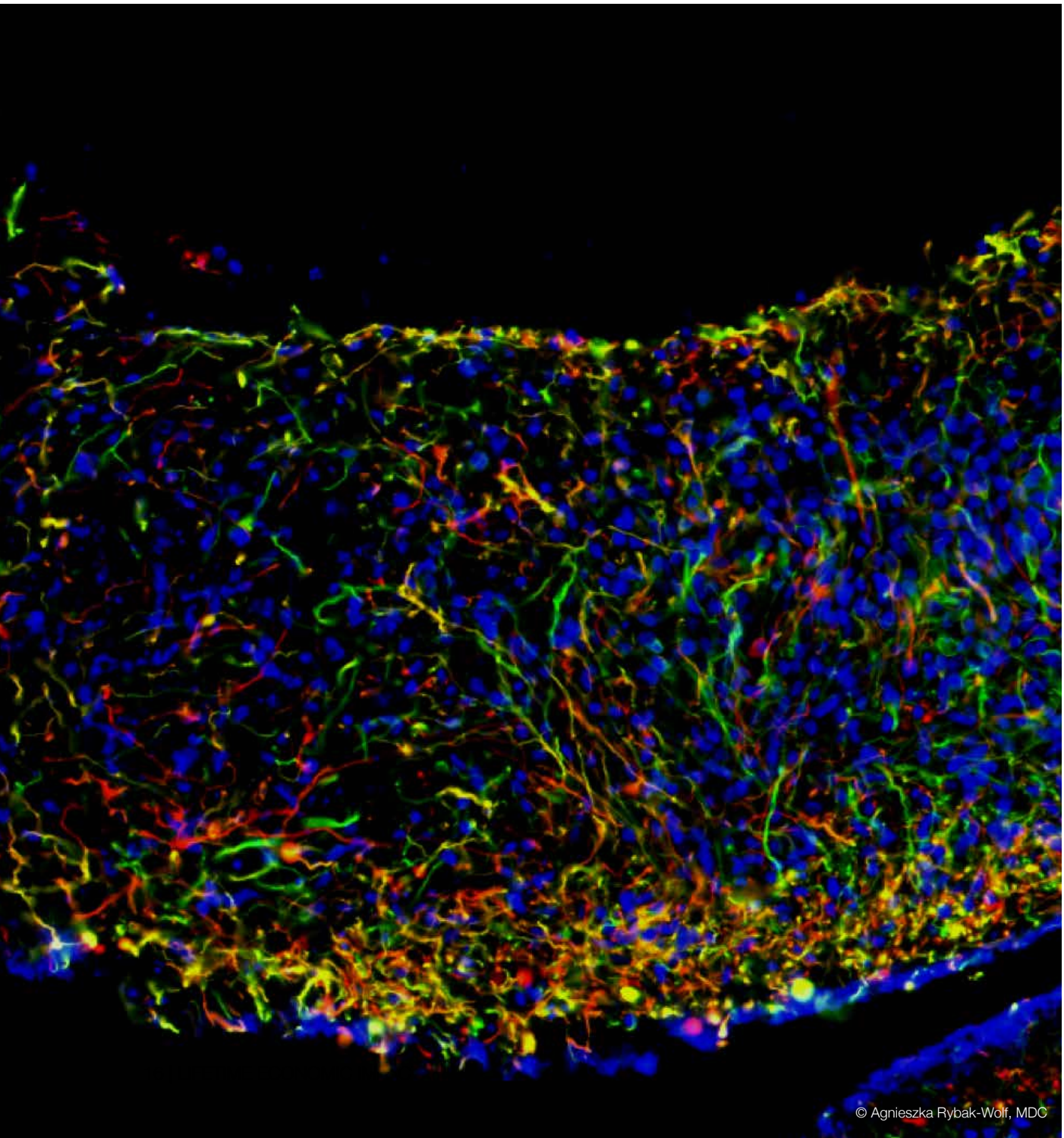
The utilisation of laboratory supplies in the field of single-cell multi-omics research is predicted to grow similarly for all end customers, i.e. academia, industry, and hospitals and diagnostic facilities. The latter data interestingly reflect the fact that, in the next years, the presence of physician-laboratory partnerships will increase, allowing the transition of single-cell analysis techniques into the clinical practice, especially for activities such as selecting the distinct cell types that need to be investigated for a particular disorder.

[16] "Global Single Cell Multi-Omics Market – Analysis and Forecast, 2019-2015", BIS Research, 2019.

2.2.4 The 3D cell culture Market

The 3D cell culture market is predicted to grow at a 15.7% CAGR over the period 2019-2024, to reach the size of USD 1.85 billion globally. While the US are currently dominating the market, Europe is predicted to grow at the fastest rate until 2023, mostly in relation to "the growth of its pharmaceutical and biotechnology industry, recent commercialisation of microfluidics-based products, the increasing presence of major market players, and a large number of research activities conducted in the region"[17]. In addition, it is foreseeable that hospitals and clinics will grow their interest towards such market, in relation to increased medical applications and near-the-patient testing[18].

[17] "3D Cell Culture Market", Markets And Markets, 2018.
[18] Internal research and analysis (May 2020).



2.3 Overview of current investments

Globally, the field of precision medicine and specifically single-cell research is highly competitive with many consortia-led initiatives facilitating collaboration between industry, academic institution, government bodies and other organisations. The maturity and structure of these consortia vary significantly, from loose-knit collaborations with no dedicated funding, to well established structured initiatives with dedicated funding from governments or large funding bodies.

Funding is the foundation required to continue the advancement of single-cell sequencing research. It is no surprise that the US organisations have the most access to capital and published almost four times more publications on single-cell multi-omics compared to Germany, France, Spain, Italy, and UK from 2010 to 2018[19]. Funding is driven by both public and private investors, with the latter often a result of increased public funding. Another requirement to increase the amount of funding from private investors is to ensure there is sufficient pull funding from the market and industry to make investment more attractive. Providing the required level of capital to drive further research in single-cell sequencing is a combination of push (public and private funding) and pull (market and industry) funding, and public bodies e.g. government, may have to make the first move and provide capital to attract more private and industry interest.

The use of consortium-led initiatives is vital to scale novel research into more commercially viable technology and guide the industry forward. In the following sections, we will explore the variety of consortium led initiatives and what frameworks and funding models drive their progress, with a focus on Europe, US and China markets.

2.3.1 Precision medicine initiatives

Government bodies across the world are making important investments in the field of precision medicine, specifically in terms of creating useful patient database/registries. In addition, steps are taken to form harmonised regulatory policies, co-working with industry partners, involving manufacturers, clinical laboratories, research organisations, and payers. Several initiatives are being funded internationally to support R&D around precision medicine, as exemplified in Table 1.

[19] Internal research and analysis (May 2020).

Project	Sponsor	Funding size (USD)	Duration	Goal
Europe				
Innovative Medicines Initiative (IMI) 2	Public/Private partnership	4,000 million	6 years	Accelerating the development of new treatments by supporting major research projects on next-generation medicine, vaccines, and treatments
1+ Million Genomes' Initiative	European Commission	n/d	4 years	Cooperation towards access to >1 million sequenced genomes by 2022, linking access to genomic database across EU, ultimately improve disease prevention, personalised treatments and clinical research
100,000 Genome Project	UK Government	352 million		Sequence 100,000 genomes from around 85,000 NHS patients affected by a rare disease or cancer
Precision Medicine Catapult	Innovate UK	70 million	5 years	Development of diagnostic tests and therapies for precision medicine
US				
Precision Medicine Initiative	US Government	320 million		Accelerating the R&D activities regarding precision medicine
Precision Medicine Initiative (PMI) Cohort Program	NIH	142 million	5 years	Establish the world's largest research-cohort biobank (1 million or more US participants) to support the advancement in precision medicine, and understand individual differences in health and disease
BRAIN Initiative	US Government (White House Office of Science and Technology Policy, OSTP)	100 million	2 years	Understanding of brain functions, and development of innovative technologies
China				
China Precision Medicine Initiative	Chinese Academy of Sciences	9'200 million	15 years	Secure global lead in personalised/ precision medicine

Table 1 Selection of recent initiatives and programmes in the field of precision medicine.

2.3.2 Single-cell multi-omics initiatives in Europe

In addition to LifeTime, the leading European initiative around single-cell multi-omics research, other initiatives and programs are being worked upon to increase acceptance and funding of the single-cell technology across European markets. Some of the key European initiatives and platforms are presented below.

European Human Cell Atlas pilots

The European Commission is funding six pilot actions, within the Horizon2020 Research and Innovation Framework Programme, which started in January 2020. These pilots are part of the European contribution to the global Human Cell Atlas initiative (section 2.3.3). The six pilots are summarised in Table 2.

Pilot name	Description	Coordination
BRAINTIME	Molecular atlas of the brain across the human lifespan	Karolinska Institutet, Sweden
DISCOVAIR	3D molecular mapping of the lung	Academisch Ziekenhuis Groningen, The Netherlands
ESPACE	Multi-omic mapping of human pancreas from >1 million cells, in healthy adults and during prenatal development	Charité – Universitätsmedizin Berlin/ Berlin Institute of Health, Germany
HCA ORGANOID	Initially focused on colon and brain, will establish single-cell multi-omics patterns and time-series imaging for several thousand organoids and matched primary tissue to provide a baseline for disease studies	CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Austria
HUGODECA	Atlas of the cellular composition and organisation of the developing human gonads	Institut National de la Sante et de la Recherche Medicale, France
HUTER	Transcriptomic, genomic and spatial changes of the uterus throughout the menstrual cycle as well as across lifespan	INCLIVA Instituto de Investigacion Sanitaria, Spain

Table 2 Overview of the European HCA pilots funded by Horizon2020
Source: Human Cell Atlas, European Pilot Actions to Build the Foundations of the Human Cell Atlas

Innovative Medicine Initiative (IMI)

IMI is an EU public-private partnership, which funds health research and innovation, and is currently hosted under EU's Horizon 2020 programme. The goal is to develop the next generation of medicines, vaccines and treatments. While the focus of the initiative is broader than precision medicine, the latest 2014-2020 IMI2 agenda focused on delivering "the right prevention and treatment for the right patient at the right time".

Specifically, one axis of research was focused on "target validation and biomarker research". The current budget amounts to almost EUR 3.3 billion, half of which coming from Horizon 2020, and most of the rest coming from EFPIA and its member companies. There are currently several funded projects looking at novel targets, including multiple applications for Alzheimer's and neurodegenerative diseases.

Also, IMI issued in 2020 a specific call on tumor plasticity[20], focused on single-cell sequencing approaches that can unravel the mechanisms underlying drug tolerance in specific tumoral subtypes that can act as

[20] "IMI2 – 20th Call for proposals", Innovation Medicines Initiative, 2019.

reservoir, and lead to drug resistance with time. By characterising the altered pathways, specific combination therapies could be designed in the future. IMI will contribute to this specific call with EUR 7 million, while EFPIA members will provide in-kind contributions for indicatively EUR 8.5 million.

IMI impact is measured mostly in scientific/medical terms, such as:

- Number of relevant WHO-defined priority medicine areas addressed
- Number of guidelines, tools, technologies improved/approved for use in R&D
- Resources (e.g. database, biobanks, etc.) shared beyond consortium

but also, more broadly as engagement with non-pharma stakeholders and SME support.

Berlin Institute of Health (BIH), Charité and Max Delbrück Center (MDC) focus area on single-cell technologies

LifeTime partners have a close link to a structured German cooperation, in which BIH and Charité are contributing with clinical expertise via different capabilities (bioinformatics, imaging, machine learning, biobanks, diagnostics and biomarkers) and the MDC/BIMSB is offering technological and scientific expertise in single-cell biology and gene regulation.

The cooperation is based on two pillars. The first is around creating four bridge research groups across BIMSB and Charité, so that these groups will have physical access to single-cell technology platforms and leading scientists (BIMSB), and on the other side identify clinically relevant topics (Charité). The second pillar is around the development of a clinical “Single-Cell Sequencing” pipeline, which encompasses a central bio-portal (patient sample collection, characterisation and processing), as well as integrated genomic and bioinformatic services.

Single Cell Accelerator

In 2018, the VIB research institute, an excellence-based entrepreneurial institute that focuses on translating basic scientific results into pharmaceutical, agricultural and industrial applications located in Belgium, launched a program whose primary focus is to boost research and enable access to various innovative platforms. The pharmaceutical company Janssen is collaborating with VIB in the Single Cell Accelerator program, reflecting the importance of this initiative. The initiative will run for a 2-year trial period. Under this program, Tech Watch Initiative is responsible for the development of single-cell technologies through its funding and additional support.

2.3.3 Single-cell multi-omics initiatives in the US

The consortium driven approach of the US is characterised by close collaboration between industry and academia and a mixture of funding models, drawing resources from public and private funders. Transparency is a driving ethos that all consortia aim to follow, and manifests itself in embracing open source approaches to technology and releasing data after standardisation. The cross-collaboration between different initiatives creates a loose ecosystem that maximises resources and drives innovation and the exchange of ideas (Figure 4).

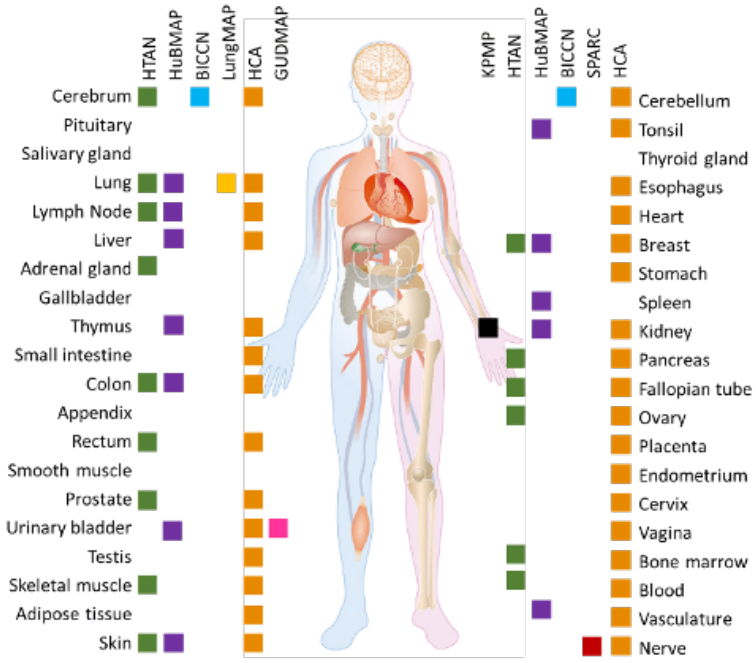


Figure 4 Overview of the tissues and organs analysed by NIH atlas-building initiatives. Among others, the Human Cell Atlas (HCA, orange), Human BioMolecular Atlas Program (HuBMAP, violet), and the Human Tumor Atlas Network (HTAN, green) are displayed.
Source: Wellcome Sanger Institute Blog (2020), adapted from Uhlén et al. (2016). Mol Syst Biol 12:826 (DOI:10.15252/msb.20155865)

Human Cell Atlas (HCA)

The HCA is a US-led global initiative and is an example of a mature formal consortium that uses a loose grassroots funding model, combined with public funding, to bring together researchers from across the globe. The main funders include the NIH, the Chan Zuckerberg Initiative (CZI), EBI, the Broad Institute, and UCSC. While it is hard to calculate the total funding raised by the HCA, it is estimated that this may reach USD 50- to 100 million yearly. CZI donated at least USD 68 million to support multiple projects, while the UK-based Wellcome Trust donated GBP 7 million over the last two years[21]. The global nature of the HCA allows it to tap into multiple funding sources from a diverse range of donors.

[21] Experts' opinion (internal research and analysis, May 2020).

The HCA mission is to create comprehensive reference maps of all human cells - the fundamental units of life - as a basis for both understanding human health and diagnosing, monitoring and treating disease. The initiative is based on an open source, cloud-based model – transparency and openness being central themes; data generated from hundreds of labs around the world are organised and standardised by the consortium and made freely available to researchers without limitations.

HCA utilises a pilot-project approach to develop learnings on effective sampling and analysis strategies and reveal early insights. Main pilots focus on Brain & Nervous System, Cancer, Developmental Cell Atlas, Epithelial Tissue, Gut, Immune System and Pediatric Cell Atlas. At present, the HCA includes data from 4.5 million cells & 34 organs, 29 projects and 81 labs.

Human BioMolecular Atlas Program (HuBMAP)

The HuBMAP is a formal NIH-funded consortium that brings together researches to map healthy cells in the human body. The goal of the consortium is to construct an accessible framework for mapping the human body at single-cell resolution. It differentiates from the HCA as it focusses on the relationships and interactions of cells within the body and the effect on individual health.

The HuBMAP consortium brings together a diverse range of experts and has organised into three components: (1) Tissue Mapping Centres; (2) HuBMAP Integration, Visualisation and Engagement collaborative components; and (3) innovative technologies groups.

Similarly to HCA, HuBMAP revolves around transparency and openness. The tools and framework for mapping cells are openly available, and data are released after initial verification. Alongside this, the consortium does not operate in isolation, but integrates with existing initiatives such as HCA, and aligns with other funding agencies, programs and biomedical community in general.

HuBMAP is funded by an initial USD 54 million grant over the seven-year project.

Human Tumor Atlas Network (HTAN)

Human Tumor Atlas Network (HTAN) is a National Cancer Institute (NCI)-funded initiative that brings together a network of research centers and data coordination centers to define critical processes and events throughout the human cancer lifecycle, as cells evolve from precancerous lesions to advanced disease, by constructing 3-dimensional atlases of the cellular, morphological, and molecular features of human cancers.

HTAN brings together ten research centers, one data coordination center and two pilot projects that were previously funded by NCI for a total 5-year investment of more than USD 60 million.

2.3.4 Single-cell Multi-omics Initiatives in China

The Chinese government has recently included precision medicine in their five-year plan, enabling tremendous opportunities for several established and start-up companies to develop targeted therapeutics based on the molecular profiles of patients. The total public investment size is unknown, but might easily exceeds other initiatives' size, considering large procurements of fast sequencing machines, enabling the researcher to gain insights on the gene expression level, protein expression level, and cell-to-cell heterogeneity[22].

The Beijing Genomics Institute (BGI) Group is a 6,000-employee company that manufactures sequencing equipment, sells diagnostic tests, and performs research for drug companies; their business is primarily been driven by the governmental encouragement of deploying genomic research initiatives at a large scale. The company was initially founded under the umbrella of the Chines Academy of Science, and spun-off in 2007. BGI vision is to "become the first full-stack genetics company: manufacturing sequencers, running them 24/7 with samples, and using research fueled by the resulting data to push the field forward, in turn creating even more demand for sequencing"[23]. BGI currently sells equipment from USD 12,000, ideally suited to low-/middle-income markets, to the USD 1 million top-of-the-line machine, which can sequence 60 human genomes a day.

China is currently lacking a regulatory framework around data protection such as the US Genetic Information Nondiscrimination Act or the European GDPR, and efforts in this direction are expected internationally[24].

10 Million Single-Cell Transcriptome Project (scT10M)

The scT10M project was launched in November 2019, led by the BGI Group and the China-Europe Life Health Innovation Center in Riga. The project goal is to sequence the RNA of 10 million cells to "understand life" at single-cell resolution by the end of 2021. The effort is based on the DNB technology (held by the MGI), which allows ultra-high throughput (1 million/batch) single-cell profiling. Details around the project state, the involved stakeholders and the funding structure have not been disclosed so far.

National Science and Technology innovation plan

The initiative focuses on studying disease types at molecular-level, and is a strategic collaboration between pharmaceutical companies and academic institutions to integrate genomic sequencing as well as data analytic capabilities. The goal is to develop a platform for emerging sequencing solutions that will aid drug development.

The Center for Precision Medicine Multi-Omics Research (CPMMR)

[22] Cyranovski (2016). The sequencing superpower. Nature, 534:462.
[23] Campbell, M. & Lyu, D., "China's Genetics Giant Wants to Tailor Medicine to Your DNA", Bloomberg, 2019.
[24] "China: Minority region collects DNA from millions", Human Right Watch 2017.

The Peking University-affiliated CPMMR is a multidisciplinary precision medicine center, focusing on the research, scientific and technological transformation to accelerate the growth of the single-cell multi-omics market.

2.3.5 Private investments

The single-cell multi-omics market has witnessed many technological advancements thanks to several new entrants bringing to the market state-of-the art technology. In addition, some of the key players not only offer a wide range of solutions for single-cell analysis, but also contribute to academic R&D by providing financial support in the form of e.g. commercial agreements, or development of products specifically tailored for some research activity. For example, the Human Cell Atlas consortium benefits of multiple of such forms of private support.

Among all, 10x Genomics, Pleasanton CA is the player that revolutionised the field of single-cell multi-omics analysis, by launching its “low-cost” instruments, Chromium, which is able to separate and analyse at high resolution up to 10,000 cells simultaneously. The uptake of 10x Genomics devices has been phenomenal, and the company, founded in 2012, generated USD 246 million of revenue in 2019, which represents +68% over the previous year. The company went public in September 2019,with positive response from the market.

Illumina, San Diego CA, is an established player and global leader in sequencing and array-based solutions for genetic and genomic analyses. Their whole-sequencing devices have been fundamental for the execution of the Human Genome Project. The revenue in 2019 amounted to USD 3.5 billion. In June 2020, Illumina received the first FDA Emergency Use Authorization for a Sequencing-Based COVID-19 Diagnostic Test.
Takara Bio is a Japan-based life science company operating across bioindustry, gene therapy, and agribio business. Takara originally developed the SMART sequencing technology for full transcriptome analysis. Despite facing competition from newer players, l Takara was able to generate revenues for USD 334 million in 2019.

While most of the key players in the field are based in the US, a number of companies are emerging in the field of single-cell analysis and organoid in Europe too, such as Scailyte AG, a Swiss-based young company developing diagnostic tools based on single-cell analysis, and a:head AG, an Austrian biotech company using brain organoids to test and develop novel therapeutics

2.3.6 Drivers and barriers

Drivers

Early diagnosis is a key marker for successful disease management and treatment. However, a lack of non-invasive diagnostic techniques can hinder the ability of Health Care Professionals (HCPs) to diagnose patients early, as many of the traditional diagnostic approaches can be costly and painful. This delay in diagnosis has a material impact on disease outcomes and research has shown that early diagnosis is a key factor for cancer survival and treatment cost[25]. The growth of the biomarker discovery fields, driven by the success of non-invasive pre-natal testing (NIPT) and liquid biopsy, is enabled by single-cell sequencing technology and this technology has led to the earlier diagnosis of various types of cancer, neurodegenerative diseases and other conditions. The growing demand for non-invasive diagnostic approaches is driving the growth of single-cell analysis.

The field of personalised medicine promises to revolutionise healthcare by moving away from the one-size-fits-all model to individualise a patient's treatment based upon their specific disease and situation. To realise the benefits of personalised medicine and develop treatments, detailed information is required about the biological mechanism and cellular characteristics of the disease. Single-cell sequencing enables this characterisation and biomarker discovery to allow for the development of target-based therapeutics. As the field of personalised medicine continues to grow, single-cell sequencing will continue to drive that growth and see a surge in demand.

Underpinning these drivers for single-cell sequencing are the advancements in single-cell sequencing techniques that have made the approach feasible. Second- and third-generation methods for genome and transcriptome sequencings have been developed that give deep insights on the genotype and phenotype of a cell. These advancements in single-cell sequencing techniques have allowed the technology to be more widely adopted and supported its growth.

Barriers

The expansion of the single-cell sequencing market is somewhat tempered by certain limitations. The volume and complexity of data generated from single-cell sequencings requires significant computational skill and power. In order to enable the continued growth of single-cell sequencing and the true value it can provide computational advancements must be realised. This also highlights the need for cooperation between different disciplines and institutes. Therefore, the continued success of single-cell sequencing is dependent on international collaboration and requires the creation of strong ecosystem grouping research consortia, initiatives and funding bodies to have an awareness of the ongoing research and foster a transparent and cooperative community.

Single-cell sequencing requires advance technology and infrastructure to support its growth. The development of this technology and infrastructure requires a significant capital investment that might represent a barrier for deserving small/medium entrants into this field, as well as limiting scalability and growth for existing organisations. Alongside the initial investment, the consumables associated with single-cell sequencing

[25] American Cancer Society (2016). Cancer Prevention & Early Detection Facts & Figures 2015–2016. USA, Atlanta, GA: American Cancer Society.

also contribute towards a high capital investment. It is a common trend for emerging technologies to be associated with a high investment cost; as the field expands, these investment requirements may reduce, but in its current form the absence of considerable capital investments around single-cell analysis research could prove a barrier to expansion.

Strictly correlated to the previous point is the potential lack of expertise to support research. When strong supporting infrastructure and collaborative platforms are not in place, educating students and researchers to work across disciplines and techniques might prove challenging. The need to create and retain talents to drive innovation further highlights the need to support long-term investments around single-cell multi-omics research.

Finally, data protection regulations and a growing concern of data security and ownership may introduce elements of complexity in this research field. The EU General Data Protection Regulation (GDPR) became enforceable in 2018 and introduced some elements of legal uncertainly about the capture, storage and sharing of genomics data. Genetic data is categorised as sensitive data (under article 9) and requires enough organisational and technical safeguards, such as pseudonymisation. If the data is anonymised, the European law states that this is no longer within scope of GDPR regulations. When working with genetic data captured during techniques such as single-cell sequencing, it is a necessity to consider data protection regulations and their impact, as well as what safeguards and considerations need to be established to protect personal data. In addition to this, there is growing distrust amongst patients and the general population of data privacy[26] and this could have implications on willingness to share sensitive data moving forward. In order to continue the expansion of single-cell sequencing, concerns around data privacy and data protection regulations have to be mitigated.

[26] "Health Ambitious Study", Aetna, 2018.

3. Economic impact of LifeTime research

3.1 LifeTime unique value

The international expert community gathered around LifeTime strongly believes that the consortium is characterised by a unique and winning approach to early disease interception. In just over one year of exchange and collaborative work, LifeTime members are positively impressed by the sense of community, constructive leadership and scientific excellence characterising the network, and look forward to strengthening collaborations[27].

LifeTime's value resides at the interface across disciplines, as it gathers basic scientists, computational scientists, engineers, clinicians, large corporate organisations, SMEs in the field of e.g. life sciences, medtech and IT/data science. The collaboration among these parties has the potential to create valuable findings and technological advances, which can be pursued and developed end-to-end to reach the final overarching goal of intercepting diseases in European patients early on. In addition, LifeTime collaboration does not happen only across disciplines, but also within disciplines, with scientists working in basic and applied research, or clinicians working on different diseases, brought together. The COVID-19 crisis has shown how crucial basic research is, and how strongly clinicians and policy makers need input from basic research to address societal questions. LifeTime builds a model of exchange among all relevant actors in healthcare, which will be crucial in times of public emergencies.

LifeTime consortium is in the position to compete with similar consortia shaping up in other regions (primarily US and China), and will enable single-cell multi-omics research to grow throughout Europe, a crucial aspect considering the competitive pressure to innovation coming both from US and China research systems (see section 2.3).

The ability of US consortia to generate innovation is well known, and strongly driven by the proximity and strong exchange between academia, industry and investors, typically happening at well-renowned clusters, such as Cambridge area (where the Broad Institute, hosting the Human Cell Atlas project, is located) or San Francisco Bay area. From this perspective, LifeTime will deal with slightly less well-established collaboration and exchange mechanisms and culture. However, scientists, industry, SMEs, funders/investors are all aligned on the opportunity that LifeTime will provide to reshape healthcare delivery, and to create commercially viable applications[28]. This increased collaboration is supposed to happen around existing multidisciplinary centers, and even more strongly, around the newly conceived Cell Centres.

LifeTime will also bring the patient perspective into the field of single-cell multi-omics research, as remarked and appreciated by multiple industry and academic experts. We consider the European regulatory framework as an added value to foster discussions and initiatives around the concept of data protection, data as public goods, and data donation. Moreover, LifeTime plans on committing resources to look specifically at the potential ethical, legal and societal issues raised by the development of LifeTime technologies and research on selected diseases.

[27] Opinions collected among leading LifeTime scientists and clinicians (internal research and analysis, May 2020).
[28] Ditto

Finally, considering that Europe is not hosting any of the big technology giant companies that dominate the global landscape, an interesting role will be carved out for SMEs and generally new entrants and players in healthcare. Therefore, from a global health perspective, LifeTime will represent an inclusive approach to innovation, which might inspire emerging economies leapfrogging towards innovation in healthcare.

3.2 Scenario definition

We assumed a scenario in which LifeTime would benefit from a large, long-term investment of e.g. EUR 1 billion over 10 years. LifeTime would direct e.g. EUR 100 million to each disease area research, for a total of EUR 500 million across all areas. The remaining funds would be required for long-term infrastructure building (i.e. Cell Centres, data platform), innovation, education, ethics, and coordination across all workstreams.

LifeTime scientists, industry representatives and private funders unequivocally agree on the tremendous impact that LifeTime could generate for European patient's health, if the initiative had resources available for long-term planning and exchange[29]. This would be driven by multiple factors, such as:

- **Disease area scientists and clinicians' ability to leverage findings, technologies and models coming from other laboratories/ research streams, leading to an efficient, coordinated and faster pathway to innovation**
- **Ability to attract industry investments, rather than sparse and unfocused support of small, unimpactful pilots**
- **Education of the next generation of single-cell multi-omics scientists, driving sustainable innovation on the long term – especially considering that the new generation of precise medicines will reach the market supposedly in 10 to 20 years from now**
- **Construction of long-lasting infrastructure, able to generate critical mass and clusters of innovation, collaboration and partnership**
- **Definition of a "value chain" and processes supporting scientific collaboration and exchange along the whole lifecycle, and particularly between basic and applied research**
- **Creation of an integrated European system of advanced labs and data platforms that could serve public health goals (such as testing, screening, predictive modelling, etc.) during potentially upcoming health crises – similarly to the role taken by Broad Institute and other institutions worldwide during the COVID-19 in spring 2020**
- **Think tank on Europe-wide relevant frameworks concerning e.g. patient centricity, data protection and usage, global impact of LifeTime research, innovation models**
- **Finally, an advocacy role for LifeTime, as a strong actor able to influence healthcare transformation in the next years, also by shaping national and international research agendas.**

[29] Ditto

If LifeTime will not have the opportunity to work as a collaborative initiative, many of the synergies mentioned above will be lost (Figure 5). Innovation will still happen in Europe, but a lower speed, and likely at a significantly less impactful scale. As a consequence, Europe might lose attractivity for investors, funders and talents interested in single-cell multi-omics research.

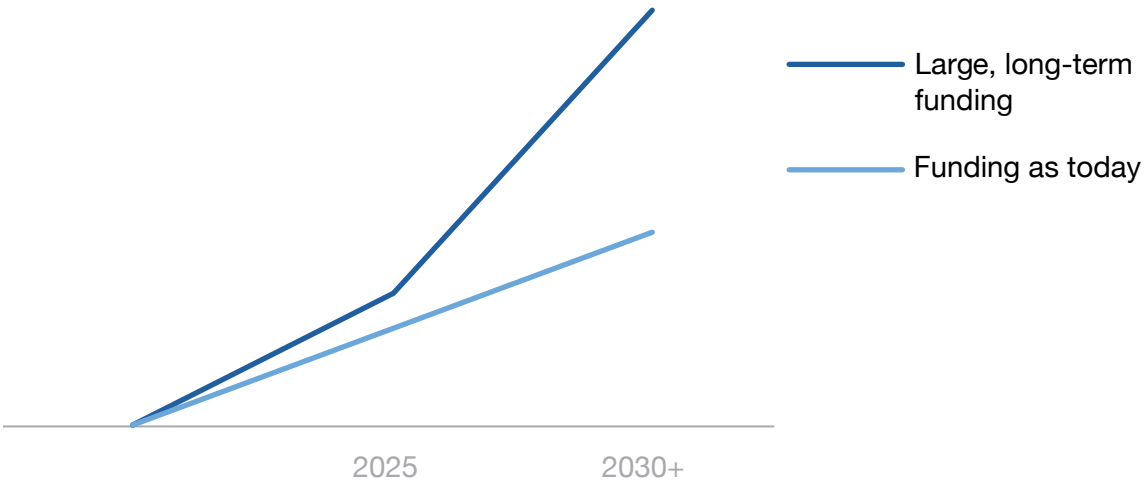


Figure 5 Predicted impact of LifeTime based on funding strategy (illustrative)

3.3 Expected impact

3.3.1 The impact of public research

The European Commission has repeatedly shown interest towards the quantification of the benefits generated from research activities on the European society and economy. It is well known that the "public sector research has a significant positive effect on productivity", generally estimated for academic research as a long-term elasticity of 17% and above[30].

In terms of return of investment (RoI), the overall value generated by public research typically represents three to eight times the investment; this translates into annual rates between 20% and 50%. Notably, public R&D is characterised by scale effects, i.e. the larger the total investment, the higher the return rate[31].

With regards to publicly-funded translational biomedical research, there are have been a few attempts to quantify the economic impact and RoI. Most of the studies are designed retrospectively, and look at selected economic components, such as the creation of job places, the number of patents or SMEs funded. The RoI for translational research tends to sit in the higher side of the range identified for academic research in general (Figure 6).

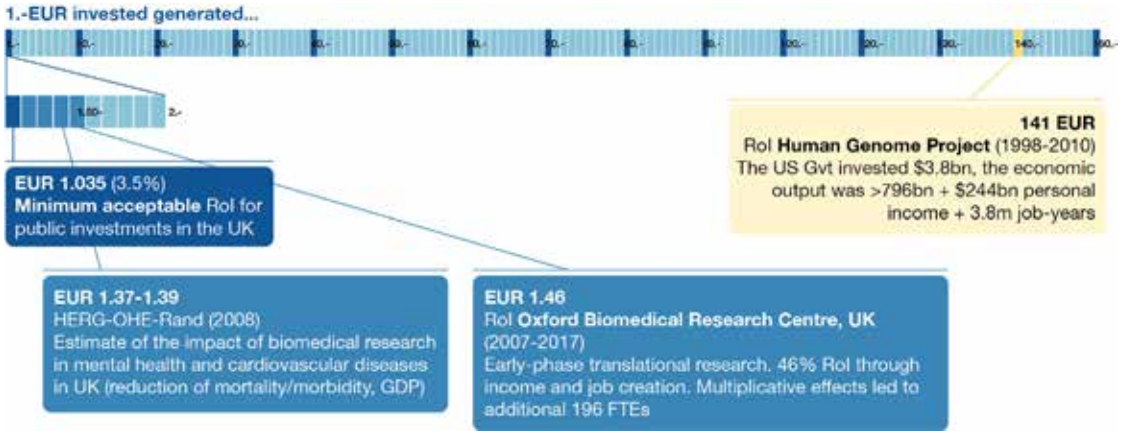


Figure 6 Expected RoI for biomedical research investments. Internal research & analysis (2020)
Sources: Tripp & Grueber (2011), Smith et al. (2019), PLoS ONE 14(4): e0214361, "Value of research", Research, Innovation, and Science Policy Experts European Commission, 2015

The best-known study on the impact of translational research is the 2011 Battelle study, which quantified the economic impact of the Human Genome Project. According to it, the USD 3.8-billion investment made by the US Government from project inception until 2003 "generated an economic impact of USD 796 billion, personal income exceeding USD 244 billion, and 3.8 million job-years of employment". This output corresponds to USD 141 generated for each dollar invested over the whole period considered[32]. A further announcement on Nature described such impact to have increased up to USD 1 trillion to US economy by 2013[33].

[30] "Value of Research - Policy Paper by the Research, Innovation, and Science Policy Experts (RISE), European Commission, 2015.
[31] Soete et al. (2010). Systems of Innovation. In Handbook of the Economics of Innovation, Vol. 2, pp. 1159 – 1180. Elsevier.
[32] Tripp & Grueber, "Economic Impact of the Human Genome Project, Battelle Memorial Institute", 2011.
[33] Wadman, M. (2013). Economic return from Human Genome Project grows, Nature, 2013.

We anticipate that LifeTime research will positively affect the European economy, mostly in terms of industrial growth (section 3.3.2) and potential healthcare cost savings (section 3.3.3).

3.3.2 Flourishing innovative industry and increased European competitiveness – the impact on industrial economy

The variability and openness of the future landscape in multi-omics industrial landscape, together with the intrinsic uncertainty related to the 10+ year time horizon that we are considering, does not allow to generate robust quantitative assumptions on the extent of the industrial growth and reshaping. Therefore, we will focus on identifying and discussing the key impact areas and dynamic trends in the context of industrial economy that LifeTime will shape, based on expert input[34].

The transformation of the healthcare industry

In the next decades, the industrial field developing around single-cell multi-omics research and precision medicine will require the creation of innovative business models and strategies, as many key industrial players will likely adapt their product/service portfolio and focus in order to best position themselves in the new healthcare landscape.

For example, today's life science equipment providers might expand in the direction of in vitro diagnostic products, e.g. precast or customised kits, to be used in combination with their instruments. Alternatively, sequencing services for institutional clients (e.g. hospitals) could be developed. Similarly, SMEs today focused on discovery services will need to work at the business models oriented around a product- or service-based approach. Also, for the pharmaceutical industry, individualised solutions might require new supply chain and manufacturing solutions, as it is already the case today for advanced cell-based therapies.

Unlocking value from data

The evolution of today's regulatory framework around data protection and usage could unlock new opportunities and requirements, for example if steps will be taken in the direction of Business-to-Government (B2G) data sharing and the "reusage of data for the common good"[35]. Industry players and academia will need to define new business models, data generation strategy, and monetisation options to get the most impact of their work.

[34] Internal research and analysis (May 2020).
[35] European Commission (High-Level Expert Group on Business-to-Government Data Sharing), Towards a European strategy on business-to-government data sharing for the public interest. Luxembourg: Publications Office of the European Union, 2020.

Revolutionary innovation in healthcare delivery

LifeTime has a transformative approach towards healthcare delivery, as personalised interventions for those in need will require newly defined patient pathways. For example, the future delivery of care may imply:

- Run screenings and diagnostics based on novel, early biomarkers – which will require the uptake of single-cell based analytical techniques in clinical settings, and/or the creation of hybrid clinics/laboratory structures, where physicians will be in the conditions of running individualised assays

- Prescribe patients the best suited treatment, by e.g. running organoid-based in vitro tests specific for an individual patient, or using novel stratification biomarkers combined with predictive AI/machine learning algorithms – which will require advanced laboratory capabilities and skilled professionals to run and interpret tests and imaging outputs

- Design personalised treatments – which may require innovative and flexible manufacturing solutions for the most innovative applications.

The increased role for laboratory diagnostics will favour the overall market growth (as described in section 2.2.3), which, at least for what is concerning single-cell multi-omic laboratory equipment and consumables, will reach already USD 5.32 billion size in 2028[36] – and will likely grow well beyond that to face increased demand from academia, industry, and hospitals/clinics.

Investments from large pharmaceutical companies in single-cell multi-omics research

The interest from pharmaceutical companies around single-cell multi-omics research is ever growing, as shown by the nomination of Dr. Aviv Regev, formerly an executive leader at the Broad Institute of MIT and Harvard, and Co-Chair of the Human Cell Atlas project, as Head of R&D at Genentech, a frontrunner company in the field of next-generation therapeutics. Roche's CEO acknowledged her efforts in the field of single-cell analysis as "[…] leading to foundational discoveries in immunology, neurobiology, development, inflammatory disease, cancer and evolution[37].

Overall, the interest of the pharmaceutical industry towards single-cell analysis is rising[38], and reflects LifeTime's potential to unlock new possibilities in data-based drug discovery and development.

Pivotal initiatives such as LifeTime have an enormous potential impact on the entire industrial ecosystem. Single-cell multi-omics research stems from the historical Human Genome Project, which applied a bulk sequencing approach to characterise the human genome. The impact of the project is lasting till today and went well beyond the pure medical applications – which per se transformed biomedical research and the clinical practice.

[36] "Global Single Cell Multi-Omics Market – Analysis and Forecast, 2019-2015", BIS Research, 2019.
[37] "Changes to the Roche Enlarged Corporate Executive Committee", Genentech, 2020.
[38] Internal research and analysis (May 2020).

Besides the important genomics industry that was born upon the project success, an important consequence of it was the drastic reduction of the cost of the sequencing technology, which was driven by industrial development from leading companies such as Illumina, Life Technologies and Veritas Genetics. Companies are still investing to develop technologies that will allow to sequence a human genome at even more affordable prices.

Today, the race is open around the rising field of liquid biopsies, where several players are investing to develop affordable technologies. Grail, Menlo Park CA, raised more than USD 1.9 billion, including USD 100 million invested by Bill Gates, Jeff Bezos (CEO of amazon.com) and Illumina to develop a blood-based ctDNA screening test for the most frequent types of early-stage cancers[39].

The field is equally crowded in the cancer detection space, where hundreds of companies distributed across the US, Europe and China are using new technologies (omics, immunotherapies, antibody conjugates, etc.) to develop cancer diagnostics. The global in vitro diagnostics market is currently valued at USD 60.8 billion, and it is projected to growth at a 4.4% annual rate until 2028[40].

Infrastructure and Technology

LifeTime network plans on developing Cell Centres to foster exchange and innovation. While some clusters of multidisciplinary research already exist in Europe, LifeTime will build and leverage new hotspots where multiple disciplines can meet and grow.

In the US, the Human Cell Atlas is hosted at the Broad Institute, a research centre that was founded in 2004 to build upon the success of the Human Genome Project. Today, a 3,000-scientist community - combining biology, chemistry, mathematics, computation, and engineering with medical science and clinical research – refers to the Institute, in a creative and open environment. Broad Institute is connected to Harvard University, MIT and nearby academic hospitals, and works particularly close with the industry, so that very favourable conditions exist to uptake innovation, and translate them into commercial products that can reach patients. In 2020, Broad patented 39 discoveries across all disciplines, and 18 patents where issued in the past few years specifically around single-cell technologies. Nevertheless, the Broad Institute maintains an open approach to innovation, privileging non-exclusive agreements with pharmaceutical companies, where possible, or trying to limit the scope of exclusivity as much as possible.

It is also important to note that advanced research infrastructure can be leveraged during public emergencies, as having the potential of rapidly converting into large-scale testing facilities. This was recently the case, in the occasion of the COVID-19 outbreak, for the Broad Institute[41], but also for many other research centers worldwide, such as the center for Genomic Regulation (Barcelona, Spain), the German Cancer Research Center (DKFZ, Heidelberg, Germany), or the Weizmann Institute of Science (Israel). LifeTime contributed by creating a joint registry with the Human Cell Atlas, sharing tools, data and knowledge[42].

[39] Herper, M. "A Single Blood Test For All Cancers? Illumina, Bill Gates And Jeff Bezos Launch Startup To Make It Happen", Forbes, 2016.
[40] "In Vitro Diagnostics Market Size, Share & Trends Analysis Report By Product, By Technology (Molecular Diagnostics, Clinical Chemistry), By Application, By End Use, And Segment Forecast, 2020 – 2027", Grand View Research, 2020.
[41] "How Broad Institute converted a clinical processing lab into a large-scale COVID-19 testing facility in a matter of days", BROAD Institute (2020).
[42] Human Cell Atlas – LifeTime COVID-19 Joint Registry

Moreover, an integrated international network would have supported a better international monitoring of the epidemic spread across the entire European region, but also e.g. a better information exchange, as well as procurement of instruments and consumables – a public health capability that was largely insufficient in Europe during the past COVID-19 outbreak.

In summary, on the footprint of Broad Institute and similar facilities, LifeTime Cell centers in Europe would have the potential to provide an excellent environment to develop public-private partnerships, create innovation, and serve the community by offering potential testing, processing and data analytics support.

3.3.3 Healthcare cost savings

In order to reflect the magnitude of LifeTime's potential benefit for the European patients and society, we modelled and quantified the potential cost savings in healthcare. Assumptions are based on expert opinions and perspective about plausible innovation that will happen with a horizon of 10+ years from now in Europe, if LifeTime research will happen as suggested in this Strategic Research Agenda.

Cancer

About one-tenth of the world population lives in Europe, yet until today 25% of all cancer diagnoses occur in European countries[43]. In many of these, more than 30% of people are expected to be diagnosed with a form of cancer during their lifetime[44]; in addition, more than one-fourth of all deaths in Europe are caused by cancer, making it the second most common death after cardiovascular disease in this region. If no further improvements in cancer care and prevention are enhanced, an additional 775,000 new cancer cases are expected to be diagnosed in 2040[45].

The increasing prevalence and high mortality rate put a high burden to society and economy. From an economic perspective, cancer generates a heavy burden, involving both direct and indirect costs all along the patient journey – from e.g. diagnosis, initial treatment, informal care at disease onset, to costs related to morbidity-induced productivity losses, as well as costs for end-of-life treatments and productivity losses from premature mortality.

Overall, in 2018, European and EFTA[46] countries had to sustain EUR 199 billion spend due to cancer, of which EUR 32 billion spent on medications and EUR 70 billion attributable to total productivity losses (EUR 50 billion due to premature mortality and EUR 20 billion due to morbidity[47]). Assuming a 2.3% cost increase in cancer-related costs per year, total productivity losses due to cancer would increase to almost EUR 99 billion in 2030.

[43] Ferlay et al. (2018). Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. European Journal of Cancer, 103: 356 – 387.
[44] Jemal et al. (Eds.). (2019). The Cancer Atlas. 3rd Ed. Atlanta, Ga: American Cancer Society.
[45] Hofmarcher et al. (2019). Report on Cancer in Europe 2019 – Disease Burden, Costs and Access to Medicines. IHE Report: 7. IHE: Lund, Sweden.
[46] EFTA: European Free Trade Association, a regional trade organisation and free trade area consisting of Iceland, Liechtenstein, Norway, and Switzerland.
[47] Hofmarcher et al. (2020). The cost of cancer in Europe 2018. European Journal of Cancer, 129: 41 – 49.

Today, we are able to cure roughly 60% of all cancers[48], which means that the remaining 40% of patients die somewhat prematurely. LifeTime research in cancer will focus on multiple patient management strategies including early screening, better patient stratification in relation to therapy response, and newly designed targeted therapies, overall leading to the advanced/next generation personalised cancer models as the basis for the future generation of precision medicine. It is expected that these combined approaches will dramatically improve both patient morbidity and mortality. If we assume that more informative multi-dimensional biomarkers and more precise therapies will allow to achieve an overall cure rate of 75% (vs today's 60%) in a decade from now, European countries could reasonably achieve EUR 6.1 billion only in productivity gains[49], without even accounting for better quality of life and lower burden on the families direct medical costs.

LifeTime's research output is expected to allow earlier breast cancer diagnosis, an impactful result for all women. This will lead to a better prognosis and cure rate. Breast cancer is the most commonly type of cancer diagnosed to European women, and accounts for almost 30% of all cancers in Europe[50]. Despite several screening and early detection measures and improved treatments, breast cancer incidence and mortality are increasingly affecting women of all ages. Breast cancer management leads to the highest healthcare costs of all cancers in Europe. In addition, 54% of all patients with breast cancer are of working age, with resulting morbidity- and mortality-induced productivity losses of EUR 5 billion in 2009[51], predicted to rise to EUR 9.5 billion in 2030. However, if we assume that more informative biomarkers and personalised therapies will bring the 10-year survival rate up to 95% (vs today's 84%[52]), the improvement would translate into EUR 1.3 billion of productivity gains[53] - which is only a small part of the overall benefits related to increased survival for women and their families.

Single-cell based approaches to diagnosis are also expected to improve diagnosis accuracy. While data on mis-diagnosis are hard to retrieve, experts believe this rate could be around 1 to 5% in the most advanced healthcare systems. LifeTime's research can help develop methodologies to improve such rate. For example, a 40% improvement would translate into savings for up to EUR 842 million in relation to wrong treatment prescription throughout Europe (2030+). In addition, it is reasonable to assume that such improvement in accuracy would be accompanied by better safety, with savings on costs related to the management of cancer treatment side effects.

[48] Experts' opinion (internal research and analysis, May 2020).
[49] Assuming that one third of the cured patients would be fully productive again, and two thirds had a productivity loss by 30%.
[50] Aljohar et al. (2018). Breast cancer in Europe: Epidemiology, Risk Factors, Policies and Strategies. A Literature Review. Global Journal of Health Science, 10 (11): 1.
[51] Luengo-Fernandez et al. (2013). Economic Burden of Cancer Across the European Union: A Population-Based Cost Analysis. Lancet Oncology, 14(12): 1165-74.
[52] "Doctor-Approved Patient Information", Cancer.Net, 2020.
[53] Assuming that one third of the cured patients would be fully productive again, and two thirds had a productivity loss by 30%.

Neurological and neuropsychiatric diseases

From a societal and economic perspective, the growing prevalence of Alzheimer's disease represents one of the most difficult challenges our communities are facing. According to recent estimates, up to 25-50% of 85+ year-old individuals are affected by a form of dementia, with Alzheimer's representing more than half of such cases[54].

While disease symptoms typically manifest rather late in life, usually after the retirement age, a heavy burden is placed on families and caregivers of affected patients, in terms of financial resources, time constraints, and emotional commitment. It has been calculated that the overall cost burden of Alzheimer's and other neurodegenerative diseases will reach in 2050 total amount of EUR 357 billion across Europe, basically doubling 2010 expenditure[55]. This amount includes the cost of exams, hospitalisation, pharmacological and non-pharmacological treatment, emergency service, home nursing service, rehabilitation, and laboratory tests, home environment modifications, transport and overheads. Indirect costs will mostly be represented by loss of productivity by caregivers, but also by patients themselves, as it is estimated that 1.6 – 1.7% of the 60 – 64-year-old European population is already affected by Alzheimer's syndrome (for a comparison, Multiple Sclerosis affects 0.1 – 0.4% of the European population).

Experts believe that LifeTime's efforts to understand disease mechanisms at the single-cell level will lead to the identification of new biomarkers for patient stratification, and novel drug targets. Overall, if the Alzheimer's dementia onset be delayed by 5 years via improved biomarkers and drugs, almost EUR 150,000 per patient could be saved by healthcare systems, without even accounting for the improvement in quality of life and emotional relief for caregivers. This means that, if the disease was delayed by 5 years in early-onset patients (before 65 years old), more than 20 billion could be saved across Europe compared to today.

However, numbers hardly capture the early, quasi-silent onset of the disease likely happening during the 50s or 60s of a future Alzheimer's patient, i.e. much earlier than the dementia appearance – today considered as formal onset of the disease. A LifeTime approach to diagnosis will reveal the disease onset much earlier than the appearance of macroscopic behavioural changes, and appropriate interventions might improve quality of life, productivity and impact of medical care, further contributing to the generation of cost savings around the patient management and care.

In summary, LifeTime will focus on a preventive approach to neurogenerative disease, with the characterisation of a healthy brain "aging curve", a goal only pursuable with a single-cell analysis approach. This approach will be increasingly important in the next years, also driven by wearable technologies, helping collect novel types of patient data, such as voice analysis, eye movement, and gait performance in conditions such as depression, Alzheimer's disease, and Parkinson's disease.

[54] Maresova et al. (2016). Alzheimer's and Parkinson's Diseases: Expected Economic Impact on Europe - A Call for a Uniform European Strategy. Journal of Alzheimer's Disease, 54: 1123 – 1133.
[55] Maresova et al. (2016).

Infectious diseases

Increasing antimicrobial resistance and pathogen infections and outbreaks pose a major threat to public health and economy, not only in the developing economies - which are typically perceived as most vulnerable to communicable disease epidemics - but in high-income countries too. In fact, the 2020 SARS-CoV-2 outbreak represented the major public health threat globally over the last century, with evident consequences, which we still do not fully understand, from a healthcare-, social-, and economic perspective.

The economic burden of COVID-19 outbreak can be measured from several angles; short-term consequences include:

- The direct healthcare costs related to the massive wave of patients in severe conditions requiring hospitalisation and/or ICU
- The productivity loss for those patients aged from 50 to 65 years that were hit by a severe form of COVID-19, considering several weeks of recovery time required after long ICU stays
- The excess mortality
- The health consequences for non-COVID-19 patients, which could not receive any hospital or office-based treatments for weeks during the outbreak peak, translating into likely disease progression/ worsening and complications that will be dealt with by the healthcare systems at a later time
- The mental and physical consequences for adults and children living for weeks under strict contact constraints, without the possibility of socialising, doing adequate physical activity, and receiving appropriate education
- The massive productivity loss for the wider society, in relation to multiple weeks of lockdown and restrictions of all non-essential activities.

Early estimates predicted that the monetary loss related to COVID-19 would represent 2.4-3% of the 2020 GDP globally[56], and data from the EU Statistics Office showed a 3.8% contraction for the first 2020 quarter in Europe[57]. The University of Cambridge estimates that, in the next 5 years, the global loss could range between USD 3.3 and 82 trillion, depending on the economy recovery time[58].

[56] "Forecasted monetary global Gross Domestic Product (GDP) loss as a result of COVID-19 in 2020, by scenario, Statista, 2020.
[57] "German economy in recession as coronavirus hits – as it happened", The Guardian, 2020.
[58] "$82 trillion over 5 years? Cambridge study counts the cost of coronavirus", World Economic Forum, 2020.

However, while different organisations are still quantifying the macro-economic impact of COVID-19 and making predictions on how the economy will get back to the pre-pandemic state, worldwide almost 30 million cases of COVID-19 have been reported so far, of which almost 950,000 were lethal. Europe accounted for more than 5 million cases and more than 225,000 deaths[59]; in addition, 32% of the cases resulted in hospitalisations[60,61], and 2-5% of cases required respiratory support and/or ventilation.

Another major threat related to infectious diseases is sepsis, which is caused by the body's response to an infectious agent and represents one of the leading causes of mortality and disability, with more than 670,000 deaths in Europe, and yet increasing numbers of severe cases and septic shock. Since many cases are only detected or diagnosed with a delay, an estimated two million survivors may suffer from long-term disability leading to increased direct and indirect healthcare costs. In Germany, one patient surviving severe sepsis costs to the healthcare system more than EUR 59,000 and a patient who dies from it around EUR 52,000[62,63].

COVID-19 and sepsis, and their wide-reaching consequences, show that there is a need to tackle and prevent infectious diseases. LifeTime research will lead to the validation of personalised, biomarker-based approaches for patient stratification and disease interception. In addition, it will reveal immune dysregulated pathways in patients with disparate symptoms and enable screening of available immunomodulatory drugs in established disease models. This may translate practically into shorter hospitalisation, and particularly ICU stay.

For example, today it is not possible to predict the disease progression of hospitalised COVID-19 patients, if not via quite generic tests administered around day 8 of hospitalisation. Only once the patient is moved to ICU, immunotherapy is started. The availability of an early biomarker and/or model to predict the disease course, for example around day 5 or 6, would allow to identify high-risk patients early on, and to treat them appropriately, by monitoring closely the conditions and administering an immunotherapy before the respiratory function was compromised. This early detection approach would likely translate into better clinical outcomes, shorter ICU stays and faster recovery. Considering that one day in ICU costs about EUR 1,500-3,500, every day spared in ICU would represent considerable savings (in the range of EUR 155-360 million per day in the COVID-19 outbreak happening in Europe in Spring 2020). Indirect costs from productivity losses should be considered as well. In general, it takes two weeks to recover from the mild form of disease, while more severe or critical patients need three to six weeks to recover[64], which affects considerably their productivity.

[59] WHO Coronavirus Diseases Dashboard (18/09/2020).
[60] "Statement – Where do we stand today on COVID-19, and what have we learned?", WHO, 2020.
[61] "Rapid Risk Assessment: Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update", ECDC, 2020.
[62] "Interdisciplinary action needed to tackle sepsis", European Society of Intensive Care Medicine, 2019.
[63] "Sepsis cases are rising", Healthcare-in-europ.com, 2014.
[64] "WHO Director General's opening remarks at the media briefing on COVID-19" – 24 February 2020.

Chronic inflammatory diseases

Today, half of the IBD patients do not respond anymore to the prescribed treatment after one year. This is why, in the mid-term, LifeTime will focus on identifying ways to monitor therapy response and disease control state for chronic inflammatory diseases, for example via biomarkers and/or organoid models that would support the choice of the most suitable treatment for each individual patient.

Patients in an uncontrolled disease state are significantly impacted in their ability to work and to enjoy leisure time, as well as in their overall quality of life and mental health. This creates an enormous burden, especially when considering that IBD is typically diagnosed between the ages of 15 and 35. It has been shown that IBD patients are afflicted by heavy personal costs, which may represent up to USD 14'135 per year in Crohn's disease, according to systematic reviews looking at data collected in North America and European countries[65]. Numbers about disability rates vary considerably according to studies and methodology, but nevertheless there is wide consensus around the observation that IBD heavily impacts on professional life by causing repeated sick leaves/absenteeism, under-/unemployment, and presenteeism (i.e. working despite poor health conditions). IBD affects behaviour on the workplace and career progression, with 44% of patients having quit or lost a job because of IBD. 52% of patients even declare that IBD negatively affected their education[66].

Single-cell based approaches to guide therapy selection might have an enormous impact on patient's life, as medical professionals would have a systematic approach to select the right treatment for each patient, rather than a trial-and-error approach, as today. A conservative estimate shows that increasing today's 50% treatment response rate up to 75% would translate in 2030 into a yearly productivity gain of EUR 3,049 for a Crohn's disease patient and of EUR 1,818 for an ulcerative colitis patient. Considering the disease prevalence in Europe, this would translate into productivity gains for more than EUR 10 billion overall (summing up Crohn's and ulcerative colitis). In addition, healthcare systems would be relieved from the quite resource-intensive process required today to follow up patients, including repeated blood tests and specialistic appointments to adjust or switch therapy every time the patient state requires it, or hospital stays in case of acute flare ups – which occur on average in 52.7% of European Crohn's patients within 10 years from the diagnosis[67].

On the long-term, LifeTime may contribute to identify the causative cell populations, allowing to design reprogramming strategies for long-term deep remission. This would further decrease long-term costs in terms of loss of productivity and quality of life, hospitalisations, tests and surgical procedures – considering that on average an IBD patient costs EUR 1'871 per patient-year over a 10-year period (including outpatient care, diagnostics, hospitalisation, surgery, medication) – and that a hospitalised patient has a 10-fold higher cost than a non-hospitalised patient.

[65] Kawalec (2014), Indirect costs of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. A systematic review. Arch Med Sci 2016; 12, 2: 295–302.
[66] Burisch et al. (2013). The burden of inflammatory bowel disease in Europe. Journal of Crohn's and Colitis, 7: 322 – 337.
[67] Burisch et al. (2013).

Cardiovascular diseases

According to recent data, in Europe almost 49 million people live with cardiovascular disease, leading to numerous deaths in older patients, but also in working-age individuals. While cardiovascular death rates are decreasing, morbidity is increasing, meaning that more people survive, but they suffer medium- to long-term consequences caused by the disease. In particular, heart failure's estimated prevalence is around 1-2%, translating into more than 10 million people potentially affected across Europe.

Heart failure events dramatically change people's lives, especially in terms of physical ability to run routine actions, but also ability to productively work; consequences can be longlasting. It has been calculated that heart failure is responsible in most advanced economies for about 2% of all healthcare expenditure. A study from the Imperial College London estimated the costs related to heart failure in Europe to amount to EUR 29 billion every year, mostly driven by frequent hospitalisations[68].

Heart failure is typically caused by coronary heart disease. Several factors can increase the risk of generating a heart failure event, including pre-existing conditions such as diabetes, obesity, chronic obstructive pulmonary disease, chronic kidney disease, and hyper-cholesterolemia, and behavioural risk factors, e.g. poor/fat-rich diet, smoking, alcohol abuse, and a sedentary lifestyle[69]. Interestingly, familial factors also play an important role, possibly via a genetically-driven component. A 2006 study run on the Framingham Offspring cohort[70] revealed a strong familiarity of heart failure, with an adjusted risk of heart failure of 2.72% in individuals with a parent with heart failure, vs 1.62% in the other individuals. Even after multi-variable adjustment, the risk of having a heart failure was 70% higher in the offspring with an affected parent. Many factors could explain this association, and the genetic component is believed to play an important role in 18% of all heart failure cases[71].

The genetic component of health failure is particularly interesting from a precision medicine perspective, as it is reasonable to assume that LifeTime research might lead to the discovery of novel targets based on multi-omic patterns shared by specific patient subpopulations. A rather young high-risk population (e.g. children of heart failure patients) could be screened via novel biomarkers for their predisposition to develop a heart failure later in life and treated accordingly. The prevention of 25% to 50% of the familial heart failure cases, would represent a EUR 2.1 to 4.1 billion of overall savings in treatment costs, including hospitalisation, compared to today. In addition, a relevant fraction of the potential patient population would be relieved from negative consequences in terms of productivity and quality of life.

[68] "Heart Failure and Cardiovascular Diseases", European Heart Network, 2019.
[69] European Heart Network. (2019).
[70] The Framingham Offspring Cohort is a cohort of children from individuals enrolled in the famous NIH-funded Framingham Heart Study, a longitudinal study started in the late 40's in the US.
[71] Lee et al. (2006). Association of Parental Heart Failure with Risk of Heart Failure in Offspring. The New England Journal of Medicine, 355: 138 – 147.

4. Interpretation and recommendations

4.1 Relevance of scenario analysis for European Commission and policy makers

In this study, we assumed a funding scenario (see section 3.2) in which LifeTime benefits from a large, long-term funding managed by the scientific community for research, infrastructure, cross-cutting activities and coordination; alternatively, research areas would be funded individually in similar way as today, for example via smaller pilots projects with around EUR 10-million grant assigned to small consortia of 5-10 laboratories over 4-5 years.

LifeTime scientists and clinicians, as well as external industry representatives and private funders, largely favored the first funding scenario[72], i.e. a long-term funding to LifeTime, for multiple reasons – as described below.

i. **Large and coherent funding of LifeTime activities would allow synergies to be generated, speed of discovery to be increased, and achieve long-lasting impact, as demonstrated historically by large-scale initiatives that were funded mostly by public entities with strong public health goals in mind (see Table 3 – case studies).**

Case study: Human Genome Project
The Human Genome Project was generously funded by the NIH with USD 3.8 billion along the whole length of the project. The funding decision was taken in 1990, with a target completion date of 2005. The NIH investment attracted commitment from other funders, including Governments and private parties. The project was completed on budget and two years ahead of schedule, and generated a long-lasting revolutionary impact that is still paying off these days (see section 3.3.1 for additional information).
Case study: HIV/AIDS research funding
HIV/AIDS infected more than 70 million people and caused more than 30 million deaths since its appearance. In 1986, the NIH started to massively finance HIV/AIDS research. Today, the US are still heavily committed on HIV/AIDS funding, with more than USD 34.8 billion spent in 2019. The US led the race to find a treatment for the disease, which today, even though not "curable", can be considered a manageable chronic disease thanks to the therapeutics that were developed and tested. In addition, today the US are funding domestic prevention-, care-, treatment programmes and housing assistance programmes (USD 25.5 billion), as well as domestic research (USD 2.6 billion) and global activities, including international research and contributions to the Global Fund (USD 6.8 billion)[73]. While the amount of funds devoted to HIV/AIDS research is enormous, this spending is largely compensated by societal and economic returns: it has been shown recently that benefits are worth 6.44 times the resources invested globally[74]. Another study calculated that, via a USD 14 billion investment over 10 years, 18.5 million life-years and USD 12-34 billion through increased labor productivity, averted orphan care, and deferred medical treatment for opportunistic infections and end-of-life care would be returned[75]. The NIH today has a budget of over USD 40 billion devoted to biomedical research[76].

Table 3 Case studies. Public health goals achieved by sustained public commitment. Internal research and analysis

[72] Internal analysis (May 2020).
[73] "U.S. Federal Funding for HIV/AIDS: Trends Over Time", Kaiser Family Foundation, 2019.
[74] Lamontagne et al. (2019). The economic returns of ending the AIDS epidemic as a public health threat. Health Policy, 123(1):104-108.
[75] Resch et al. (2011). Economic Returns to Investment in AIDS Treatment in low and middle income countries. PLoS One, 6(10): e25310)
[76] NIH Budget 2020.

ii. **Europe needs to uniquely position itself with regards to next-generation precision medicine and big data revolution. The expectation is that the US will likely lead the race on the innovation side, because of the strong focus on translating knowledge into commercial opportunities, the conducive regulatory environment, and the well-established financial/ investors landscape. On the other hand, Chinese initiatives will be able to generate and process data on a very large scale and speed, gaining considerable competitive advantage. In this context, there is room for Europe to take a humanistic and ethical approach - in line with its cultural heritage - generating knowledge which is directly applicable to the clinical practice, and addressing key challenges related to data protection and/or "data as public good", which will be crucial to protect innovation and maintain a patient-centric approach in the future medicine.**

iii. **Europe has the opportunity to develop a model of collaboration which is inclusive of SMEs and new entrants in healthcare. This would represent an interesting model to bring innovation and next-generation medicines to low-/middle-income countries, with a resulting positive global footprint.**

iv. **LifeTime aims to foster harmonisation of healthcare systems/healthcare delivery across Europe, considering that next-generation drugs will likely require a closer collaboration between laboratories, clinics and manufacturing facilities. This model will reshape today's varied healthcare delivery practices, therefore creating space for some level of cross-system alignment on the way diagnostics and therapeutics are brought to the European patients.**

v. **LifeTime has captured the attention of the industry, from large companies to small ones, across pharmaceuticals, medtech and life science segments. Many players started to look at the field of single-cell multi-omics research and are building capabilities of their own (see section 2.3.5).**

vi. **Large, long-term investments in single-cell multi-omics research are taking place primarily in the US and China. This research branch is taking off worldwide (see Figure 7), and the most promising young researchers in the field, or even established group leaders, will understandably seek to develop their research projects in world-class laboratories and innovation clusters. In the absence of comprehensive funding for this type of research, there is a concrete risk that the most promising talents will not be retained in Europe.**

vii. **Europe does not host any of the digital giant companies (Google, Amazon, Facebook, Apple, Microsoft, and Snap - headquartered in the US; and Alibaba and Tencent -headquartered in China). The trends show that China may capture the next innovation wave, together with the US, leaving Europe behind.**

viii. **Leading private funders, such as Wellcome Trust and Chan Zuckerberg Foundation are already extensively funding single-cell multi-omics, most notably via the Human Cell Atlas (see section 2.3.3), which *per se* is an indicator of the strength and appeal of these large-scale research initiatives.**

ix. **Single-cell analysis could reshape healthcare delivery in 2030+; in order to secure the uptake of the future technologies, Europe needs to invest now in suitable infrastructures where different competencies can come together and generate knowledge and technological advancements.**

x. **The European industry is watching LifeTime and other consortia's activities in order to take up innovation, and bring new targets, biomarkers, and drugs/treatments to the clinical phase.**

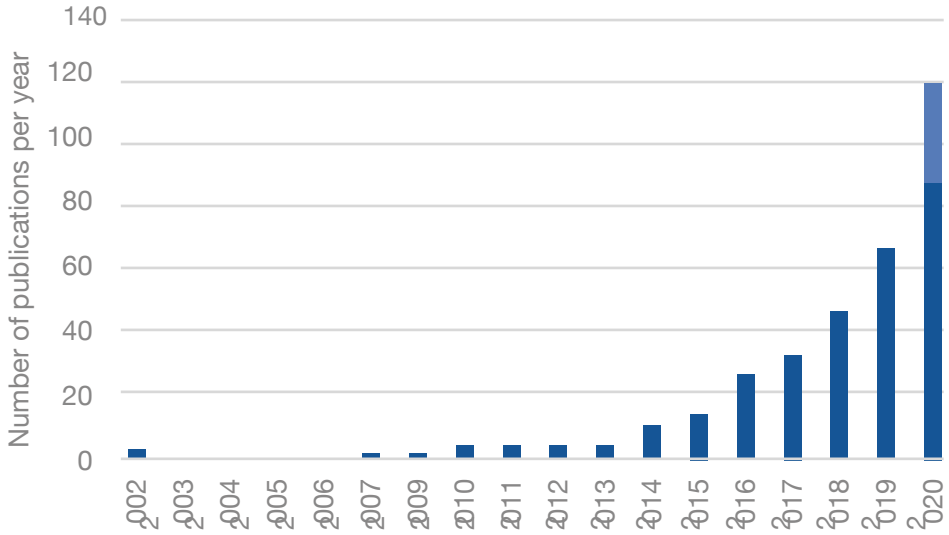


Figure 7 Number of publications on "single-cell multi omics" per year. 2020 data projected until the end of the year (light orange), assuming linear growth of the number of publications. Internal research and analysis.
Source: PubMed (data retrieved on 18/09/2020)

4.2 Emerging economic impact of LifeTime research in Europe

LifeTime scientists as well as European industry stakeholders and funders agree on the remarkable impact that LifeTime research is expected to have in Europe, and globally[77]. The time horizon for single-cell analysis driven innovation will have a considerable impact in 10+ years from now, with the first innovations that could potentially hit the market in "waves":

- **2+ years, biomarkers related to the emerging COVID-19 pandemics – in relation to fast-track pathways and prioritisation of research/commercialisation activities**
- **5+ years, innovative biomarkers**
- **10+ years, novel drugs/therapeutic treatments**
- **15-20 years, clinical practice transformation, e.g. routine use of single-cell analysis techniques for disease prevention/interception, diagnostics, treatment, and monitoring.**

The growth will also be potentially driven by demographic and social megatrends, such as aging population and increased chronic disease prevalence, accompanied by improved patient empowerment and expectations around their health management (see section 2.1.1).

We anticipate that the main players will need to make critical decisions around their future business model (e.g. product- vs service-oriented), and portfolio (e.g. custom services vs precast solutions, basic research products vs in vitro diagnostics, large-scale manufacturing vs individualised manufacturing, etc.). Currently, leading companies are attentively observing research findings and competitive landscape evolution, trying to stay particularly close to "innovation", not to lose competitive advantage.

Investments in fundamental biomedical research are typically highly rewarding (see section 3.3.1), and LifeTime research is expected to deliver returns on the higher side of the spectrum (see Figure 6), in relation to type of research, solid scientific basis, unmet needs, and technology advancements/costs, even though speculations about the actual overall return of investment cannot be made at this point in time. Therefore, we focused our quantitative assessment on potential healthcare cost savings, basing our assumptions on scientists' vision of the potential future scientific achievements. For all disease areas that we took into examination, LifeTime research has the potential to bring considerable improvement over the current clinical practices, accompanied by budget savings as detailed in section 3.3.3, and summarised in Table 4.

[77] Experts' opinion (internal research and analysis, May 2020).

Therapeutic area	Cancer	Neurological diseases
(Example) disease	**All cancers (and breast cancer)**	**Alzheimer's disease**
Today's situation	• Overall cancer cure rate is 60% (breast cancer, 10-year survival rate 84%) • Mis-diagnosis rate estimated to be between 1 and 5% in most advanced healthcare systems	• Symptoms typically manifest late in life but heavy social and financial burden is associated with the disease • Increasing disease prevalence in <65-year-old patients
Current standard of care	• Limited tools to target therapies, not able to treat metastases • Patients suffer long-term disability after cancer therapies	• Diagnosis occurs when disease is in an advanced state • No disease modifying therapeutic options
LifeTime innovation	• Diagnostic/prognostic biomarkers • Risk stratification/ treatment selection biomarkers • Novel targeted drugs	• Risk analysis/ patient stratification via early biomarker • New drug targets, targeted therapies
Expected benefit	• Overall cure rate to reach 75% (breast cancer up to 95%) • Diagnosis/treatment selection improved by 40%	• Delayed onset of disease by 5 years • Better quality of life • Lower informal care costs/ treatment costs and family burden • Earlier/more accurate diagnosis
Economic impact in Europe	**EUR 6.1 billion** from productivity gains across all cancer cases (**EUR 1.3 billion** for breast cancer) **EUR 168-842 million** savings from inaccurate treatment prescription	**EUR 150,000** per patient whose disease onset is delayed by 5 years. For early-onset patients (before 65 years old), the total amount saved each year of delayed onset corresponds to **EUR 4 billion**

Table 4 Expected economic impact of LifeTime research in the focus disease areas (selected components)

Infectious diseases	Chronic inflammatory diseases	Cardiovascular and metabolic diseases
COVID-19	**Inflammatory bowel disease**	**Heart failure**
• Some patients develop a severe respiratory disease, leading to a long ICU stay	• Response rate declines to 50% after 1 year of treatment	• Some patients show signs before acute event, but others appear healthy
• Disease course evaluated at day 8-10 of hospitalisation • Immunotherapy starts once patient is in ICU	• Not possible to determine disease course and/or treatment response • Very expensive treatment	• For sudden cases, nothing can be done before the acute episode
• Early prognostic biomarkers for disease course	• Novel biomarkers • Targeted therapy	• Early disease onset biomarkers • Targeted therapy for high risk patients with family history
• High-risk patients would start immunotherapy earlier • ICU stay shortened, or avoided	• Increase response rate after 1 year up to 75% • Better quality of life • Lower healthcare spending on medication	• Prevention of 25-50% of all familial heart failure cases (estim. ca. 500,000 cases) • Better quality of life, Increased productivity • Lower hospital/ drug costs & family burden
In spring 2020 COVID-19 outbreak, **each ICU day saved** would have led to **EUR 155-360 million per day** of savings and faster patient recovery	**EUR 10 billion** from productivity gains across Crohn's disease and ulcerative colitis patients	**EUR 2.1-4.1 billion** savings in direct medical costs

4.3 Key take-aways

LifeTime has a unique value proposition around cell-based interception medicine, which will contribute to the next generation of precision medicine and the transformation of healthcare delivery. Not only will single-cell based strategies derived from LifeTime research allow considerable healthcare cost savings compared to today, but the entire initiative has the potential to drive innovation and push economic growth in Europe by creating a market for new services and products, by supporting clinical research and product development, and by making long-term infrastructural investments that will serve as international collaborative platform, sustainable education/innovation network, technology development incubator. LifeTime also aims to be an important advocate for patient-centric research and medicine, a key dimension in data-driven research.

Therefore, supporting LifeTime and allowing the initiative to grow could contribute towards better healthcare, impactful innovation, and considerable economic return.

Appendix 1. Methodology

Data collection

Data were collected from several sources, including primary research from expert interviews (scientists, clinicians, industry leaders) and secondary research on company- and market forecast reports, peer-reviewed scientific articles, proprietary databases and press releases. Instances where no data could be retrieved from secondary research, or where data were but not consistent or not sufficiently up to date, data and assumptions provided by disease area experts were used.

For primary data collection, individual expert discussions were conducted by one or two independent consultants in May-June 2020. Interview programme included:

- 7 LifeTime scientists/clinicians, covering all five key disease areas;
- 6 EU-based executive representatives from large pharmaceutical companies, including IMI representation;
- 2 EU-based industry association representatives;
- 4 EU-based start-up company representatives (single-cell multi-omics and organoids)
- 4 EU-/US-based life science company representatives (sequencing instruments/ consumables)
- 1 EU-based research funder and 1 US-based research funder.

Discussions were based on a set of guiding questions around LifeTime value, expectations on the future benefits & challenges, expected impact on industrial economy, expected impact on healthcare cost savings, consortium funding. All feedback was pooled and kept blinded throughout the study, unless differently agreed.

Generation of assumptions

Assumptions on future LifeTime research benefits (e.g. future cure rate, future response rate, etc.) were provided and/or validate by LifeTime scientists based on their expectations and knowledge of the respective disease areas.

We assumed LifeTime's research output to be commercialised and fully taken up by 2030. There are limitations to this assumption (see section "Limitations").

Calculation methods

In general, a retrospective analysis of available sources was done. For 2030, the data forecast is based on WHO databases and secondary research, providing epidemiology data for specific diseases or forecasts for expected disease-related costs. If no prospective data were available, and/or retrospective data were outdated, relevant data for the years of interest were extrapolated based on a set of assumptions.

Both top-down and bottom-up approaches were used to calculate current and future epidemiological data and healthcare costs, and to calculate potential future cost savings.

For top-down calculations, extensive desktop research was performed for each disease area. For some diseases, only macro-datasets (e.g. total European population, or share of total GDP) were available, while data for a specific disease or target population were needed. In those cases, we used the percent split for each disease area to derive numbers for the target population in focus. We applied the same methods to total healthcare expenditure and healthcare-related costs for specific disease. Once total costs for the disease and target patient population were derived, we were able to apply our assumptions, and calculate costs/cost savings per patient.

Limitations

This assessment is a preliminary high-level study, which focuses on selected aspects of health-related spend, which vary based on the disease area, e.g. productivity gains, more accurate diagnosis and general cost savings.

Assumptions used to calculate current and future healthcare spend and epidemiology were validated by primary sources. Predictive assumptions on LifeTime benefit were based on experts' experience and expectations in the respective fields, as generally concerning future innovation not yet available/published. Assumptions used to quantify LifeTime benefit have been purposely kept at high level, and similarly LifeTime benefits have been generally calculated on the whole patient population, and not stratified for e.g. disease severity, age, remission rate, etc. Once more refined assumptions can be generated, some of the calculated benefits could be reviewed to generate more granular expected benefits, for example taking into account specific patient subpopulations.

Our results depend on the availability and quality of collected data. In some disease areas, and in general for data on European population, we experienced a lack of data availability, or data were outdated.

Data collection methods varied across countries and studies, limiting their comparability. For example, studies assessing the economic burden of Alzheimer's included different cost chapters depending on study and country: some include direct costs, some others both direct and indirect costs, plus, the parameters assessed in each cost category differed across study.

Due to limited data availability, base years considered for calculations of cost savings and patient population differ by disease area. In addition, some data where only provided for EU27+ or the overall European Region. For cases where patient population and costs data for 2020 and/or 2030 were not available from primary or secondary sources, the values were calculated based on estimated yearly increase rates, which were either derived from the literature, or inferred from available data points.

We assumed LifeTime's research output to be available and fully taken up by the market from 2030 onwards. Because of the multiple variables and potentially large transformation in the market and in healthcare delivery that will occur over the next decades, a 10-year horizon has been considered appropriate to model LifeTime future benefits. Further-looking assumptions cannot be made at this point, and no existing source

that we could retrieve attempted such exercise. Therefore, unless differently specified, the model shows the potential savings achieved in e.g. 2030 with LifeTime compared to 2030 landscape without LifeTime. Assumptions concerning the timeline of innovation might be reviewed based on factors such as speed of success, funding, infrastructure availability, regulatory aspects, cost and availability of new technologies, healthcare professionals' training, as well as factors and obstacles that cannot be foreseen at present. When new data become available, it is recommended to feed such information into the model to generate more reliable estimates.

Cancer + Breast Cancer

We retrieved 2018 average cost data for all cancers in Europe. Europe was defined as EU28 plus Norway, Iceland and Switzerland. Based on the countries included, we used the Global Cancer Observatory by WHO to derive the respective epidemiology data for 2020 and 2030.

Total costs of cancers were split in direct healthcare costs on cancer and medication, and indirect costs from informal care and morbidity-and mortality related productivity losses. Since no further cost data were available for 2019 or today, data from 2018 were extrapolated to 2020 and 2030 by applying a 2.3% cost increase to all cost categories per year. LifeTime experts indicated the overall cure rate and the assumptions related to productivity (one third of the cured patients fully productive again, and two thirds with a 30% productivity loss), and future benefit. Data and calculations considered the average patient and did not account for disease severity, stage or age.

For breast cancer, the only available cost data were from 2009 and EU27 only. The same source provided also cost data for all cancers. The yearly cost increase for all cancers was calculated by using cost data from two different sources, one with data for 2009 and the other one with data for 2018. A limit of this calculation is that 2009 cost data for 2009 were provided for EU27, while 2018 cost data were available for EU28 plus Norway, Switzerland, Iceland. The relative cost increase per year was then applied to 2009 cost data of breast cancer up to 2018. From 2018 to 2020 and 2030, a general cost increase of 3% was assumed, the same as for all cancers. The cure rate of breast cancer was based on the 10-year survival rate. The same assumptions on productivity were made as for all cancers.

Alzheimer's Disease

Cost burden of Alzheimer disease (AD) was taken from Maresova et al. (2016) for 2010 and 2030. The same applies to the prevalence of AD in the respective years. Their term cost burden includes both direct and indirect costs, as it summarises data from different studies and source which used different approaches to derive healthcare costs for AD. Based on the data from 2010 and 2030, a yearly cost increase and patient population growth per year was calculated to derive at costs and prevalence for 2020. Since secondary sources rarely provide any prevalence on patient ≤ 65 years, we used the 1.6% prevalence rate indicated by LifeTime experts to derive at 5-year costs savings for patients with AD who are still in their working age.

COVID-19

For COVID-19, a bottom-up approach was used, with data per capita, such as average costs for one day on Intensive Care Unit (ICU) per patient, used to calculate the costs for the entire stay on ICU per patient, and then for the entire patient population.

The main limitation of this model is the uncertainty around the timing and extension of a potential new COVID-19 outbreak, therefore, cost savings were calculated based on 2020 data (as opposed to the 2030 horizon used for other areas). In general, we calculated the savings that could have been achieved in 2020 outbreak if cell-based disease interception tools were available.

Inflammatory Bowel Disease

Prevalence for Crohn's diseases (CD) and Ulcerative Colitis (UC) was based on the maximum average number per 100,000 patients in 2006. The same prevalence rate was applied to the following years, during which the total European population increased. Productivity losses per patient years were provided for both diseases separately. Productivity losses were measured in USD in 2013. We used the currency exchange from 31 December 2013 to derive at costs in EUR (1USD = 0.73 EUR). The same costs due to productivity losses were applied for each year, however we have applied a yearly 2.5% inflation rate.

Heart Failure

We obtained data on healthcare expenditure in EU27 from 2012 to 2017. Based on these data, we calculated the yearly expenditure increase of 3% and applied it to the following years to derive data for 2020 and 2030. In addition, we obtained healthcare-related costs spent on heart failure for 2014 from secondary sources. Having both the total healthcare expenditure in 2014 and the costs spent on heart failure in the same year, we were able to calculate the share of healthcare expenditure spent on heart failure, which was 2.46%. This rate was then applied to the total healthcare expenditure of the following years to derive at the healthcare-related costs spent on heart failure in 2020 and 2030.