05
Implementing an Ethically Responsible Strategic Research Agenda

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

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

5.1 A LifeTime Ethics Mechanism

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

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

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

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

5.2 Mitigating Ethical and Societal Risks

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

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

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

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

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

Important aspects include whether the incidental findings concern treatable or untreatable conditions, whether the outcome depends on tackling the disease earlier, or whether the disease can impact family members and their decision to be screened or treated when possible[1]. As it might be impossible to find a single way to proceed, LifeTime recommends to develop an adequate disclosure policy for returning clinically relevant findings to patients and donors, with the flexibility to deal with incidental findings. In addition, establishing a reference system covering all possible scenarios, will provide guidance to appropriately deal with each possible outcome.

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

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

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

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

5.2.2 Innovative Technologies in Research and Healthcare

The use of patients' material naturally raises ethical questions, especially when we consider the novelty and level of information provided by the LifeTime technologies. While some of the concerns raised by single-cell technologies are equivalent to concerns previously raised by genomics testing[1], LifeTime recommends close consideration of issues related to the use of technologies that are more novel in healthcare and biomedical research such as the establishment of personalised disease models and the use of artificial intelligence (AI).

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

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

5.2.3 Emerging Issues in Healthcare

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

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

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

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

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

5.3 Engaging Citizens

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

A previously used and successful strategy is the creation of public engagement activities that challenge both scientists and the public, such as exhibitions or performances at the crossroads of art and science (Science Gallery International). Additionally, we will encourage scientists and clinicians in our community to reach out to the public and participate in science outreach activities, podcasts and interviews. All these activities should be organised in parallel with LifeTime's technological developments and implementation of its research and innovation programmes, allowing a truly public dialogue and considering public opinion throughout[4]. To understand the public's opinion, fears and expectations regarding LifeTime's vision, we recommend the organisation of public consultations, where we can assess public awareness on LifeTime's technologies, or citizen's attitudes towards the societal and ethical implications of LifeTime. These activities should always be organised timely, so that public opinion can influence strategic decisions.

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

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