Report on the social implications of LifeTime technologies

Contribution to the development of the LifeTime Roadmap

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Knowledge & Innovation

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Executive summary

This report deals with expectations and concerns related to the technologies the LifeTime initiative is focused on (single-cell biology, AI applied to single-cell data, personalised organoid disease models), in the perspective of the further development of precision medicine. The report is based on two main sources:

- A **literature review** on the scientific, social, ethical, and organisational implications of LifeTime research and technologies, also including the public consultations carried out on similar issues in the last two decades
- A **set of 15 qualitative in-depth interviews** (overall involving 17 persons) with researchers, clinicians and representatives of European patient associations. The outputs of the literature review have been used to identify the main issues to be included in the in-depth interviews.

The study adopted both a **transformational perspective** (focusing on discontinuity between the present situation and a future situation where the new technologies will be fully operational) and a **contextual perspective** (instead focusing on continuity, by addressing the transition process in different contexts of application of the new technologies).

As for the **transformational perspective**, respondents have shown high expectations about the impact of LifeTime technologies, even though their level of knowledge of such technologies greatly varies, particularly among representatives of patient associations and (to a lesser extent) clinicians. Moreover, if interviewees tend to have similar expectations about the future application of the new technologies, their worries seem more diversified: researchers mainly worry about limitations to research due to ethical or social reasons; clinicians especially worry about the difficulty of applying LifeTime technologies in their daily clinical work; patient groups representatives are more worried of possible negative impacts on patients' experience of disease.

As for the **contextual perspective**, different contexts which could be impacted and transformed by the new technologies have been investigated. These are: professional and organisational arrangements, data-management issues, patient experience, role and profile of medical doctors, access to care, public confidence. Each context has been discussed with the interviewees, using the issues which have emerged from the literature review to structure the interview guide.

The **main outputs** from interviews are summarised in the schemes below for the different contexts.

Area	Issue
Redefinition of professional and organisational arrangements	– Extensive and direct cooperation among the many actors concerned with personalised medicine will be increasingly required – Many factors of different nature (cultural, organisational, ethical) are expected to hinder closer cooperation – Increasing competition in the research environment is particularly highlighted as a hindering factor to manage, which makes cooperation more difficult – Various tools to manage these factors (e.g., training activities, open data policies, greater focus on outpatient care and illness prevention) are suggested by the respondents

Area	Issue
New data-management aspects and dilemmas	– Risks related to data management in the context of genetics and genomics research are highlighted, that can also be applied to single-cell technologies. They concern, e.g., data ownership, inconsistent regulations, management of informed consent, and risks of social discrimination – These risks are prevalently linked to the overarching tension between the use of data for research and the patients' right to data protection – In general, identifying effective approaches is difficult. Some possible strategies are proposed, including reinforced dialogue, development of citizen science arrangements (where patients maintain the ownership of the data they contribute), open data mechanisms, greater involvement of patient associations
Effects on the experience of patients	– LifeTime technologies are expected to have important impacts on patients' life – The possibility to make early and detailed diagnoses is likely to induce a deep change in how the conditions of health and illness are perceived – In practical terms, they will probably have ambivalent potential effects (triggering preventive behaviours, but also inducing negative social and psychological implications) – One of the main risks evoked is that too much responsibility is put on the shoulders of patients about their health conditions
Changing role and profile of medical doctors	– Both patients and clinicians feel that medical authority is challenged by many factors, connected to (or reinforced by) LifeTime technologies: the increasing amount of information and data doctors have to manage, closer relationships with other health and non-health professionals, increasing autonomy of patients – Because of the increasing complexity of diagnostic and therapeutic pathways, many feel that trust-based doctor-patient relations should instead be reinforced – Doubts are cast on the capacity of doctors to interpret the new clinical data for patients, and some clinicians call for a revision of university curriculums
Effects on access to care	– Many respondents, from all three categories, highlight the risk of unequal access to the new technologies, also connected to the role of the private sector – A majority tend anyway to show a pragmatic approach: while the public sector will necessarily continue to play an important role, the private sector is also needed, because resources are limited; on the other hand, this is not something new; regulations will need to adapt to the new context and moderate inequalities – More concern is expressed about the cost of medicines: while screening tests are expected to cost less with time, the costs of drugs developed for personalised medicine, according to many, are destined to remain high, also because of the increasing cost of clinical trials

Area	Issue
Further factors potentially affecting public confidence in LifeTime technologies	– Ethical issues (other than data-related ones, see above) are in general not particularly emphasised in relation to the LifeTime technologies – The only exception is the management of incidental findings, viewed by both clinicians and patient representatives as a serious problem – Researchers and clinicians particularly highlight the need to carefully manage expectations around LifeTime technologies, as research institutions risk over-promising about their impacts and traditional and social media risk feeding excessive and distorted hopes

The final part of the report provides some methodological and substantive orientations for the **development of a stakeholder consultation** on expectations, as well as social and ethical issues, surrounding LifeTime technologies. Grounded on a reconsideration of the main outputs of the literature review and the interviews, three **main objectives** for the stakeholder consultation are identified: 1) assessing and increasing knowledge and awareness of LifeTime technologies; 2) assessing the attitudes towards social and ethical implications connected to them; 3) generating new knowledge on the conditions of application of LifeTime technologies.

Based on a brief analysis of the methodological options, a **scheme for the stakeholder consultation** is proposed. It includes an online **targeted consultation**, using a semi-structured questionnaire and focused on the issues related to objective 3, involving key stakeholders, and an online **public consultation**, using a structured questionnaire and focused on the issues related to objective 1 and 2, addressing the public at large. A set of **issues to structure the questionnaire** for both consultations is then proposed.

Introduction

LifeTime is a project funded by the European Commission and conducted by a consortium of 17 institutions and 3 linked third parties from 15 countries, led by the Max Delbruck Center of Molecular Medicine (Germany) and the Institut Curie (France).

LifeTime is overall aimed at developing a Roadmap to take a major step beyond the genomic revolution through quantifying, modelling, and predicting cell trajectories in tissues and whole organisms. LifeTime's long-term vision is to make it possible for physicians to assess the molecular state of patient tissues in a timely, patient specific and detailed way, leading to early diagnosis and effective interception of disease.

LifeTime is based on the development, integration and application of three key technologies:

- The methods of **single-cell biology** to map the gene activity of cells during disease, with the possibility to intercept a wide range of diseases well in advance of the onset of symptoms and to further develop personalised medicine approaches
- The use of **artificial intelligence** (AI) on a large scale to interpret the data generated by single-cell analysis
- The development of **organoids** (mini-organs) obtained from the cells of patients which allows developing personalised cellular models of human diseases, and thus to better understand the causes of disease and identify possible treatments.

The Report is part of this overall effort. It deals with the **expectations** surrounding the LifeTime technologies, as well as their **social implications**, addressing ethical, organisational, cultural, and policy issues to be considered in the development of a Roadmap. In addition, it discusses **contents and methods of a stakeholder consultation exercise** to be possibly organised in the future on these same issues.

The report is organised in **three parts**.

Part One contains the description of the study and its theoretical and methodological setup.

Part Two, the focus is on the identification of expectations and social implications of the three LifeTime key technologies, on the basis of a literature review and the 15 in-depth interviews conducted with a panel of researchers, clinicians, and representatives of European patient associations.

Part Three provides some methodological and substantive orientations for the development of a possible stakeholder consultation around the issues connected to the LifeTime project.

The study was conducted by Knowledge & Innovation srls. The team was composed of Luciano d'Andrea, Marina Cacace and Alfonso Alfonsi (Knowledge & Innovation srls). The report has been drafted by Luciano d'Andrea and Marina Cacace.

PART ONE

DESCRIPTION OF THE STUDY

LifeTime is aimed at developing a Roadmap to take a major step beyond the genomic revolution through the development and application of innovative technologies (single-cell biology, AI applied to single-cell data, personalised organoid disease models), in the perspective of the further development of precision medicine.

The study presented in this Report is part of this overall effort. It deals with the **expectations** surrounding the LifeTime technologies, as well as their **social implications**, addressing ethical, organisational, cultural, and policy issues to be considered in the development of a Roadmap. In addition, it discusses **contents and methods of a stakeholder consultation exercise** to be possibly organised in the future on these same issues.

The theoretical and methodological frameworks informing the study are briefly summarised in the next sections.

1. Theoretical assumptions

In developing the study, three theoretical assumptions have been adopted.

1.1. The fields opened by LifeTime technologies as undersocialised spaces

Like any other highly advanced research fields and technologies, also those related to LifeTime can be understood as opening new "social spaces", i.e., areas of actions and opportunities which were previously unknown to society. Lifetime technologies are creating new social situations, like having the chance to know that one will be ill before the illness occurs, knowing in advance how personal behaviours will impact on the life of one's own children, getting treatments on the basis of diagnoses or therapies developed by learning machines which are largely out of the control of individual technicians or physicians, or on the basis of "living models" (organoids) made up of one's own cells.

As such, these spaces are under-socialised, i.e. they are not yet "filled up", if not partially, with those social meanings, contents or experiences at any level (cognitive, emotional, economic, political, ethical, etc.)[1] which would help make them socially manageable. The first to enter these areas are researchers and technicians, creating their "social meanings" to interpret them. However, other actors contribute to the socialisation process, including ethicists, public authorities, experts, different kind of involved stakeholders, and finally ordinary people. This process of social signification (Veltri, 2016) implies the interaction and often conflict among different actors bearing their own views, interests, competencies, and strategies.

[1] There are some pieces of literature speaking of the "socialisation of biology" or the biosocial dimension, to show the strong connection between the social and the biological. See, for example, Harris, K.M., & McDade, T.W. (2018). However, the concept of socialisation used here is larger in scope, since it concerns any new discovery, especially – but not necessarily – those which lead to some forms of technological development.

1.2. Public consultation as an anticipatory process

In this framework, the stakeholder consultation cannot be viewed as simply the collection of opinions and attitudes about a given issues or technology. It should instead be understood as the effort made by respondents to anticipate the possible social meanings – be they positive or negative – which are expected to be attached in the future to the "social spaces" opened up by LifeTime technologies. This process is based on the respondents' personal feelings, concerns and experiences, and it proceeds by analogy with other similar, already established, "social spaces" with which LifeTime perspectives are in continuity (for example, genetically modified organisms).

The anticipatory nature of the consultation is given by the fact that none of the respondents (including researchers) have an experience of the social implications of LifeTime technologies and none of them have a clear idea about how and even to what extent the perspectives made available by LifeTime technologies will be actually socialised (for example, the advent of precision medicine is sometimes questioned – see, for example, Feiler, Gaitskell, Maughan, & Hordern, 2017).

1.3. The need for both transformational and contextual perspectives

The anticipation process can be stimulated by adopting different perspectives. In this regard, two main perspectives have been integrated here, i.e., the transformational perspective and the contextual perspective (Hedgecoe & Martin, 2008), so as to be able to capture both radical and incremental change.

- The transformational perspective stresses discontinuity and novelty. In this perspective, the future social implications of new discoveries or technologies are seen as producing a break with respect to the existing social (and therefore organisational, ethical, legal, economic, etc.) context.
- The contextual perspective, on the contrary, stresses continuity. In this perspective, the social implications of new discoveries and technologies are viewed as the output of the historical process and considered in continuity with already occurring social changes. In the contextual perspective, therefore, the interest is focused on the transition process, i.e., how and in which ways the social spaces opened by the new technologies will be socialised, i.e., absorbed and managed by society.

2. Methodological approach

To attain its objectives, the study adopted **two research strategies**.

The first strategy was implementing a **literature review** on the scientific, social, ethical, and organisational implications of LifeTime research and technologies. Considering time constraints, the review was not aimed at developing a systematic analysis of issues and approaches, but rather at identifying recurrent issues to be considered in the study. The outputs of the literature review were meant to support the development of interview grids to

be used in the study (see below). A specific section of the review has addressed the public and stakeholder consultations carried out on similar issues in the last two decades.

The second strategy was conducting a **set of in-depth interviews** according to a **qualitative methodological approach** (see the box below).

The qualitative methodological approach

Qualitative research in the social sciences is characterised by the basic choice to focus on non-numerical data to privilege information providing an in-depth view of the set of phenomena under investigation (Turner, 2006). Qualitative research is mainly adopted for better understanding the meaning-making process (how meaning is attributed to different objects, people and life events) underlying social phenomena (Krauss, 2005), so as to provide information about why and how selected phenomena may occur (Lune & Berg, 2016). The open-ended character of the questions used in in-depth, qualitative interviews allows collecting information on unanticipated issues, to analyse issues about which very little is already known and to deepen specific issues (Turner, 2006). The results of a qualitative study, involving a limited number of respondents, cannot be generalised to the entire reference population. However, the analysis, precisely because it goes in depth into the investigated phenomena, has a potentially strong explanatory power in itself.

Respondents have been recruited following a purposive sampling strategy, aimed at actively identifying persons holding relevant pieces of knowledge to the aim of the objectives of the study. For this reasons, three categories of respondents have been identified: **researchers** in relevant fields, **clinicians** and **representatives of patient organisations**.

Given the exploratory, qualitative approach adopted, no statistical representativeness has been sought. An attempt to **diversify the pool of interviewees** was anyway made, aimed at including – as far as possible – different perspectives. To this aim, a minimum balance was pursued across different criteria: gender, European region of residence[2], research field and clinical specialty[3]. As for patient associations, European-level ones have been selected. As for researchers and clinicians, potential interviewees have been identified who have not been directly involved with the LifeTime project.

Overall, 17 persons have been interviewed online in 15 interviews (a group interview was carried out with three researchers from the UK). Basic information about the interviewees are provided in Tables 1 to 3.

[2] **Western Europe** (Austria, Belgium, France, Germany, Ireland, Luxembourg, Netherlands, Switzerland, United Kingdom); **Northern Europe** (Denmark, Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Sweden); **Eastern Europe** (Belarus, Bulgaria, Czech Republic, Georgia, Hungary, Moldova, Republic of, Poland, Romania, Russia, Slovakia, Ukraine); **South Western Europe** (Italy, Malta, Portugal, Spain); **South Eastern Europe** (Albania, Bosnia and Herzegovina, Croatia, Greece, Macedonia, Serbia and Montenegro, Slovenia, Turkey).

[3] The effort has been made, for patient associations and clinicians, to include – as far as possible – respondents connected to different, large disease/clinical areas, namely: cancer, neurological diseases, cardiovascular and metabolic diseases, infectious diseases, inflammatory and autoimmune diseases. The representative of a patient association focusing on genetic diseases has also been interviewed, considering some analogies with the perspectives implied by LifeTime technologies, particularly in terms of social and – above all – ethical implications.

Table 1 – Interviewees: Representatives of European patient associations

Disease area	Gender	European region*	(Country)*
Cancer	F	South-Western	Italy
Cardiovascular diseases	F	Western	Belgium
Genetic diseases	M	Western	France
Infectious diseases	M	Western	Switzerland
Neurodegenerative diseases	F	Western	Belgium

* Since European-level patient associations have been selected, the European region/country of residence of the interviewed representative have been indicated.

Table 2 – Interviewees: Researchers

Research field	Gender	European region	(Country)
Cancer	F	South-Western	Italy
Epigenetics	M	South-Western	Spain
Genetics	F	Eastern	Poland
Pharmaceutical biosciences	F	Northern	Sweden
Computational genetics	F	South-Eastern	Turkey
Molecular medicine	M	Western	United Kingdom
Single-cell analysis applied to haematology	M	Western	United Kingdom
Functional genomics and machine learning	M	Western	United Kingdom

Table 3 – Interviewees: Clinicians

Clinical specialty	Gender	European region	(Country)
Cancer	M	Northern	Finland
Cardiovascular diseases	M	South-Eastern	Greece
Inflammatory and auto-immune diseases	F	South-Western	Italy
Neurology	F	Eastern	Poland

Summing up, respondents reside in 11 different countries, with a larger group (7) from Western Europe (mostly because of the group interview with three UK researchers). As for the other regions, 4 interviewees came from South-Western Europe, and 2 each from Northern, Eastern and South-Eastern Europe.

Most interviewees (7) are in the 35-49 age class, while 6 are in the 50-64 class and 4 are above 65 years of age.

Interviews have been recorded, transcribed and analysed using the qualitative data analysis and research software ATLAS-ti. Respondents are kept anonymous, and their perspectives are presented in this report using a code, identifying if the person is a researcher (RE) clinician (CL) or patient group representative (PG) and adding a progressive number.

The results of the two strategies described above (literature reviews and in-depth interviews) also allowed developing a **proposal for the stakeholder consultation** which is presented in the third part of this report.

3. The structure of the interviews

The theoretical assumptions summarised in Section 1, above, have led to the definition of the structure of the interviews.

Interviews have been interpreted and designed as anticipatory exercises involving qualified respondents. It was decided to include both the transformational and the contextual perspective. This is the reason why the interviews have been organised into two parts.

- The first part was aimed at exploring the social, clinical and scientific advancements related to the LifeTime technologies, considering both potential benefits, risks and implications, without exploring their relations with the existing contexts.

- The second part was aimed at identifying possible impacts on a set of specific, current social contexts.

A social context has been operationally understood as a set of relations involving specific bundles of actors, institutions, and technologies which are aimed at producing some expected outputs for society.

In the case of this study, the contexts presented in Table 4, below, have been considered.

Table 4 – Main features of the contexts

Context	Expected outputs	Main actors
Research and innovation	Production of new scientific knowledge and development of new technologies	Scientists, scientific institutions, funding agencies, policy makers on science policies
Healthcare services	Application of new knowledge and technologies in the clinical work	Clinicians, healthcare providers, patients, health agencies, policy makers on health
Market	Commodification and commercial exploitation of new knowledge and technologies	Enterprises, investors, regulatory agencies, policy makers on science policies and on health
Social life	Use and management of new knowledge and technologies in different aspects of social life (e.g., individual life, family life, social groups, etc.)	Patients, citizens, healthcare providers, patient associations

Based on the literature review, a set of key issues for the different contexts have been singled out and included in the interview grids. The limitations of the current study made it impossible to interview representatives from all different categories of actors. Questions related to the four contexts have anyway been included and discussed with respondents, as appropriate.

This approach is partly reflected in the structure of the second part of the report. In general, transformational perspectives are analysed in **Part Two, Section 1**, collecting respondents' points of view and expectations as concerns the **longer-terms benefits** connected with the introduction of LifeTime technologies, in scientific, clinical and social terms. Subsequent **Part Two sections (2-7)** are instead mostly adopting a contextual perspective, addressing how **current social contexts** are being (or will be soon) affected by ongoing change. However,

boundaries are sometimes blurred, and the two perspectives tend to crosscut the various topics.

Not all the issues have been considered with all respondents. Some have been considered only in the interviews with the representatives of patient groups, some only in those with researchers and some others only in the interviews with clinicians (see Table 5, below).

Table 5 – The issues considered in the interviews (PG – Representatives of patient groups; RE – researchers; CL-clinicians)

Area	Issue	Repondents
Redefinition of professional and organisational arrangements	Organisation of the research work	RE
	Relations between research and clinical work	RE, CL
	Healthcare provision models	PG, CL
New data-management aspects and dilemmas	Management of personal data and biosamples	PG, CL, RE
	Informed consent	PG, CL
	Bias and profiling	PG, CL, RE
Effects on the experience of patients	Concepts of health and illness and consequences on personal identity	PG
	Personal responsibility for health	PG
	Patients and citizens engagement	PG
Changing role and profile of medical doctors	Medical responsibility and authority	CL
	Doctor-patient relationships	PG, CL
Effects on access to care	Equitable access to care	PG, CL, RE
	Public-private relations	PG, CL, RE
Further factors potentially affecting public confidence in LifeTime technologies	Ethical implications of new research and technologies	PG, CL, RE
	Trust in research institutions and researchers	PG, CL, RE
	Management of the expectations raised by the new technologies	RE

It is worth noting that the choice has been made not to deal with social and ethical aspects separately, creating a necessarily de-contextualised inventory of similar issues in a taxonomic perspective. Instead, a cross-cutting, contextualised approach was adopted, each time presenting the different set of relevant issues (be they ethical, organisational, or societal in a broader sense) connected to the various contexts potentially affected by LifeTime technologies. As a consequence, specific social and ethical issues are occasionally addressed more than once, as they manifest themselves in different contexts.

PART TWO

ISSUES EMERGING FROM THE LITERATURE REVIEW AND THE INTERVIEWS

This part of the report describes the main issues connected to LifeTime research and technologies as they emerged from the literature review and the interviews, as described in Part One.

The literature review allowed to identify 17 key issues, partially overlapped, which have been used as the general framework for conducting the interviews. They have been afterwards grouped into 7 clusters, presented in sections 1 to 7, below. The seven clusters are:

1. General perception of LifeTime research and technologies
2. Redefinition of professional and organisational arrangements
3. New data-management aspects and dilemmas
4. Effects on the experience of patients
5. Changing role and profile of medical doctors
6. Effects on access to care
7. Further factors potentially affecting public confidence in LifeTime technologies.

Each section briefly presents the main issues singled out in the literature and the most relevant elements emerged from the interviews.

1. General perception of LifeTime research and technologies

1.1. Inputs from the literature review

There is a wealth of literature about the general perception and the expectations connected to the advancement of LifeTime research and technologies.

However, it is to observe that, while specific scientific and policy pieces of literatures have been identified about societal-level implications of AI in healthcare and the development of personalised organoid disease models, the **literature on the implications of single-cell technologies is intertwined with the one dealing with genomics in general**. Not surprisingly, the literature on the broader impact of single-cell technologies is also strongly connected to the more established literature addressing precision medicine (or personalised medicine), as its overarching framework.

The promises of **personalised medicine** are quite clearly identified (European Science Foundation, 2012; Youth Health Parliament, 2016; Aroh & Cata, 2017; Personalized Medicine Coalition, 2017), and can be summarised as follows:

- Directing targeted therapy and reducing trial-and-error prescribing
- Reducing adverse drug reactions
- Revealing additional targeted uses for medicines and drug candidates
- Increasing patient adherence to treatment
- Reducing high-risk invasive testing procedures
- Helping to control the overall cost of health care
- Detecting risk factors

- Developing personalised health management plans
- Making a more efficient use of resources in the long run.

These benefits are made possible thanks to the application of **Artificial Intelligence** in many areas of healthcare provision, including prognostics, diagnostics, image analysis, resource allocation, and treatment recommendations (Nicholson Price II, 2017). In particular, AI is viewed as the necessary building block for the application of single-cell analysis into personalised medicine, allowing unbiased comprehensive molecular profiling enabling the identification of the molecular pathways involved in pathological and physiological processes within every individual cell (Walter & Schickl, 2019).

As for the **organoids** (Lehmann et al., 2019), they offer the possibility to:

- Study human tissues at the same level of scientific scrutiny, reproducibility, and depth of analysis as has been customarily possible only with nonhuman model organisms.
- Recapitulate morphogenetic events in human development that lead to tissue and organ formation.
- Study mechanisms of disease acting within human tissues, generating knowledge and tools applicable to preclinical studies, including drug testing.
- Study of variability among human individuals at the tissue level, as well as the cellular mechanisms leading to complex disease phenotypes.
- Develop numerous applications for tissue engineering, drug discovery, and regenerative medicine.

1.2. Inputs from the interviews

In general, all respondents were fully informed about **precision medicine** and the increasing role of **AI** in healthcare. Representatives of patient groups and – to a lesser extent – also some clinicians, tended to conflate genomics and **single-cell** biology. Similarly, representatives of patient groups and some clinicians declared to be only superficially informed about human **organoids**.

Researchers – as those more directly involved with the three technologies – are also those who express the higher degree of enthusiasm about **future research perspectives** and promises of single-cell technologies in general.

> *It's a wonderful technique. It works. There is an immense power beyond this technique.* (RE1)

> *I think that single-cell technologies are quite a big breakthrough (…). We can check what's happening on the single-cell level with a very high resolution, even to sub-gene level, to see which part of the gene is affected. This is definitely big, (…) it is extremely powerful.* (RE3)

> *I think that there are big advances to come in single-cell, multi-omic approaches, where you combine different single-cell modalities, so that you get information from epigenetics, genomics, transcriptomics, proteomics, all from the same cell. (…) That's going to be a major advance.* (RE7)

Other specific advantages of **single-cell** biology and connected technologies are highlighted.

- It can add **a dynamic** dimension to genomic research.

  It will be super-important, and it's not the data on the single cell per se which will be the most useful. The transition from healthy cell state to cancer state, the transcription profile from one state to another … that will be really informative, that will give us new insights, and it applies for all the -omics (…). Once we have that information, it will be super important to apply artificial intelligence. (RE2)

  One thing that I think is very interesting and informative for single-cell analysis is live cell imaging, so the ability to track single-cells through time. That's going to be a very powerful approach. (RE7)

- It allows to understand **diversity** in tissues.

  Increasingly, with single-cell technology, we can see how the old definitions of tissues were limited and how much diversity there is. (…) Now, with single-cell technologies, coupled with AI clustering methods, we can disentangle all those tissues in a computer. (RE7)

  Single-cell technology is very important because we understand the heterogeneity of tissues, tumours, whatever we're analysing. We work up the molecular heterogeneity in those systems. (RE5)

- It helps putting the pieces of a complex **puzzle** together.

  By incorporating all these data, you can finally look at interactions between all the cells, look at the organs and between organs, and also take into account the space around them, and then all the different signatures that may come up, metabolic, cellular, all this. I think this is a major advancement. It can only be done if you incorporate all these different assays together. (RE1)

  Another connected advancement that is coming over the next few years in a big way is in situ *sequencing: understanding the spatial relationships between single cells.* (RE7)

Artificial intelligence is key to reaching these objectives, even if AI models will take time to actually deliver what is expected of them.

I think the ultimate objective would be to have the map of a disease. Then you get a patient and you put this patient's characteristics into this artificial intelligence programme. The programme will come out and say, 'Okay, this is what you need to do for this patient', based upon everything that already was integrated in it. I think that would be the future scenario. (RE1)

It starts to become possible, to an extent, to have models that are able to predict genomic phenotypes. At the moment, it's very much a black box modelling approach, but it does mean that you have a computational machine that is able to take the DNA and predict what kind of phenotypes to expect (…). Of course, these models are not, to be honest, very good at the moment. There's room for improvement, but I think that is the exciting improvement. (RE7)

Organoids are also credited important advantages, along with technical limitations, at this stage.

Of course, we have animal models. The problem is that I think it's going to be more and more difficult to work with animals (…). The organoids are 3D models and they are very close to the way the cells really are in our body and so you can really assess how, for example, the drug that you want to test will work. I think once you establish the technique, it is incredibly powerful. (RE1)

For the last 40, 50 years, people have had the idea that we could take embryonic stem cells and then we could programme and re-programme them just as we wished. The truth is we can partly do that in a dish, but it doesn't work in the same way that it works in the body (…). The next thing really is to

try and put all of that back together again and see if one can get an organoid that reproduces exactly what happens in the body. (…) I think that's a major hurdle, but there has been a lot of progress. (RE6)

The interviewed researchers also strongly expressed their confidence in a relevant **translational impact** of the new technologies, even if not all can be predicted now.

My personal view is that [this] *will really help to work on prevention. I think that if we can somehow catch a disease before it's too late, that will definitely move science and medicine forward. One way to do this is to really catch a cell before an event happens. What is then the event that triggers the disease, whether it's cancer, or another disease? (…). How can we prevent it?* (RE1)

The ability of really looking at a single-cell level, combining this with genomics, is extremely powerful. I'm really confident that this opens up totally new possibilities for scientific discovery and for medicine alike. (RE3)

I've got a view about clinical application and that is that if you look at the breakthroughs in clinical medicine, they often come from breakthroughs in basic science and basic understanding. I think the thing to follow is to try and find out exactly how things work, what the mechanism is, what the basic principles are, and I think that the applications to medicine would follow on from that. I think trying to predict what's going to happen in clinical medicine, how things will be applied in clinical medicine, it's interesting, but you can never easily tell what's what. (RE7)

On the same line, the interviewed **clinicians** identify potential benefits of the new technologies for clinical practice. The importance of having tools to dynamically analyse personalised pathways leading to disease is highlighted by some.

It's really clear that the genomics in itself is not enough, because quite often it's not actionable, and we don't know what to do with that. We need more functional studies, like the single-cell studies (…) and also these ex-vivo *models like the organoids.* (CLI1)

Nowadays, as the population is aging, we have to focus on degenerative diseases. (…) The factors behind the degenerative diseases are both life and age-related factors in general and inherited and genetics-related factors. (…) In my view, innovative medicine of the next decades will be mostly oriented to investigate pathways [leading to] *degenerative diseases.* (CL2)

Clinicians, however, also mention **difficulties and limitations** in actually accessing and applying these technologies. Even if current application contexts will be addressed in the next sections, they seem, in some cases, to impact clinicians' perception and expectations in relation to new technologies and personalised medicine.

You know, personalised medicine and diagnosis have been talked about for a long time. It's obvious that it's a slogan, if it can't be brought into clinical practice. (CL3)

We need these types of technologies, but we need to have access to them. We need to have sufficient data analysis capabilities to translate the information to patient care. You can easily generate huge amounts of data for each patient, (…) but no doctor can handle that amount of data. You need systems to integrate the data in a rational way. That's why you need the artificial intelligence and machine learning. That's a big bottleneck today. (CL1)

Even if less familiar with the specific implications of the three LifeTime technologies, the **representatives of patient associations** which have been interviewed express a number of expectations with respect to the benefits of tools supporting personalised and anticipated

diagnosis and treatment, with a particular focus on their respective disease areas. A few excerpts about their expectations are reported below.

- Increased **effectiveness**.

  For cancer, the opportunities are related to identity the disease earlier, reducing costs, and targeting the treatment to that specific patient, which will improve outcomes. Of course, it could also be identified in advance if that individual is at risk of a specific disease, so that preventive measures can be put in place. (PG1)

- **Early diagnosis** and **drug testing**.

  I think that, especially for neurological diseases, it's really important to get the diagnosis as soon as possible, because what's lost is lost. (…) I think single-cell technology will help, so I think that's really important. (…) Organoids, I think, are also a good way to test a lot of medicines, even already existing medicines … What is it doing to the nerve cells? (PG5)

- More **accurate prognosis**.

  In genetic diseases, we can consider that in many cases the disease is known from very early stages of life. Now, for us, the major question is about the prognosis, because some diseases, as genetic renal diseases, can be diagnosed by the genetic sample, but still, you don't know how [they] *will progress. It's like you have a Sword of Damocles on your head, but you don't know when the disease will really hit you. (…) So, that's one thing that would be really important for us.* (PG3)

- The possibility to **manage the interaction between different conditions**.

  People with cardiovascular diseases often have other conditions as well. These conditions interact with each other. (…) Potentially, what you are saying about single-cell technologies or the creation of an organoid could help clinicians to see what the interactions between the diseases are towards the vessels of the heart, and identify what would be the most appropriate course of action. That will be, I think, valuable indeed, in the future, especially in our healthcare systems, where the pathways of patients are disaggregated. (…) It could help give a holistic picture of what is happening. (PG2)

- Innovative **solutions to long-standing problems**.

  In general, I would say that cancer is more important to personalised medicine than infectious diseases. But, if you're talking for instance about HIV, that would be relevant. (…) Do you know these latent cells? There is HIV. You take a medicine, and at the end, you don't have HIV in your blood, but you have it in latent cells. This is important, to take HIV out from the cells. I think here there could be promising developments. (PG4)

- Welfare **costs reduction**

  In general, this could have a huge impact in terms of the costs of the welfare system. If somebody has a chronic condition and cannot work, or can only partially work, (…) this is a huge cost and a loss of productivity. With more and more personalised medicine, these costs could be prevented and (…) chronicity reduced or its progress slowed down. (PG1)

GENERAL PERCEPTION OF LIFETIME RESEARCH AND TECHNOLOGY
Key points to highlight from the interviews

- All respondents appear to be **fully informed about precision medicine** and the **increasing role of AI in healthcare**.
- Representatives of patient groups and some clinicians tend to **conflate genomics and single-cell biology** and are only superficially informed about human organoids.
- All respondents have **high expectations** about the future application of LifeTime technologies. In this regard, they highlight many advantages, including the possibility to, e.g., add a dynamic dimension to genomic research, produce more integrated views of the interaction among different components (cells, organs, etc.), develop reliable models of diseases, reinforce preventive medicine, managing degenerative diseases, anticipate diagnoses, make prognoses more accurate, increase the effectiveness of healthcare systems, reduce health-related costs, better manage the interaction between different conditions, and find solutions to long-standing problems.
- **Clinicians** seem to be **particularly sensitive to difficulties and limitations** in the access to and application of LifeTime technologies.
- **Researchers** tend to place the application of **AI models** and even more of **organoids** in a middle- to long-term perspective, while considering **single-cell technologies** as more advanced.

2. Redefinition of professional and organisational arrangements

2.1. Inputs from the literature review

The development of genomics and single-cell multi-omics is destined to **blur the lines between basic and translational research and clinical work**.

Scientific research is expected to be increasingly **integrated with healthcare** to ensure effective translation (Harvey et al., 2012) and sharing of tools and process for data collection and analysis (Ginsburg et al., 2016), so as to develop a "learning health care system that systematically captures, analyses, and shares findings from every clinical interaction and research milestone into a continuous feedback loop" (Personalized Medicine Coalition, 2017).

This is expected to require **new training inputs**, especially addressing medical professionals (McGrath & Ghersi, 2016), to allow researchers and clinicians to work together. However, there will be also the increasing need to learn how to **cooperate with professionals and researchers with diverse backgrounds**, including non-medical disciplines like computer sciences, statistics, mathematics, and even the social sciences, and with the different **epistemic frames** reflecting their disciplinary training (Fagan, 2017).

Another frame for research-clinicians collaboration is on **ethical issues**. Presently, ethical issues are dealt with separately by research institutions and healthcare providers. In the future, due to the increasing interaction between research and clinical work, roles and responsibilities of research ethics committees and clinical ethics committees should be also redefined in order to take into account the ethical issues which now simultaneously affect research and healthcare provision (Australian Health Ministers' Council, 2017).

It is also to consider that the development of **new health policies** promoting precision medicine are requiring, or are expected to require, stronger links between researchers and clinicians, but also between them and patient groups and industry (Barnes & Hudson, 2017). This means that the configuration of professional, organisational and social relations among health-related actors is going to be strongly modified.

The development of LifeTime research and technologies also affects the **organisation of the research work**. It is to notice that these changes are part of general trends highlighted by different **interpretive models of science-society relationships** like the Mode 1 - Mode 2 model (Nowotny, Scott, & Gibbons, 2001), Post-academic Science (Ziman, 2000), the Triple (or Quadruple) Helix Approach (Etzkowitz & Leydesdorff, 2000; Carayannis, Barth, & Campbell, 2012) and Post-Normal Science (Funtowicz & Ravetz, 1993), which do not concern only biosciences, although these are particularly affected.

On the other side, other trends are affecting science, and especially biosciences, connected to an emerging **hyper-competition** in the research and innovation sectors (Alberts, Kirschner, Tilghman & Varmus, 2014; Schatz, 2014; Fochler, Felt, & Müller, 2016) with serious impacts on, e.g., the reliability of data (Ioannidis, 2005), publication practices (Young, Ioannidis, & Al-Ubaydli, 2008), the structure of research organisations (Slaughter & Rhoades, 2000; Ylijoki, 2014 Dijstelbloem, Huisman, Miedema, & Mijnhardt, 2014) and career practices (Müller, 2014).

All these dynamics may play a critical role also in the development of LifeTime research and technologies and especially in their application in the framework of precision medicine.

Finally, the development of personalised medicine – supported by technologies as those LifeTime is focusing on – is going to change **healthcare provision models**. This is expected to imply profound transformations of professional practices, communication approaches, distribution of roles and organisational solutions.

Personalised medicine is expected to be increasingly delivered in **out-patient settings**, based on coordinated, multidisciplinary care involving expert centres, clinical labs, and researchers. Furthermore, a move towards **more preventive approaches** to healthcare is expected, substantially relying on "the active participation of citizens, who not only will need to collect data and make the information available, but also to own and control the personal data" (PerMed, 2015).

Different open **critical issues** related to this move towards personalised medicine can be identified (Pritchard, 2018), including:

- Physicians may resist the shift to personalised medicine, perceiving this shift as requiring additional time and work

- Current management processes supporting clinical decision-making are not well-equipped to integrate patient biomarker information
- Current clinical guidelines are unprepared to integrate the concepts and practices of personalised medicine
- There is a lack of infrastructures and data management systems to support personalised medicine
- There is a lack of geneticists, genetic counsellors and molecular pathologists to be involved in the activities of health centres
- There is a lack of sustainable business models for healthcare providers adopting personalised medicine
- There is a lack of products and services, especially in rural settings, sustaining the shift towards personalised medicine.

Driving the change will therefore require a **broad set of actions**, including training physicians for precision medicine, creating new healthcare specialists, establishing new regulations and insurance schemes, developing new communication mechanisms and data sharing, and incorporating genomic and other molecular data into clinical care and research (Florin & Escher, 2017; Ginsburg, & Phillips, 2018). Moreover, important **changes in budget allocations** on health are needed, so as to move more resources on preventive medicine (National Consultative Ethics Committee for Health and Life Sciences, 2016).

2.2. Inputs from the interviews

The interviewed researchers highlight how new technologies are sustaining **closer relations between research – even basic research – and medicine**. This, however, would need new working models to be adopted, and **open data** policies and practices, which are currently insufficient, even within the same scientific community.

> *Tremendous opportunities* [are opening up]*, because you can really cross fields, basic science with medicine. For example, (…) with cervical cancer, head and neck cancers, there was a basic scientist discovering a virus and how it causes tumours and what we can do with that. (…) These things intersect a lot. Clinicians need scientists and scientists need clinicians. The thing that I think we need to scream out to the world is that we have to open our data. We have to share. That is the secret to future success.* (RE1)

> *We should be exchanging expertise. We should be exchanging data and output. I think we need better interaction in the scientific community to make stuff from that data and interpret the results properly. It would also help the reproducibility problem. All the good data which is being produced on single-cell technologies, clinical samples, and all that … but then one analysis' results can be completely different from the other, so we have to cross-validate our results.* (RE5)

However, **cooperation is not always an easy task** yet, not even among researchers from different fields.

> *A couple of years ago – it was also in the newspapers – one professor, an experimentalist, called the computational scientists 'parasites'. He called us parasites just because we use their data. We don't do it without permission, obviously, the data is public because it's produced on public money. The data has to be public, it's public's property, taxpayers' money.* (RE5)

Cooperation among **researchers and clinicians** – which is consistently reported as an increasingly urgent necessity – can be even more challenging.

> *Scientists need to know what the unmet clinical need is. We need to ask the clinicians, 'what do you need?' And clinicians to tell us scientists, 'Can you do this for us?' That's how it should always work.* (RE1)

> *I think it's not easy. I mean, in the ideal world, we would want to have the basic, translational and clinical research as close as possible, but they have quite different approaches and different rules, and they are not necessarily mixing. (…) I think it's a different research philosophy, and maybe also a different ethics about how to use patient data. I think that this is actually quite a complex issue. The way I see it, it's still quite separate at the moment, but (…) more connection will be definitely beneficial.* (RE3)

> *I think an important aspect is implementation research. (…) It's not easy to just tell people, 'Now you should collaborate, and you should do this together', because people are asking questions like, 'who has the responsibility? Who is responsible for what? Who has the final responsibility for the patients?' There's a lot of questions, and I think the implementation in itself is research. There are people working with implementation research, and I think that domain is very important.* (RE4)

Some interviewees, among researchers, suggest that clinicians tend to be more conservative, not always welcoming the **introduction of new technologies** deriving from basic research.

> *It's a cultural issue. It will change. My perception is (…) that research institutes are more open to collaboration, and clinical departments are still more closed. That's changing, but probably it's changing little by little. Of course, it depends on every particular hospital, every particular department.* (RE2)

> *The clinicians are broadly quite conservative in their approach to introducing new technologies, so they like everything to be carefully validated in independent cohorts of patients. I don't think that will change with these new technologies.* (RE6)

Others, instead, acknowledge that **medicine already changed a lot** and will continue to do so.

> *Medicine has changed a lot over the years as well. There used to be a consultant who would be in charge of everything (…), but now people realise that no one person can actually hold all this information. (…) Clinicians get together and make joint decisions. So, I don't see any reasons why, if you've got this extra layer of information, this wouldn't feed into the same process. They'll use it and adapt to it just the same way that the medical professionals adapted in the past.* (RE7)

Training and education, for both researchers and clinicians, are considered key strategies to support collaboration.

> *I think that – as always – some scientists are* [ready to cooperate with clinicians] *and some are not. (…) I think one course that they should have in university would be to learn how to be open and how to collaborate.* (RE1)

There already exist **practices** aimed at bringing the research and professional culture of researchers and clinicians closer since the beginning.

> *I think this* [obstacles to collaboration] *is happening more in Europe. I was in the US a few years ago, and MDs and PhDs were mixed together, and MDs were heavily encouraged to be involved in some research. (…) I think here is where we need to work more in Europe. In fact, in our hospital, we are*

forcing a little bit that our clinicians do a PhD, be it clinical research or some more sophisticated research, but we want them involved in that. (…) But in other hospitals, they are separated and work independently. We need to find a proper balance. (RE2)

Training is needed also in connection with developments in **artificial intelligence**, so as to be able to manage the huge amount of data that new technologies are making available, but also to support **interdisciplinary work**.

For sure, to a significant degree, medicine is going to change. It is getting more and more clear that progressively, because of big data and predictive analytics, physicians will need to have some background of mathematics. (CL2)

From my perspective from working in a research institute within a hospital, the great challenge is the access to artificial intelligence. (…) This concerns me greatly. We should connect clinicians with informatics and with technologies in this -omics approach. That's essential if we want to advance in this field. (RE2)

Inter-disciplinarity is okay for somebody at my stage. I'm senior, it's good for me to work with many different teams. But for young PIs who have to establish themselves, it is probably more difficult. It's difficult to emerge as a single scientist when you need all this expertise. That immediately tells you that we need to teach people how to do all this. (RE1)

Interdisciplinary work also needs **new ways of organising research and clinical work**.

When I was getting a PhD, you could still do anything as a single scientist. Now, you need to incorporate all expertise: the biochemist, the molecular biochemist and artificial intelligence, and work with many different teams. Of course, this provides a lot of opportunities, because by integrating all this different expertise you can really move forward. (RE1)

Definitely, we're getting into a stage where the technologies are getting incredibly complex. It's very difficult or even impossible for one person to grasp both the experimental complexity and the complex analysis that has to be done. Definitely, these approaches are becoming very interdisciplinary. They do require people working together, people being able to communicate together well (…) and share data. They're also pretty expensive. It's also something that cannot be really limited to one research group to be successful. This kind of research simply requires some teamwork. (RE3)

Cooperation efforts are however undermined by the concurrent process of **hyper-competition for accessing funds**, considering the shrinking of national research funding and the high costs associated to new technologies such as those LifeTime is focusing on. This gives way to the phenomenon of overpromising in applications for research grants and, in general, holds back open data policies.

Overpromising is an issue, and I don't think that there is a solution to that. We have to overpromise because we are competing for very limited resources. We all have to polish our project proposal ideas to get the funding. (RE5)

I feel that the whole system, how science works at the moment, invites overpromise. You're supposed to write grant proposals that cover five years and that will set the world alight. Well, that's hard to do and it's hard to get the money as well as be truthful and not overpromise things. That's unfortunate, and some people will commit fraud in that process. (RE8)

Scientists always have to sell well what they want to do in order to get the funding. There's a risk for that. I'm not sure that we know in which time frame we will be able to answer a research question, but that doesn't mean that it's not money well spent. (RE1)

This whole bundle of transformations underway already started having an impact on how health care is provided. In the next decades, new technologies, increased inter-disciplinary work and the shortening of distances between research and clinical practice are expected to translate into a substantial **re-organisation of healthcare services**. The **empowerment of patients** – thanks to communication and information technologies applied to healthcare – is part of this picture.

The **trend towards out-patient care** is often stressed, connected with a focus on **prevention** and anticipation of illness, so that healthcare systems will revolve around diagnostics even more, including **remote diagnostics**. Some interviewees, among clinicians and patient groups representatives, reflect on the change process.

I think it's really clear that it's going more and more to out-patient care, and I think there might be very different models in the future, with the advent of more active patients, and also the fact that they want to have more control on the decisions, so it might be a very different model than we have today and I think it will be very interesting to see. (CLI1)

Any period historically is characterised by certain patterns and models of healthcare provision. Nowadays, we are already talking about hospitals without wards and bedless hospitals. (…) Talking about the next 30 years, no doubt, many things will change because of electronic and personalised medicine, especially for diagnostic purposes and to some degree for therapeutic purposes. Sensors will characterise everything. If you have the opportunity to provide your symptoms through a computer, why not? If you have the opportunity to analyse everything daily with one drop of blood, why not? If you have the opportunity to analyse even your genome at a distance, why not? (CLI2)

For some things we will still go to the doctor, but most likely we will be connected with our doctor, and we have already technology for that. We can share certain health data online via applications or via specific devices, and we are already going towards that way. (…) The system will change, and healthcare officials will need to be trained completely different to be able to cope with that in the future. (PG2)

Transformations towards **multidisciplinary care** are already happening in some expert care centres, providing coordinated, patient-centred care **in close connection with research centres**.

I think patient-centred care, where you have different specialists around the patients, is really important and will help the treatment. That's really good. It happens in expert centres, that can be linked to an academic hospital or research centre, where they have the most up-to-date information and resources. They do that in Belgium. They have all the disciplines that treat certain symptoms like psychologist, physiotherapist, neurologist, et cetera, all at the same place. You go there once, and you can see everyone. I think this is very, very good. (PG5)

Networks connecting such centres can also be instrumental in promoting **successful open data policies**.

We have a European-level reference network which is a centre of excellence. (…) It is organised in a way that the data and the registries from the centres will produce knowledge and this knowledge will not be in the hands of one or two persons. It will trickle down to the reference centres and the doctors. For us, it's very, very key and it is a best practice at European level. (PG3)

REDEFINITION OF PROFESSIONAL AND ORGANISATIONAL ARRANGEMENTS
Key points to highlight from the interviews

- Respondents agree on the **need for more extensive and direct cooperation** among all the actors concerned with the development of precision medicine. This entails closer relations between researchers from different disciplines, between researchers and clinicians, as well as new working models in both research and clinical work.
- Although this process is already ongoing, **different factors are reported as hindering a closer cooperation**, especially when the relation between researchers and clinicians is concerned. They relate to, e.g., different attitudes towards innovation procedures (clinicians tend to be perceived by researchers as conservative, and clinical departments not so inclined to cooperation), different priorities (clinicians seem to be more worried about the allocation of responsibilities over research clinical work) as well as different research philosophies, epistemic frameworks and ethical sensitiveness.
- Another factor playing a role in that is the **extreme competition characterising the research environment**, especially for accessing research funds, which is producing distorting effects (e.g., overpromising about research outputs and benefits) and risks weakening cooperation links among researchers.
- **Respondents evoke different tools to manage these factors**, including training activities, especially targeting young clinicians, new research and clinical practices to pave the way for a more comprehensive re-organisation of healthcare services, promotion of open data policies, a greater focus on out-patient care and illness prevention, and reinforcement of remote diagnostics. The current, increasing empowerment of patients, especially through the extensive use of communication and information technologies applied to healthcare, is considered a key component and an enabling factor of this process.

3. New data-management aspects and dilemmas

3.1. Inputs from the literature review

The availability of increasingly larger datasets and biobanks is both a key and promising perspective and a potentially controversial area. A large literature is now available about **risks and ethical concerns** related to the establishment, management and use of personal data and personal biosamples.

Different issues can be mentioned in this regard:

- The **ownership of data**, which concerns, e.g., who is the owner of genetic data, who can exploit the data and for which reasons, how the access from third parties should be regulated and who should ensure that such regulations are respected (Australian Health Ministers' Council, 2017; Fangerau, Marx-Stölting, & Osterheider, 2019)
- The **protection of personal data**, which may concern aspects like regulations and practices related to the storage of data, the exchange of data, the use and reuse of data, or the protection of individuals' privacy (Nicholson Price II, 2017; Nuffield Council on Bioethics,

2018; Feiler, Gaitskell, Maughan, & Hordern, 2017; Future Advocacy, 2018; Blasimme & Vayena, 2019; Fangerau, Marx-Stölting, & Osterheider, 2019)

- The **rights connected to data,** often referred to as "**biorights**" (Caulfied & Murdoc, 2017), such as the right to access one's own data (especially when they are saved in private databases) or the right to keep a control over the use of one's own data (Salari & Larijani, 2017).

One of the underlying issues is finding a **balance between "genomic solidarity**" (based on the idea that biosamples and genetic data can be equated to public goods to be used for the benefits of all) **and privacy issues** (King Baudouin Foundation & Sciensano, 2018), especially when doing science is strongly motivated by market opportunities (Capps et al., 2017).

The issue of managing the **tension between the needs of research and the need of individual patients** is becoming increasingly salient, since research and patient care are shaped by "different interests, objectives, duties, and rules" (Stemerding & Krom, 2013) which are often in conflict with each other.

A relevant, cross-cutting issue is ensuring correct and effective technical, organisational and regulatory **management and integration** of **biobanks** (see, for example, Kaye et al., 2016) as well as their **financial sustainability** (Yuille et al., 2017), so as to guarantee a high level of data protection.

Another aspect entailed by the advancements in LifeTime research and technologies in the context of personalised medicine is the application of **informed consent**. Although informed consent is a prerequisite for genetic testing, its application is becoming more difficult to implement because of different factors.

One factor is the **increasing complexity of the information** obtained through genome and single-cell analyses. Indeed, it is difficult to obtain a truly valid informed consent when patients are not in the condition to fully appraise all the implications of the testing process and the possible uses of the information produced (King Baudouin Foundation & Sciensano, 2018). Hence the need to associate informed consent with a greater level of "genomic literacy" of patients and citizens (Salari & Larijani, 2017; Australian Health Ministers' Council, 2017), allowing them to better manage their consent.

Another factor concerns the **duration and use** of personal data. In a context where it is increasingly hard to predict who will be accessing the data in the future, for which purposes and under which conditions, the traditional concept of informed consent is challenged, since informed consent should be specific about the duration of the use of personal data and contain clear limitations. This is problematic for researchers, since research may lead to unpredictable uses of genetic data and biosamples, and it is problematic for patients too, since the possibility to withdraw consent is practically impossible (McGuire & Beskow, 2010).

To address these problems, some (Fangerau, Marx-Stölting, & Osterheider, 2019) have thought of a "**dynamic consent**", i.e., consent which can be kept dynamic so as to avoid that researchers should constantly have to obtain new or updated consent, or a "**broad consent**", i.e., consent which is all-encompassing and open-ended (against a targeted and specific "narrow consent"). However, according to some authors (see, for example, Blasimme &

Vayena, 2019), the infinite uses of data and the linkage of disparate data sets make even the notion of "broad consent" too weak to be usefully applied.

Similar problems also emerge when the issue of **confidentiality** is considered. Genetic data are expandable to families and next generations and can influence their quality of life, since they can predict the risk of future diseases in individuals or their offspring. Therefore, it is not clear how to manage the issue of confidentiality when other persons are *de facto* concerned. **Interfamilial privacy issues** and the **right of family members to be informed** about the risk of a disease which may influence their life should be balanced against the patient's right to privacy (McGuire & Beskow, 2010; Salari & Larijani, 2017). This could also concern other rights related to pregnant women, newborn children and foetuses, people with disabilities (including mental disability and dementia) and deceased persons (Australian Health Ministers' Council, 2017).

Still another issue is the risk of social, ethnic, and gender **profiling** (or profiling according to other categories), potentially leading to forms of **discrimination and stigmatisation** of large groups and subgroups.

Risks of "**genetic discrimination**" (i.e., forms of bias and social profiling based on genetic data) already exist (Australian Health Ministers' Council, 2017), but may **exponentially increase** with the development of personalised medicine, which could amplify the problem by considering even slight genetic differences which may have a relevant biological and economic impact (Salari & Larijani, 2017).

The psychological and social effects related to the **fear of being discriminated against** are also to be considered. This emotional attitude largely varies across sub-groups and social contexts. For example, concerns for genetic discrimination appear especially high when issues like the **access to insurance protection** are considered (Salari & Larijani, 2017) or in relation with specific groups of patients (for example, those affected by Huntington's disease), who perceive more than others the risk to be exposed to discrimination (Wauters & Van Hoyweghen, 2016). Although genetic tests cannot be presently required to people asking for a health insurance, law and regulations largely vary across countries and are constantly modified over time (Lefebre, Pascutiu, Salgaonkar, & Zimmerman, 2019). Hence the risk that genetic testing may lead to unfair access to care, unless citizens prove to be particularly active in protecting their right (Keogh & Otlowski, 2013).

As mentioned, the **use of AI in healthcare** may also favour discrimination because of "the use of biased machine-training datasets that lead to sub-optimal performance for underrepresented social groups creates an ethical bottleneck" (Blasimme & Vayena, 2019).

It is also to consider that **normative approaches** aimed at addressing genetic discrimination suffer from important limitations, implying rigid formulations, lacking public visibility, ensuring narrow protection and being characterised by complex implementation procedures. This could suggest that fighting genetic discrimination only using the law is not necessarily the best strategy to adopt, unless it is supported by a strong engagement of and negotiations among stakeholders (Joly, Feze, Song, & Knoppers, 2017).

The **involvement of citizen in the active management of their own data** is also suggested, and takes sometimes the form of **citizen science**, favouring the direct participation of citizens and patients in setting research agendas, partnering with academic investigators, analysing and

disseminating results, and learning from research in the context of personalised medicine (Petersen et al., 2019).

3.2. Inputs from the interviews

All interviewees have shown, even if to different extents, to be **aware** of the existence of several, serious risks connected to data management in the context of genetics and genomics research, potentially exacerbated by new powerful technologies such as those promoted within LifeTime.

However, there is also awareness, particularly among researchers, that it is **very difficult to properly manage such risks**, along with the concern that doing so would imply strong **limitations to research**. Some – especially among the interviewed clinicians and representatives of patient associations – tried to identify possible **solutions**, generally in the form of establishing different forms of **partnerships with patients** and their groups to jointly protect and manage the data (in some cases based on already existing initiatives).

As mentioned, it is not questioned that the problem exists.

> *I think this is one of the challenges that we face as a community, how we can really deal with this. (…) It's really, really clear now how important ethical issues behind this are. The way you treat the data … Is it really true that no one can in any way go back to who the patient is? I don't know how this could be managed, but definitely, you need to have people that are trained exactly on how to do this.* (RE1)

> *A legal issue which we have already is how to manage the information that links one single cell to one single patient and all the -omics information. That needs to be blocked somehow. You access it because it will have meaningful information that relates to some novel therapeutic approach. It will be great if we can apply the therapy to that patient. But the legal issue for me is to block wider access to this information about the single patient.* (RE2)

Some have very pessimistic opinions about the possibility to actually address the problem. They also broaden the focus **from research to society at large**.

> *I'm not a law person, but if I had to freely express my view, my opinion is that despite all these new laws and regulations developed in the last decade, privacy is a lost case, because hacking is very easy (…) and it seems that violations will always be possible. Digital data are so well organised that it is at the same time easy to hack them and to transfer them in a massive way. I have a very pessimistic view for privacy, and even for democracy, in the next decades.* (CL2)

> *I think that it's probably one of the biggest problems that faces society in general, not just in this area, and it's about the balance between privacy and having such data available. (…) I mean, Google … they know more about you than you yourself know. And so far, those holding the data have lost people's account numbers, they've lost their passport numbers, they've lost their bank card numbers and so on.* (RE6)

For a patient group's representative, however, **the issue needs to be addressed urgently**, before patients lose ownership of their own data.

> *One thing that it is very important when we move forward with new technologies and all, is to make sure that laws, policies, regulations are in place before it is too late for patients and they lose control and ownership of their own data.* (PG1)

Data ownership is indeed brought up and questioned in several interviews.

> *Are data supposed to be completely private? Are those my data, are they community data?* (RE1)

> *That's one issue too … who owns the data. I see that the right owner is obviously, at least for me, the patient itself, but currently this is really a grey area. The investigators can say that they're the owners, the hospital can say that no, it's the hospital who owns the data, and if there's a research institute that does some sequencing or the single cell analysis, they can say it's their data.* (CL1)

> *DNA data sets are a major public resource and cannot be considered only under privacy regulations.* (CL3)

In this perspective, researchers (but also some clinicians) complain that too strict regulations risk severely **hindering research advancements** and sometimes even **proper treatment**, while current solutions do not seem sufficient.

> *We are all very keen to look at the data and to explore it, but it's actually extremely hard because of the restrictions that have been put on data sets, which make them of less value to researchers. There is a balance to be struck here. (…) A lot of my colleagues complain about how difficult it is to use the data.* (RE8)

> *Until a few years ago, it was easier than it is now. We cannot even touch a sample if there's no consent from the patient.* (RE1)

> *Privacy regulation are getting stricter all the time, and now it is also becoming more difficult to move patient-level data from one centre to the other and make bigger data collections. (…)* [There are] *solutions like federated analysis, where you just send the analysis code, while individual-level data remain on local servers, and you can do it that way, (…) but this requires quite a bit of work. That's clearly something that needs to be taken into account, as it's really crucial for personalised medicine that you access big databases, because you treat one patient at a time, so you need to put the results into a larger context and you need data from many patients.* (CL1)

The situation is made even worse by the existence of **different national regulations**. The problem is also highlighted by the representative of a patient group operating at the European level. A solution along the line of federated analysis is again suggested.

> *Last week we had a meeting here about the new rules and the new legal requirements* [at the national level]*. The problem is that at the EU-level we have same rules, but still, from country to country, there are some differences, and this makes research very difficult.* (RE2)

> *We have been in several committees to look at those things and it looks like the national barriers are terrible, because you have laws that are different from one country to the other, and even in the same country. It's very difficult to manage those things. My guess was that the best option would be to create European consortia with one institute in each country, so then you don't merge the biosamples (…) and keep them within the country, but you aggregate data anonymously at European level.* (PG3)

In a different perspective, the representative of another patient association suggests that regulatory frameworks are **lagging far behind research advancements**.

> *My opinion is that the topic is treated very superficially from policymakers and patients as well, while the research is advancing much faster. All the issues related to ethics, data handling, safety and*

security for patients and, as I said, citizens in general, are not progressing as much as research. There is a lot of superficiality on this. (PG1)

Other interviewees suggest that regulatory frameworks could be even **lagging behind the actual attitude of patients and citizens**, and they should definitely adapt to the **different use** data collection is meant for.

I feel that perhaps the public is more involved than researchers and funders are. Many people are happy to send their DNA and have [researchers] *store that data and use it to try to find new drugs, for example.* (RE8)

I think it depends on how the data is ultimately used. If you ask people, 'Are you happy for your data to be used for cancer research to find the next new fantastic cancer treatment', everyone will say yes. But [if you ask them]*, 'Are you happy for your data to be used for insurance companies to work out who they should charge more and who they shouldn't' … or 'for politicians to work out who they should target', then the answer is obviously no. The problem with trust is when the data is misused, like Cambridge Analytica. (…) I think there are often barriers to legitimate research, but the data is actually used for things that are much less legitimate without the same barriers.* (RE7)

Most patients, I think, want as much data as possible to be researched, so that they get a clear view of the disease. Many people are like, 'Let's use as much data as possible. Let's give them really a good understanding of the cause of the disease'. For that, we need data. (…) Of course, the awareness about the use of the data is important to stress. (PG5)

The representative of a patient association reports their varied experience in this regard, and how they try to **build openness and trust**, still based on the purpose of sharing personal data.

Some patients are saying, 'I don't want to see my samples or my data used for something else' and, of course, we are always saying, 'Yes, you're right. We have to prevent the misuse [of data]*, but you also have the responsibility to be part of this science development'. I'm always saying to the patients I'm dealing with, 'You are benefiting today from people who have been working with the scientists 30 years back, and they have been sending samples and all that. They have created the knowledge that you are benefiting from now'.* (PG3)

In this perspective, a sort of **data solidarity** exists, that needs to be encouraged.

Our key message is: you have the right to be treated, you have the right to have a fair treatment of your disease, but you also have the duty to sustain research development. (…) No knowledge without data, no knowledge without biosamples, no knowledge without research. That's the point of view of the patients, I would say. (PG3)

Building on these attitudes, **partnerships between researchers, clinicians and patients** are being developed, to guarantee both the right of citizens to see their personal data protected, and the interest of researchers and clinicians – and society in general – to support the creation of new knowledge and the identification of more effective drugs and treatments. Some suggest launching a **social dialogue** among researchers, citizens and policy makers.

Well, the patients should manage their own data. That is the only way. Then, their data can be used for clinical and research purposes. There must be a partnership agreement between the patient, who is the ultimate owner of the data, and the public health sector for clinical reasons and the research sector for research purposes. (…) The problem is that this relationship should be transparent and clearly regulated. (PG1)

I agree that we need to advance technology and help research to advance. These issues would need to be discussed with society, around security, etc. in a social dialogue, forming the basis for a new type of social contract within societies, where people negotiate solutions with policymakers. (…) This is what we want, these are the guarantees that need to be in place, so that we can move forward. (PG2)

Citizen science arrangements – where citizens actively cooperate with researchers and clinicians in the research process – is mentioned by some as a tool to **empower patients to manage their own data and contribute to research** without losing control over them. An example is provided by the representative of a patient association.

You can empower people to participate in science. (…) We are building a platform where citizens can securely collect their data, (…) as secure as it is possible nowadays. You collect your data and it's only your data, it belongs to you, but you can share it for clinical trials or with different researchers. (…) We will empower people to collect the data, but also to compare it with data from others, for instance if you have like a sensor to test for blood sugar, and better understand how you are doing. This is what we guess would work, for both citizens and research. (PG4)

The complexities around data management issues are reflected in the difficult **management of informed consent**, which can create obstacles to research. In general, in informed consent,

You have to be very clear with patients. What we will do and what we will not do with those samples, and how that information will be managed. (RE2)

This, however, can create problems when researchers want to **re-use the data** for different purposes than the original ones, even if still aiming at research and clinical outputs. Patient associations involved in citizen science find the same obstacles.

We cannot do, for example, a retrospective study because we cannot access the patient's data. (…) They didn't sign 20 years ago the consent for the study. What can we do with that? (RE2)

There was one project [the association was] *involved in where there was the idea of using biosamples that were used for genetic diagnosis long time ago. They have been conserved in a biobank, and now the project was trying to use them to see, with new technologies, what would have been possible to diagnose on those samples and confront this diagnosis or prognosis with the real life of the patient. We had very strong difficulties because the consent was given for diagnosis and not for something like research. It was a nightmare, I would say.* (PG3)

Also new research can have the same problem, that is, not being able to clearly define all the uses that will be made of the collected data. The representative of another patient association, still involved in citizen science efforts, reports having started to work with **data pioneers** (a smaller – more experienced – group of patients), paving the way for the involvement of a larger group.

We started with the Citizen Science project and we said, 'Okay, we make a first cohort and then we call these people Data pioneers'. These people get a share of the stage and this is like a small clap. We want to start with this because it's very difficult to explain everything in the consent form. You can explain, but no one will read 200 pages, and to write these 200 pages, it takes some time. This is why we decided to start with this small group of people who understand what we are doing, because they're experienced already. Then, when we will be running the big cohort, next year, we will think about more details of content, but we already have this experience with the pioneers, which makes it easier for other people to join. (PG4)

A last issue connected with data management issues in the context of new genomics-related technologies – and particularly artificial intelligence – is the risk of social, ethnic, or gender **bias and profiling** (or profiling according to other categories), potentially leading to forms of **discrimination and stigmatisation** of large groups and subgroups of the population.

As for **bias**, it is observed by some interviewees that the **datasets used for the AI algorithms** can already be biased, for instance by including or excluding certain groups. This will then inevitably affect the results that the algorithms will produce.

> *Underrepresented groups are also underrepresented in genomic efforts. That's really a matter of fact (...) and we need to change that. We need to, because we can learn from the genetics of different ethnic groups.* (RE1)

> *Samples are mostly coming from Western societies and more local ethnical screenings have to be done to offer alternative therapies to different genetic backgrounds.* (RE5)

On the other hand, privacy regulations risk making the effort of diversifying datasets less useful, if **national/ethnic provenience** cannot be tracked, with potential negative consequences also for patients and treatments.

The problem exists. I tell you that by one particular project we are running now. We are working on childhood obesity. We have now seven hundred samples or so. We cannot access the ethnicity of these patients. On the one side that's great, because of potential bias, but on the other, [that info] *is super important, because not all ethnic groups have the same risk of obesity. (…) The same is true for gender, etc. The more information we have, the better. (RE2)*

The risks that genomic data, when used to different purposes, can lead to discrimination and stigmatisation on different grounds, particularly through the opaque mechanisms of **AI algorithms** creation, is recognised by many of the interviewees in all categories (researchers, clinicians and representatives of patient groups).

> *There's a big ethical issue beyond that, that's extremely important.* (RE1)

> *The utilisation of this information to other purposes can be absolutely biased. It's a risk.* (RE2)

> *I think it's a concern. I think there's always a bias whatever we do. We have personal biases and we have societal biases, but then the question is that if we rely on machine-generated decisions, will that be less or more biased? It will be biased anyway, because it depends on who programs that and their biases, so it's not realistic to say that we will have a non-biased system. It's something that we need to think about and have controls for. However, I still think that the machines could be potentially less biased than humans.* (CL1)

> *The risk is there, and it is a huge risk. Again, what happens if there are leaks in the information system, in the technology, what if the information ends up into the hands of the wrong people?* (PG1)

Other interviewees, mostly clinicians and researchers, while acknowledging that there could be a risk of profiling and stigmatisation in the diffusion of large datasets and biobanks, tend to point out that **discrimination already exists**, and it needs not this kind of sophisticated information.

Discrimination based on genetics, well, it's already being done. Most of the time, you can see someone's genetics just looking at their faces. (…) You don't need the data. You can discriminate based on accent, based on colour. (RE5)

If you want to discriminate, you can start just looking at the colour of the skin. (…) I don't think that if we had the opportunity to store massively the genome of the whites or the genome of the blacks, this will represent a specific challenge. (CL2)

It can happen, but I still think that discrimination will always be more on a cultural and social basis. (CL3)

This is a social problem, and discrimination has been here for ages. (CL4)

A specific form of discrimination risks derive from the very fact of **defining someone as "sick"**, which is something that single-cell and other technologies could anticipate indefinitely before the onset of symptoms. Insurance issues are the most frequently reported consequences.

Knowing in advance is a double-edged thing, because knowing more, knowing better is one good thing, but it can also be difficult. (…) One of the problems of knowing in advance about the disease is that when you have to sign a document, like if you buy a house, or if you have to sign for insurance, you have to declare that you are in good health. (…) Then if you know something, then you have to declare it. Of course, no one is able to verify that it's true or not, but if it happened something to you related to the disease that you have not declared, then you will suffer consequences. We are confronted to this already now. (PG3)

I could imagine that in the countries like the USA, where the system is much more based on private insurances, finding out things about you, about your kind of health or DNA or whatever could be leading into some kind of discrimination. (RE3)

We need to be a little bit careful, because if such data will be, for example, disclosed to insurance companies, you can have a problem. This is particularly true where, like for example in Switzerland, there's no government insurance but only a private insurance system, and people need to pay for their insurance themselves. (PG4)

NEW DATA-MANAGEMENT ASPECTS AND DILEMMAS
Key points to highlight from the interviews

- Respondents are **well aware** of the existence of several, serious risks connected to data management in the context of genetics and genomics research and the necessity to urgently address them. However, most of them also recognise that it is very **difficult to manage them properly** and some are even **pessimistic** about the possibility to find real solutions.
- **Different kinds of critical issues** related to the management of data and biosamples are identified by interviewees, including data ownership, presence of different national regulations impeding a coordinated European policy, delays in the development of legal frameworks for scientific and technological advancements (and in the corresponding evolution of patients' and citizens' attitudes), management of informed consent, risks of discrimination and stigmatisation of groups of people based on genomic or single-cell related information, and limitations in accessing insurance and credit services.

- **Possible solutions**, according to respondents, could come from, e.g., increased dialogue and partnership among all the concerned actors (researchers, citizens, clinicians and policy makers), development of citizen science arrangements allowing patients to keep control over their own data while contributing to research, open data mechanisms facilitating the exchange of aggregated data, or the involvement of patient associations to reassure and stimulate patients to get involved with the management of their own data.
- Respondents also highlight the presence of an overarching **tension** between the needs for research to access patient data and the patients' right to data protection which, to a different extent, affects all data management-related issues.

4. Effects on the experience of patients

4.1. Inputs from the literature review

Advancements in single-cell biology and personalised medicine may have an impact on the very concepts of health and illness, as well as on personal identity. An increasingly active role of patients and citizens, both individually and collectively, is required in this framework.

As for the **concepts of health and illness**, it has been observed (see National Consultative Ethics Committee for Health and Life Sciences, 2016) that while, currently, illness is defined clinically, in the near future, thanks to genomics and single-cell analysis, diseases will increasingly be intercepted before the symptoms appear, with the consequence of blurring the boundaries between being sick and being healthy. However, genomics and single-cell technologies do not totally coincide in this respect. In fact, while genomics is leading us to think that ill health begins with a predisposition, single-cell analysis additionally allows detecting molecular mechanisms driving changes in gene expression and in cellular function, in populations of cells with mixed phenotypes. In this way, personal behaviours and environmental factors enter even more significantly in the very definition of health and illness, with effects, not only on one's own life, but also on the life one's own offspring (Lo & Zhou, 2018). Hence the need to complement and coordinate "technoscientific" objectivist approaches to the definition of illness, (which hold especially for serious genetic diseases), with a "constructivist" subjective view of what people and patients think about the actually meaning of being ill (Kleiderman, Ravitsky, & Knoppers, 2019).

This is where single-cell medicine and genomics differ the most. The former, in fact, do not share the risk of the latter of supporting forms of **genetic determinism**[4], **reductionism**[5] **or essentialism**[6] (Condit, 2011, Australian Health Ministers' Council, 2017), while posing new questions connected to epigenetic perspectives, such as those related to personal lifestyle or environmental conditions.

[4] The concept of "genetic determinism" refers to the belief that the phenotypic character of human beings (including physiological features and psychological dispositions) is fixed by their genetic makeup (Carrier & Finzer, 2006).

[5] The concept of "genetic reductionism" refers to the belief that biological traits can be totally explained in terms of specific gene functions (Arribas-Ayllon, 2016).

[6] The concept of "genetic essentialism" refers to the belief that genes underlies a person's identity or that human beings as essentially consisting of their genes (Heine, Cheung, & Schmalor, 2019).

As to anticipated diagnoses, they may affect the **notion of personal identity**. This also concerns the very idea of personalised medicine. The French National Consultative Ethics Committee for Health and Life Sciences (2016), for example, highlights that personalised medicine "enters the patient into a narrative that is not limited to that individual's own person, but includes his or her ancestors and descendants". This may have an impact on personal autonomy, affecting individuals' decisions regarding behaviours and lifestyles. In turn, the European Group on Ethics in Science and New Technologies (2015) observes that the advancements in the field of genetics, diagnostics and health information may affect one's perception of "self" and define an image of one's life and body which could be difficult to reconcile with the lived experience. Feiler, Gaitskell, Maughan, & Hordern (2017) also notice that "individual beliefs and values (...) may become submerged in healthcare systems as expectations of the predictive and therapeutic powers of genomic technologies come to dominate the hopes of patients and healthcare professionals alike".

According to different authors, advancements in genomics such as those leading to single-cell biology are showing how the distinction between social life and biological life is becoming obsolete (Meloni, Williams, & Martin, 2016). There is the need to a **new biosocial approach** (see, for example, Hopcroft, 2016; Walsh, 2017; Harris & McDade, 2018) able to analyse and interpret the multiple connections and reciprocal influence of biological and social dimensions of life. Concerns about genetic reductionism (see above) are again out of target here. Single-cell technologies, indeed, lead to a more holistic view of the individual patient, as a biological entity, but also as a consumer, or as a responsible citizen (Vegter, 2019).

LifeTime research and technologies are expected to have implications also on the perception and scope of **personal responsibility for health**. Undoubtedly, these new technologies are **empowering patients** to know, not only that they have a genetic predisposition to a specific illness, but also how aspects of their lifestyle or their environment will have an impact on their health, including that of their offspring (National Consultative Ethics Committee for Health and Life Sciences, 2016). This may also have direct effects on the life of people. Indeed, patients may feel they are "left alone" (PerMed, 2015), since they are asked to become more responsible for managing increasingly complex treatment regimens. Hence the importance to reinforce the support which may be provided by patient advocacy groups and networks of patients with the same disease.

The increasing responsibility of patients and the increasing use of medical devices outside health centres may also lead to **new forms of surveillance** (Blasimme & Vayena, 2019) and "**medicalisation" of society** (European Group on Ethics in Science and New Technologies, 2015), which could have distorting effects on people's freedom in managing their life and health.

In this framework, **patients and citizens engagement** becomes crucial in the socialisation process of the new health-related technologies (see above, Part One). Personalised medicine is based on a **proactive role of patients**, for example in providing information, deciding about their personal data and taking clinical decisions (Nuffield Council on Bioethics, 2018). This seems to be even more necessary with the massive use of AI in healthcare (Barret et al., 2019). Patient engagement is expected to have also positive impacts on patient compliance (Evangelista & Shinnick, 2008), improvement of patient outcomes and reduction of healthcare costs (Sarasohn-Kahn, 2013).

The **role of citizens and citizens' groups** is also expected to become increasingly important in public health, for example in addressing inequity in the involvement of different population groups, in orienting health research or in setting priorities for health policies (Corbett, d'Angelo, Gangitano, & Freeman, 2018).

Therefore, the question is how to support patients and citizens enabling them to perform these roles. One way is increasing **"genomic literacy", awareness levels** and **education** of patients and citizens (Parker, Bakken, & Wolf, 2016; Ginsburg et al., 2016; Salari & Larijani, 2017; Australian Health Ministers' Council, 2017; Pritchard, 2018), so as to also increase their capacity to obtain, process and understand basic health information and services, enabling them to make appropriate health decisions.

Another way is **citizen science** which, as already mentioned (see Section 3, above), aims at favouring the direct participation of citizens and patients in setting research agendas, managing personal data, partnering with academic investigators, analysing and disseminating results (Petersen et al., 2019). However, citizen science can be difficult to access for different reasons (social conditions, education levels, age, etc.). It is therefore important to **diversify tools and policies in the development of personalised medicine** in order to take into consideration "the heterogeneity of backgrounds, abilities, and resources among citizens" (Budin-Ljøsne & Harris, 2015).

4.2. Inputs from the interviews

As to the notions of health and illness, it emerges from the interviews how the fact of **being acknowledged as "healthy" or "sick"** has profound social and psychological implications. While this is particularly sensitive when genetic predispositions are concerned, it is on the other hand also hard to address when it is directly connected to one's lifestyle or living conditions (in the epigenetic perspective), creating a lot of day-to-day stress.

A first concern is that of being discriminated against, or anyway isolated from the rest.

> *I get surprised over and over, how sensitive this is. (…) We're just trying to help patients and identify those who are at risk, so the intention is to support and help them. From my side, I have difficulties in understanding it, but my experience is that some people are interpreting this information in a different way than I do. You say, 'You require a different treatment because this and this, you have this gene …'. It doesn't imply anything negative. But somebody will say, 'Well, why do you single me out? Why are you saying I'm sick?'* (RE4)

One of the promises of single-cell biology, that is, anticipated diagnoses, adds another crucial factor, which is time. **Prolonged time** (either before the illness shows, or during a chronic disease) makes the notion of being sick less recognisable and acceptable, as reported by the representative of a patient association.

> *The concept of illness varies from person to person. (…) Working in this area, I'm realising that people who have chronic conditions don't feel ill. (…) It helps them to feel better. Cardiovascular patients, they don't feel they are patients. They know they have a cardiovascular disease. They only feel patients when they are hospitalised, or when they have an incident. When that passes, they're just fine. If you ask them, 'Are you a patient?' They will say no. You say, 'But you have a heart condition'. 'Yes I had. Now I'm taking my medication, I'm fine'. (…) And if the doctors are able to predict whether*

I'm going to develop an illness in the next 10 years or 20 years or 30 years ... Does this make me ill? No. (PG2*)*

Indeed, knowing to be ill entails a lot of **psychic stress**, as well as knowing you will get sick in the future.

With more and more personalised medicine, (…) we really need to make sure that all the ethical filters and barriers or challenges are taken into consideration, including preparing psychologically the patient. Because for me, knowing today that I am at risk to get cancer in 10 years, it has a huge psychological impact. Also, who should know? I should know, but should my employer know? (PG1)

I waited a really long time for the definite diagnosis because I was afraid I would get depressed. (…) I think that's true for a lot of patients. They really don't want to know if they have the disease. (…) Okay, [some say] *I could have done things that I can't do now, like climbing a mountain or something. (…) But I think the majority of people don't want to know it before.* (PG5)

Moreover, if the disease is diagnosed early, but it is going to display much later in life, the diagnosis can have a **disruptive effect on future perspectives**. In genetic diseases, this experience is common.

Some of the diseases are known from the very beginning, but still, they will keep quiet until you are 40, or 50, or even later. So, what can you do with that? If you declare it when you are young, probably you cannot be recruited by some institutions like the police or this sort of things. You are closing doors by knowing things. (PG3)

It happens that **people opt for not knowing** about it.

If you are diagnosed with something (…) which has a long-term perspective, like you are 30, but you may have a disease at the age of 50, this will create you psychological problems and you will not know how to deal with that. When people are confronted with someone telling them about their future, some say, 'Okay, I don't want to know, leave my life quiet. I want to spend my life and I will see'. It's a reaction to a determination based on facts which are 90% sure, but maybe not 100% sure. In these cases, we have as a rule that if there is a very clear way of avoiding that illness, then we should be informing the patients. (PG3)

On the positive side, knowing in advance to be prone to a specific disease can trigger positive reactions in the sense of **prevention** (when this is a meaningful perspective), entailing the assumption of long-term personal responsibility for one's health.

I see that people who know that they are expected, or can be expected [to develop a disease]*, they will change, they will change their lives, they will change diet, food, activity and so on. You can empower people if you give this information.* (PG4)

The possibility of early diagnosis can imply **other undesirable consequences**, beyond psychological stress. Among these, the **excessive personalisation of the responsibility** for one's health, to the extreme of blaming the sick for their illness.

On the long term, it might be that … how can I say that? You will have more responsibility on your shoulders about your own health by taking or not taking risks according to the initial diagnosis, but I don't know how it will be reflected in terms of healthcare. The State can say, 'Okay, I will guarantee you a good health as long as you are following these rules, because it has been defined according to

the specific diagnosis made on the single-cell biology, for instance. If you follow these rules, then I will support you. If you don't follow the rules, if you are taking risks, I may withdraw my support'. (PG3)

Personal responsibility is going to change. There will be precautions built into the system, (…) like, 'From now on, you will be fully aware. You have the right to choose A, which is good, and you have the right to choose B, which will end up being bad, but there will be consequences'. If there are heavy consequences, that's not the right way to go, I think. If it will be like, 'We won't be covering you if certain conditions will develop', I'm not sure that's the right way to go. (PG2)

There are already countries where insurance companies do not pay for cancer treatment if the patient doesn't quit smoking immediately. What if they will also say, 'Well, we don't provide the treatment because you did not behave properly, and you ate too much sugar'? (PG1)

Moreover, an interviewee (still a representative of a patient association) stresses that many conditions are not caused just by genetic or lifestyle factors, but (also) by concurrent **environmental conditions**, thus relieving the excessive responsibility which risks weighting on the shoulders of patients alone. In this case, it would be necessary for the state to acknowledge **shared responsibility**.

In a way, the responsibility would have to be shared between patients on the one side, and then the society on the other side, because if you discover that, for instance, exposition to pollution on diesel particles or whatever is killing you, then you may ask, 'Why should I move to a remote place where I have no job? My job is here, my everything is here, so why society is not trying to create a healthy environment?' (PG3)

Beyond personal responsibility, there could be room for **collective responsibility** exercised through citizen or **patient organisations**, as actors in the position to support the socialisation process of the new technologies avoiding the mentioned risks. To this aim, patient involvement will need to be more active in both treatment and research areas.

Patients, especially younger patients, are extremely active today, and also the role of patient organisations is becoming more and more important, also in directing treatment and directing research. (CL1)

As for **treatment**, the representative of a patient organisation remarks the importance of having **citizens involved since the design phase** in the development of products intended to support patient autonomy.

Health literacy and digital literacy can be a challenge. (…) From a technological point of view, it depends on how systems are designed. Systems need to be designed to allow laypersons to have control over their data and be able to understand the tools they are using. (…) People, whether citizens or patients, or a mix of citizens and patients, need to be involved from the design phase. (PG2)

As for **research**, **citizen science** efforts are to be recalled here, often aiming at making personal data available for research, while at the same time protecting the right of patients and citizens to maintain control over their own data (see above, Section 3).

More in general, patient organisations could take up an **intermediation role** between the different actors involved in managing the transition towards new medicine: researchers, clinicians and patients. An interviewee, on the same line, suggests taking a broad perspective – involving all potentially affected actors – in discussing the implications of the LifeTime project.

We need to promote a sort of synchronisation of all the actors in understanding how the context is changing. (PG2)

I would say that you need to have many different types of associations sitting together with you and preparing, discussing, and progressively elaborating policy issues related to this LifeTime project. Because, again, all patients are different and the people who are not patients, they should also be part of the discussion. (PG3)

EFFECTS ON THE EXPERIENCE OF PATIENTS

Key points to highlight from the interviews

- Respondents – especially representatives of patient groups – largely agree that the new technologies based on genetics and single-cell analysis are **modifying the perception** of being healthy or sick.
- Indeed, the possibility they offer to make early and detailed diagnoses **trigger positive reactions** in the sense of prevention, empowering patients to better manage their own health. However, this same possibility has **social and psychological implications**: it may induce in patients a sense of isolation, or the fear of being discriminated against; it causes an expansion of the periods of time (before the illness shows or during a chronic disease) in which the conditions of being sick or healthy are mixed up, thus feeding uncertainty, stress and discomfort; it may have disruptive effects on patients' future perspectives, to the point that patients might prefer not to know what the future developments of their condition will be.
- Genomic and single-cell technologies also impact the dynamics related to the attribution of **responsibility about health**. Respondents see the risk of an excessive personalisation, which ends up making patients the main responsible for their health (with potential negative consequences on health insurance coverage). This tendency is partially balanced when the role of environmental factors in causing a large set of diseases is highlighted, thus evoking a shared social responsibility on individual health.
- Beyond the opposition between personal and social responsibility, these technologies seem to also have an impact on **collective responsibility**. Not only patients but also citizen and patient organisations are brought to take on a greater role. They are increasingly asked to favour the involvement of citizens and patients in research and in the development of health products, as well as to play an intermediation role in the now more complex and intense relations between researchers, clinicians and patients.

5. Changing role and profile of medical doctors

5.1. Inputs from the literature review

Another aspect to consider in connection with the development of LifeTime technologies and precision medicine concerns the **responsibility and authority of healthcare professionals**.

As highlighted by many, developments in personalised medicine are making medicine more complex and dependent on the use of advanced technologies and large datasets. Increased complexity also implies increased **physicians' responsibility**, while the essence and borders of this responsibility become more unclear because of the involvement of many other actors (geneticist, researchers, technicians, etc.) in the definition of diagnoses and therapies (Salari & Larijani, 2017). Moreover, healthcare professionals' expertise is challenged by artificial intelligence (Nuffield Council on Bioethics, 2018), with the final effect of **shifting medical authority** from human physicians to algorithms (Blasimme & Vayena, 2019), often interpreted as the repository of a **collective medical mind** (Char, Shah, & Magnus, 2018). Moreover, in this scenario, it is uncertain how the established principles of medical ethics (beneficence, non-maleficence, respect for patients) can still be expected to play "the central role in the patient-doctor relationship that they have – or at least can be expected to have – now" (Blasimme & Vayena, 2019).

A connected aspect concerns the **impact of organisational changes** triggered by personalised medicine on doctor-patient relationships. As mentioned, many professional profiles are involved in delivering personalised medicine: geneticists, technicians, physicians from different specialties, and patients themselves (PerMed 2015), thus making it more and more difficult to keep physician-patient relationships actually bilateral. This is expected to **reduce the centrality of doctors**, while enhancing the role for nurses and allied health professionals (Corbett, d'Angelo, Gangitano, & Freeman, 2018).

Among the changes induced by the development of single-cell research and personalised medicine, the aspects of **information and communication** can also be highlighted. Precision medicine provides physicians with a huge amount of information about their patients, and the problem of what and how to communicate to them must be faced. One problem concerns incidental findings (dealt with in Section 7, below). Another frequently mentioned issue is that physicians should learn how to optimise the communication of increasingly complex health information to their patients (Corbett, d'Angelo, Gangitano, & Freeman, 2018). The need to increase the level of information and **education** of citizens on genomics and single-cell analysis should also increase (Parker, Bakken, & Wolf, 2016).

On the other side, medical responsibility and authority is challenged by the growing **autonomy** of patients (Artin, Stiles, Kiryluk, & Chung, 2019) and the tendency towards the **self-management** of care (Oudshoorn, 2011; Thygesen, & Pols, 2016), thanks to the increasing diffusion of personal health devices and Direct-To-Consumer/DTC genetic testing. These tools are reinforcing both empowerment and responsibility of patients (Leachman et al., 2011), modifying their behavioural and emotional patterns (Olivieri & Pravettoni, 2016), changing the role of general practitioners (Chambers et al., 2015) and affecting the relations of patients with healthcare providers (Artin, Stiles, Kiryluk, & Chung, 2019). Indeed, **hyper-connectivity** and **hyper-accessibility** are enabling "patients to establish counter-expertise in the face of traditional medical authority" (Schneider-Kamp & Kristensen, 2019) and determining a

redistribution of roles and responsibilities among all the actors involved, including patients, doctors, nurses, patients' families, and clinical laboratories (Maathuis, 2015).

Finally, the **development of digital apps related to health** must be considered, including portable diagnostic devices. This is not necessarily destined to lead to a disarticulation of doctor-patient relations. When well used, digital apps may also be used to enhance the interaction between patients and healthcare providers (Weiner & Biondich, 2006; Qudah & Luetsch, 2019). Nonetheless, the increasing diffusion of apps and personal health devices entails strong modifications in doctor-patient relationships which both the parties should be able to manage (El Kamel, 2014).

5.2. Inputs from the interviews

Interviewees have generally framed the issue of doctor-patient relations, and the evolution of the role of clinicians, in the broader context of the transformations which have been determined by the explosion of **information and communication technologies**. Other new technologies, such as single-cell and, above all, artificial intelligence, are seen as adding to what is considered and already robust change trend.

First of all, therefore, the change in **patients** is underlined, particularly by clinicians, who feel sometimes challenged by the **more informed and educated** persons they are now dealing with.

> *The roles of the doctor and the patients are changing a lot, meaning that the patients are becoming more and more active on making decisions and selecting treatments and being involved in their disease.* (CL1)

> *Dr. Google is present and working effectively. All of us, even myself, from time to time … I am visiting Google (…). Of course, one of the main future drivers is the better educated patient, and, for sure, we are already facing much better educated patients.* (CL2)

> *The position of the doctor depends on the doctor's knowledge, (…) but today, people know languages, they look for new possible therapies all over the world. (…) They are very informed, and they are much more difficult* [to deal with] *than they were, for example, 10 or 20 years ago. Back then, when you said something as a doctor, they didn't have any possibility to check it, right? (…) Right now, they are searching for knowledge.* (CL4)

> *The bilateral doctor-patient relationship is different now. For instance, I now spend 95% of my time in front of a computer. But also patients have changed. They are now much more informed and able to interact.* (CL3)

However, not all patients are the same. **Generational differences** weigh a lot, with older generations usually more attached to the traditional role – including the social role – played by the doctor.

> *If I see for example my parents, for them, it's important to have a contact with the doctor. They have always used to go the doctor. For my generation … I don't see that people go very often. If you have a cold, usually you don't need to go to the doctor. You just take three days at home. (…) I see now younger people, like my nephew. He is 20 and he always says, 'Hey, we have Google. I can see everything in the internet. I don't need to even to go to the doctor'.* (PG4)

On the other hand, having **a trusted person** helping navigate the many data which are now easy to access about one's health has a value in its own. It also entails an emotional dimension. An interviewed clinician stresses this aspect.

> *This is another big issue, the personal, even emotional relationships between patients and physicians. This relationship, which was tested during the last 2000 years, is no doubt challenged. Many things are getting much more mechanic. For example, now physicians are spending much less time speaking with their patients, because they have the opportunity to analyse in five minutes hundreds of parameters from a drop of blood, (…) but this is really a risk. I don't know, possibly another profession will be developed, something between physician and psychologist or psychotherapist … Because human beings still need to talk with their physician. (…) Technologies like Skype could give the opportunity to physicians to devote some more time to their patients.* (CL2)

Representatives of patient groups very strongly support this view. Reflecting on artificial intelligence and how it could contribute in modifying doctor-patient relations, some stress how the role of clinicians remains crucial for the **interpretation of the data**.

> *Well, of course, artificial intelligence and the use of genomic data will change the relationship between patients and doctors, but, for me, the doctor is still the one knowing how to interpret and how to use the data.* (PG1)

> *You need someone you can trust and will be there for you, and I think the physician is definitely the person who needs to be there. In regard to technicians or other professionals taking this role, I think that's far away to come.* (PG5)

> *Well, the relationship will change, with new aspects added to it, (…) but I hope that the interpersonal relationship will not change. I think seeing a person in front of you and discussing your case … I don't think this can be replaced with artificial intelligence. There's always a … I'm not sure if emotion is the right thing … but this interpersonal connection, I think it is priceless, and any person will be needing that. It might be less frequent, but it remains important. (…) Even when people will be super-digital … I don't see a future where I just talk to a machine about my condition.* (PG2)

Another patient group representative remarks that in any case **not all doctors are currently able to play this role** of interpreting for patients the results coming out of artificial intelligence data and algorithms.

> *If we are moving to this artificial intelligence era, we will be facing something that we know already for genetic diseases. If I send my sample to China, I will get my genome in a few weeks for 500 dollars or so. (…) I will get the numbers, but what can I do with this? The key is the interpretation, and this level of interpretation is in the hands of geneticians and clinicians, but there's only a few of them who can do that in a consistent way. (…) We are producing more information, but we are not producing more knowledge, at the moment. Mastering the knowledge will be the key, and the knowledge transmission between the scientists, doctors, and patients. I can see the parallel between the interpretation of the data from single-cell biology and what we are facing now in genome sequencing.* (PG3)

Some of the interviewed clinicians actually raised this problem, highlighting the need to **improve the ordinary clinician's capacities** to master new technologies.

> *Currently, these technologies (…) are sort of like a black box, and we don't really know how the algorithms were made and why did they come to the decisions that they made. I think we are in the*

early days of that too, and that's going to change. (…) There's a lot of discussion about the need that we have to open the black box and make things more explicit. (CL1)

Of course, the medical schools should change their curriculums to include advanced technological issues even in the pre-graduate studies and health economics. Everything is changing, especially in the field of diagnostic medicine (…) because of big data analysis, predictive analytics, and artificial intelligence. Using all these advanced techniques, it's getting clear that we are going to different levels of medicine. (…) Within twenty years, physicians should be well-educated and in the position to discuss the deep learning algorithm. That will take medicine to the next level. (CL2)

CHANGING ROLE AND PROFILE OF MEDICAL DOCTORS

Key points to highlight from the interviews

- Interviewees generally see the changes occurring in doctor-patient relations and the role of clinicians mainly as a consequence of the explosion of **information and communication technologies**.
- Clinicians tend to perceive **their role and authority challenged by patients**, especially the more informed and educated ones and the youth. Thanks to the access to a huge amount of information, patients are increasingly active in interacting with doctors, making decisions and selecting treatments. On the other side, also the clinical work is changed remarkably. Doctors spend now more time in front of a computer managing clinical data and less time with their patients.
- Although these processes are leading to a deep transformation, if not a weakening, of doctor-patient relationships, many respondents also highlight the **need for patients to preserve and reinforce trust-based relations with their doctors**. Indeed, doctors have, even more than in the past, a decisive role in interpreting the growing amount of data produced in the context of personalised medicine and in helping patients to navigate through them. Moreover, despite their increased autonomy, patients – in particularly stressful situations – still express the need of emotional support from their doctors.
- Some interviewees (including clinicians) are doubtful of the **capacity of doctors** to play a greater role in interpreting clinical data for patients, especially considering the expanding weight of AI technologies in diagnoses and therapies, necessarily managed according to the "black box" approach. Hence the importance to update the curriculums of the medical schools so to allow physicians to learn how to better master these technologies in the future.

6. Effects on access to care

6.1. Inputs from the literature review

Personalised and single-cell research, technologies and therapies are costly. Therefore, ensuring **fair access** could be difficult.

A first issue highlighted in the literature is access to **screening technologies**, the use of which is destined to become a business-as-usual practice. However, this process may proceed at a different pace for different social groups. Hence the need to ensure that "citizens who are not accessing these technologies are included in the healthcare system on an equal basis and not become second-class citizens" (King Baudouin Foundation & Sciensano, 2018).

A similar problem emerges when access to **new diagnostic and therapeutic technologies** is concerned. These questions affect many aspects including the allocation of research funds on a higher level, right down to the level of individual patient care. The problem is avoiding that only a limited number of patients or self-paying patients could access advanced technologies such as single-cell analysis. The exclusion of specific groups from these technologies due to excessively high costs should be anticipated and prevented. Patients with rare illnesses are especially at risk in this regard (Fangerau, Marx-Stölting, & Osterheider, 2019).

The **benefits of AI in healthcare might also not be evenly distributed**. As anticipated in Section 3, AI might work less well where data are scarce or more difficult to collect or render digitally. This could affect people with rare medical conditions, or others who are underrepresented in clinical trials and research data, such as Black, Asian, and minority ethnic populations (Nuffield Council on Bioethics, 2018).

The other key issue is access to **drugs**. The high cost of drug development based on pharmacogenomics (not covered by insurance and not accessible to all) represents a major concern in public health literature. As noticed by Salari and Larijani (2017), "the high cost of new drugs and laboratory tests which inform personalisation limits the number of patients who benefit", entailing a more general risk that personalised medicine could exacerbate existing health variations.

A separate but related aspect concern the **role of the private sector**. The development of genomic and single-cell research and technologies is fuelled by the involvement of the private companies as funders, research-performing organisations and developers of marketable innovations based on private or public research. This could entail criticalities that deserve to be appropriately addressed.

One is the **opaqueness** of the relations between the public and the private sector for what concerns, e.g., the role and interest of each actor and the management and exchange of resources. However, there are other opaque areas related to the use of LifeTime research and technologies which are not necessarily depending on the presence of private firms, but, e.g., on military and national security initiatives (Nuffield Council on Bioethics, 2016).

Beyond the actual or alleged opaqueness of the relations between the public and the private sector, it is to observe that citizens feel a **limited trust towards private companies** and especially private pharmaceutical companies (Martin & Hollin, 2014), also because the

"donation" of personal data is seen as part of a reciprocity chain ("I give my data also to benefit in the future from the data given by others") which the involvement of private interests seems to break (Busby & Martin, 2006)

Another issue concerns patenting, especially for what concerns the **patenting of human genes** (Sherkow & Greely, 2015), which has long been the subject of public debate and which has produced several consolidated narratives (Contreras, 2015), each highlighting a different aspect of the problem, such as, for example, the possible dramatic effects of patenting (the dystopian narrative), the unfairness of patenting genetic materials which have been discovered thanks to a collective scientific effort (the science narrative), or the impulse given by patenting to innovation (the innovator narrative).

A third aspect to consider is the increased **dependence of research from private funds**, which can create tensions, for example in the establishment of biobanks (Bell, 2016; Salari & Larijani, 2017). More in general, the involvement of private funds poses questions about the compatibility of private interests and the public good (Capps et al., 2017; Yuan-Chuan Chen & Hui-Fang Li, 2018), especially considering the needs of the private sector to develop marketable products (technologies, therapeutic solutions, etc.) as rapidly as possible (Boers, 2019).

Another aspect is the **risk of the weakening of the public sector** due to the economic power of private actors. Because of the higher salaries recognised to researchers in private research companies, there is the risk of a concentration of intellectual capacity in private sector organisations, with a parallel weakening of the capacity of public research to keep on producing relevant scientific knowledge in the long run (Future Advocacy, 2018).

Beyond these critical points, it is also to observe how, in the last twenty years, after a long period characterised by the competition between the public and private sector, **new and effective forms of public-private partnerships** have started to be promoted, leading to important advancements in genomic research and reducing conflicts and tensions about, e.g., the use of personal data and the management of large datasets and biobanks (Martin & Hollin, 2014).

6.2. Inputs from the interviews

When it comes to supporting the development of new technologies and treatments, the interviewees generally adopt a **pragmatic approach** with respect to private sector involvement, considering it – in different shades – useful, efficient, already established, unavoidable. Some discordant voices are there as well, though. Lack of enough funds from public systems is often mentioned.

> *I honestly think that we're going to need pharma more and more. (…) I'm personally thinking of it almost daily, because I'm realising that science has become so expensive that funds, European Commission funds, national funds, American funds, all these different grants that you're going to apply to … I don't think they're going to be enough to sustain it all.* (RE1)

> *I think it is unavoidable for the private sector, for private research institutes to enter this arena, and quite effectively.* (CL2)

A totally public system is unsustainable now. (CL3)

I believe that we cannot ignore the private sector. The private sector is fundamental to any research. I do understand that the main objective of the private sector is totally different from the main objective of the public sector, but still we cannot ignore that we need and must work together. (PG1)

I think the private sector will always be there. I think that they are a player as well as all other players in the field, and I think they are already into this [new technologies development]*. (…) I definitely think anytime you want to upscale, you need the private sector.* (RE4)

In particular, many interviewees remark that the public and private sectors have been working alongside each other for a long time, and increasingly so now, so that it is **unlikely that new problems will emerge** in connection with private involvement in new technologies.

I don't see a very big problem here. It's like in the diagnostic sector, which currently is very much based on outsourcing and buying analytical stuff from private sector. The regulations that are there for public healthcare also apply to the private sector. (…) It can be much more efficient and even cheaper, [also because] *these systems get old very quickly and you have new technologies all the time, so if you set anything up in the hospital, you end up with a lot of equipment that is totally obsolete.* (CL1)

I don't see anything new really happening here. There are public research institutions and then there is the research done in pharmaceutical companies and other companies, and this has happened for decades already. Of course, yes, there is some conflict of interest and other kinds of issues, but I don't see anything new here really. (PG5)

A clinician, however, besides positive aspects, identifies some imbalances in the current arrangement of public-private relations. In addition, the representative of a patient group, despite acknowledging that it is difficult to avoid private sector involvement in key innovation areas, expresses a **strong mistrust**.

Thinking about new technologies, one of the big challenges [in public research] *is having access to biostatisticians and data scientists who can help with analysing all the new data that are produced. Currently they are almost impossible to recruit to the academic sector, because the private sector, the drug companies and private research institutions, they take all the competent people right away, and they offer salaries that can be maybe 10 times more. This is actually a big concern. (…) It is a bottleneck for the academic sector (…) and that might lead into a situation where we are more and more dependent on the private sector for that.* (CL1)

When a pharmaceutical company gives a new indication to an existing, cheap medication, they send the price up a few hundred times … I understand that we need them, but I think that they should realise that it's not sustainable. (…) My experience in the Pharmacovigilance Committee is that the pharmaceutical industry is not always honest, when they give us the data. They leave data out. That's not what I like, but it's the reality. For them, it's so much money that they want to push it. I don't trust them. (PG5)

On the other hand, some remark that also the **public sector** can be “the bad guy” at times.

The bad guy is not only the private sector. It can also be the public sector, for instance if they don’t manage the data properly. (…) They often say that the data cannot be shared. When there is a lack of or a gap into the regulation, while the private sector tends to be more flexible, the public sector tends to be more rigid. Even if they have the data, they do not use it, they do not share it, not even for

research purposes. This is another challenge. (…) It's the whole relationship between the public, the private and the patient that should be regulated. (PG1)

Most interviewees refer to the need of **regulations** to find a balance between the public interest and the legitimate interests of private companies. Appropriate regulations can help build **trust** and also include **citizens** as a key party.

I guess we need more regulations, probably, to try to protect public interest while protecting these companies. We need to somehow find a balance. (RE2)

There's of course the problem that they want to make money. I think ethical aspects are important in terms of protecting the patients. (…) You should declare your ethical position and get ethical clearance for certain activities. (RE4)

There are some problems related to trust, (…) but we have to remember that we are regulating the private sector using the same public regulations, because the private sector should not be totally out of control. We have to survey, we have to assess, and we have to regulate it properly. (CL2)

There should be some sort of new way of modelling for making sure that companies do recuperate the investments they have made. They make the profit they need, but there is some sort of control not to have an over-profiting that looks abusive towards the public. (PG2)

Of course, the private sector can help in many ways, and if they see some profit, they will invest money. (…) And of course, we need to be careful. This is why I think we need to give data management to the citizen themselves, for them to decide what to do with their data. (PG4)

When it comes to more directly assess the consequences of the new technologies on **equitable access to care**, interviewees from the different groups (researchers, clinicians, patient representatives) tend to frame the issue within **broader societal processes** in relation to healthcare, where public systems are increasingly facing difficulties in guaranteeing high-quality care for all.

The national health system is already providing diagnostic tests unevenly across regions. For example, the BRCA genetic testing for hereditary breast-ovarian cancer is paid for by the public system only in certain regions, while everybody should be able to access it. (…) So, what happens is that only people that can go private, unfortunately, get the best care and the best treatment, just because they can pay. (RE1)

I think it's a valid concern. Of course, it is a much larger societal question. (CL1)

We know that inequality in access to healthcare always existed, and the gap is currently broadening. (CL3)

[Inequality] *is manifestly there now, I think. Even within a single country like America, health care entirely depends on how much money you have. If you're born in America, and you've got renal failure, you will not get hemodialysis necessarily. (…) If you look at infant mortality in America, the bottom end is as bad as rural Africa. There's a huge stratification in terms of provision of healthcare. Now, super-expensive boutique drugs exist that might give you an extra six or nine months of life. (…) If you wanted to use genome editing to cure somebody with sickle cell disease, it's going to cost you millions of dollars. How many countries can afford that, even though it's a result of advances in science? It's not a new problem and it's something which desperately needs to be addressed, but it's a political issue.* (RE6)

Some interviewees, however, remark that **costs may decrease with time**, eventually giving access to more people.

> *I think in the long-term, perhaps … I mean, I think the richer will always get better treatments, but the things will improve for the poorer people as well, who are getting the basic healthcare of their country. Things will improve for everybody.* (RE5)

> *Some believe that possibly, in the future, the very wealthy could use advanced techniques to improve their genome. I disagree, because what we have seen in the last decades is that any expensive technique is getting very cheap progressively. To give an example, 10 years ago, 15 years ago, a genome analysis used to cost about €15,000 to €20,000. Now, it costs less than €1,000. Even the most expensive techniques progressively become affordable.* (CL2)

> *I don't think this is any different to the problems that are already there. (…) A lot of new therapies are being developed against cancer or some neurological diseases and many are extremely expensive at the moment and can only be afforded by somebody who's either very rich or is covered by good health insurance, which is super-unfair. (…) This is a very complex ethical issue, but I think that personalised medicine, (…) once you develop it, will be accessible for more people. I think it is worthwhile investing in this direction even if it's not something that the whole world population would be able to access straight away.* (RE3)

> *At this moment, as long as it's not mainstream, access is not equal to all. I think if these technologies are going to be mainstream, then I guess that is going to change compensation systems, it's going to change the healthcare provision, and hopefully … I'm assuming costs will be different. Right now, they're still something new and research on them is very expensive, so I can understand why they are also expensive to access.* (PG2)

As noticed by some, the problem is more with **treatment costs connected to the results of the screening**, than with the costs of the new screening technologies themselves, as remarked by two clinicians.

> *The entire field must be regulated as soon as possible; otherwise, there can be serious issues for patients and for citizens in general, because you don't have to be ill to get a genomic test. Once you get the test, if you are subject to a disease, you need support. (…) But it is a trend in Europe to reduce the public health system more and more, favouring the private insurance system, and this is even more of a challenge.* (PG1)

> *Using these technologies for selecting treatments, it's clear that they can be quite expensive, but still they are a few percent of the price of the medication that you are going to use. If you use the technologies to select the right patients that are going to respond to the drug, it's still worth it. (…) I think it's more about how much we can afford the medications than the profiling tests. They're not terribly expensive, in my opinion, and they are going to be much cheaper, anyway. So, the bigger question is … can we afford the drugs?* (CL1)

> *The cost of public healthcare systems is no longer sustainable. And it's not because of the cost of new technologies, screening or diagnostics. What is no longer sustainable is the cost of what comes afterwards, that is, drugs. The cost of drugs is unconceivable.* (CL3)

The focus then shifts to the **cost of the drugs** (both developed based on pharmacogenomics and general drugs), which was widely discussed in interviews. A first perspective to address the issue is again the public-private nexus.

The issue of trust is very important here. (…) My impression is that the public sees a clear goal for companies to develop drugs. Everybody knows developing drugs is very expensive and so it cannot be done by governments, it seems. However, if you let companies do whatever they like, they will try to optimise their profit and they will. There's plenty of examples of companies hiking drug prices, and that erodes trust. In my personal opinion, I think there should be a bit more government involvement in perhaps capping the prices of drugs, to try and struck a balance between the profit to be made by a company and the public. (RE8)

When it specifically comes to the cost of **drugs developed from genomic-based diagnostic tests**, there is some uncertainty whether the usual mechanisms of market competition will substantially decrease costs with time, considering that the target group of the new drug will be each time reduced and segmented.

If you have a competitive market, you can expect prices to go down with time. This happened with medicines designed against HIV. it was like 80,000 dollars at the beginning, so that only big stars in Hollywood could buy such medicines and start some treatment in the 80s and early 90s. (…) Now you can buy this prevention HIV medicine for €30 or €40 euros. But these drugs are for all. I am not sure this is going to happen with pharmacogenomics. (PG4)

The mechanism of **clinical trials** is one of the reasons behind the high cost of drugs. In general, clinical trials are extremely expensive, but – according to an interviewee – they cannot anyway capture individual diversity and reactions as pharmacogenetic drugs would, unless engaging in large post-marketing studies, exponentially increasing costs

The problem is, once you put something in the market, that's super expensive and the cost hasn't been cut down despite the technologies improved. What is the reason? Well, you know, these three-phase trials are super expensive. If you go to three-phase trial and it fails, it's a lot of money that you would have to recover somehow. I guess that the problem is there. (RE2)

According to European regulations, clinical trials should only enrol healthy patients in phase 1. After that – since people have conditions – you stratify for different health conditions. In the end, clinical trials have huge costs. (…) However, large post-marketing observational studies in phase 4 are lacking, because they are extremely expensive if they have sufficient numbers for different subgroups. (CL3)

But how should clinical trials be adapted to **drugs developed for personalised medicine** without further raising costs? Some say that what are now post-market studies would be inherent to the development phase, and costs would be limited in the long run, because adverse reactions would be greatly reduced.

If the authorities are showing that they want this [personalised drug development]*, then this will be included in the regulatory guidelines (…) and it will not be a post-market issue, but it will be part of the drug development. Now, obviously this is more money, and that is a problem, but I think it will have an impact on adverse reactions, which are a huge cost.* (RE4)

A **specific regulatory effort** to adapt clinical trial mechanisms is anyway advocated. Some make a parallel with clinical trials for drugs targeting rare diseases.

The question is, should it [the clinical trial] *be done in the same way for individualised drugs? Do we have to do it in the same setup of controlled trials? Now, for some diseases and some situations, the regulatory agencies … if you have, for instance, a disease with very few patients or in children … they are not requiring the same evidence, because it's impossible to do it in children, or to do it in a*

disease that is so rare. So, I think that how should the evidence of drug effects be demonstrated, this is still up for discussion. I think the regulatory agencies and authorities need to give us more guidance on this. (RE4)

EFFECTS ON ACCESS TO CARE

Key points to highlight from the interviews

- **Different aspects** are considered by the respondents in relation to the effects of LifeTime technologies and personalised medicine on access to care.
- As for the effects connected with the **involvement of the private sector**, interviews prevalently show a **pragmatic approach**. All of them consider such involvement in some way necessary or inevitable and in continuity with the past. Certainly, new regulations are evoked for protecting public interests and feeding public trust towards the new technologies. However, it is also unrealistic to think that regulations could actually prevent or settle all the problems and potential conflicts connected to public-private relationships.
- Interviewees are also well aware of the possible consequences of the new technologies on **equitable access to care**. The tendency, in this case, is that of viewing the issue as part of a broader societal question, i.e., the overall capacity of healthcare systems to ensure appropriate care for all within highly unequal societies, at the national as well as at the global level. The emerging view is that the problem is certainly not new at all, and it will not necessarily worsen because of the application of personalised medicine or single-cell technologies, particularly in the longer term. Some more concerns with short-term inequality in accessing personalised medicine is anyway recorded.
- About the **costs of screening technologies**, many interviewees think or hope that they will end up decreasing with technological advances and widening diffusion. Opinions tend to diverge when the **cost of drugs developed for personalised medicine** are considered. Some respondents highlight how market mechanisms may contribute to reduce the costs of drugs over time. At the same time, various respondents remark that increasing personalisation of treatments (limiting economies of scale) and the high costs and increased complexity of clinical trials may on the contrary raise the costs of drugs. In general, there is a high level of uncertainty about this aspect.

7. Further factors potentially affecting public confidence in LifeTime technologies

Even though most issues, among those discussed so far, are influencing public trust towards new technologies in the field of healthcare (such as the three key LifeTime technologies), in this final section some additional, specific factors are considered, like **non data-related ethical implications** (for data-related ones, see Section 3, above) and **communication** issues, highlighting the importance of a correct **management of expectations** around new therapeutic perspectives.

7.1. Inputs from the literature review

The **ethical implications of research** connected to the use of LifeTime technologies (single-cell biology, application of AI in biosciences, personalised organoid disease models) are many and diversified.

One of the most ethical questions relates to the management of **incidental findings**[7]. In these cases, the **right to know** is acknowledged, but there could be also the need to protect the **right not to know** what is emerging from the genome, or single-cell analysis. The latter right, in turn, might be in conflict with duties towards the interest of third parties, such as children or relatives (King Baudouin Foundation & Sciensano, 2018). Questions concern in particular what information is to be provided to patients in cases of incidental findings on treatable or non-treatable future diseases not previously considered in the informed consent (Fangerau, Marx-Stölting, & Osterheider, 2019), or when the future disease may have implications for family members (Salari & Larijani, 2017).

Other ethical issues concerning **screening** results that emerged in genetic testing (King Baudouin Foundation & Sciensano, 2018), but could also be **relevant for single-cell analysis** include:

- The decision to make a screening (how and under which conditions genetic screening are useful)
- New-born screening (which could harm the child's right not to know)
- The application of cascade screening (i.e., screening of other family members to confirm the results of genome or genetic testing of the patient)
- Opportunistic genomic screenings (occurring when laboratories perform clinical sequencing to deliberately search for and report on a pre-determined list of incidental findings in addition to the results directly relevant to the initial reason for testing)
- Pre-conception carrier screenings (i.e., the screening of the couples before the conception of a new baby to know if they carry functional mutations for the same genetic disease).

Ethical concerns have been raised regarding the possibility of **genome editing in human germ lines**, since this can produce mutations, side effects, and unpredictable changes which may be transmitted to future generations (Rodriguez, 2016).

Even more controversial is the possibility to use **non-therapeutic genome editing** for enhancing, e.g., the performance of athletes or preventing violent behaviours. Also, sex selection for non-therapeutic reasons is largely debated (Macpherson, Roqué, & Segarra, 2019).

Some ethical issues also refer to the use of **organoid technology**, including:

- The ontological and moral status of organoids (Boers, 2019)
- The ways in which donors relate to organoids derived from their tissue (Boers, 2019)

[7] The expression "incidental finding" or "incidental discovery" refers to unanticipated information discovered in the course of testing or medical care.

- The ethical provenance of human biomaterials used for organoid and related research (for example, tissues discarded during clinical procedures can be used for research without the explicit consent of the patient) (Munsie, Hyun, & Sugarman, 2017)
- The ethical governance for the derivation, storage and use of complex human tissue products (Boers & Bredenoord, 2018)
- The specific ethical status of cerebral organoids created in vitro (for example, if they have any kinds of consciousness which should be morally considered) (Sawai, Sakaguchi, Thomas, Takahashi, & Fujita, 2019)
- The clinical translation of organoids in the field of regenerative medicine, which poses, in new ways, ethical challenges already discussed in other sectors regarding informed consent, risk-benefit evaluation, participant selection, and trial design (Boers, 2019)
- The moral status and the ethical treatment of chimeras (when cells and complex in vitro structures of human origin are introduced into the brains or reproductive systems of non-human animals) (Munsie, Hyun, & Sugarman, 2017).

Questions also emerge about the risks linked to the **use of AI in healthcare on a large scale** (see also Section 3, above). They concern, e.g.:

- The quality and representativeness of data used to train machine learning algorithms (in the existing medical data-sets adult males of Caucasian origin are strongly overrepresented) (Future Advocacy, 2018; Schönberger, 2019; Reddy, Allan, Coghlan, & Cooper, 2020; Blasimme & Vayena, 2019; Ferryman & Pitcan, 2018)
- The production of inconclusive, inscrutable or misguided evidence produced by algorithmic outcomes (Morley, Machado, Burr, Cowls, Taddeo, & Floridi, 2019)
- The difficulty to detect errors in the AI system (Nuffield Council on Bioethics, 2018)
- The tendency to over-diagnosis and non-actionable diagnoses due to the easiness with which an AI system can keep track of a person's health and perform accurate diagnostic (Blasimme & Vayena, 2019)
- More in general, the difficulty to understand how a “black-box algorithm” makes decisions, because the machine learning techniques generally cannot tell us their reasoning, and even when they can, the results are often too complex to understand (Future Advocacy, 2018; Schönberger, 2019; Reddy, Allan, Coghlan, & Cooper, 2020; Nicholson Price II, 2017).

One of the main issues related to the application of LifeTime technologies is the evaluation and communication of their **benefits, risks and limitations**, **realistically managing expectations** which could be too high. Indeed, as the experience with DNA sequencing demonstrated, the data produced risk providing information “fraught with uncertainty”, due to both the natural variability of random phenomena and the gaps in knowledge about the interpretation of these phenomena (National Consultative Ethics Committee for Health and Life Sciences, 2016).

Many problems are connected to the difficulty to assess the **risks related to the capacity of intervening at the cellular level**, such as the generation of off-target mutations and random manipulation of genes, especially in human germ line cells (Rodriguez, 2016; Yuan-Chuan Chen & Hui-Fang Li, 2018).

Other problems concern the **lack of statistical standards and procedures** allowing a correct and uniform interpretation of the large volumes of data produced by the implementation of single-cell analyses, thus “preventing a risk of over- or underestimation of correlations, misinterpretations and, in case of doubt, bad medicine working on the basis of inaccurate

data" (Fangerau, Marx-Stölting, & Osterheider, 2019). Moreover, there is a high risk of false positive, possibly leading to optimism bias (Laviolle et al., 2019).

More in general, there is still the **need for an evidence-based approach,** e.g., to assess the associations between a genetic variant and a phenotype, to quantify the risk of these associations, and identify the clinical relevance of these findings in the patients' care-path or lifestyle (Laviolle et al., 2019).

The balance between benefits and risks is therefore still the subject of discussion. Demonstrating the utility of single-cell-based technologies may take a number of years, on the one side, because of the **clinical trials** and **approval protocols** (therapies currently under development are likely to take some time yet to get into clinical practice) (Nuffield Council on Bioethics, 2016) and, on the other side, because of the need to find a **balance between regulation and innovation** (Australian Health Ministers' Council, 2017).

People's trust in research institutions and researchers is another issue which can affect the reception of LifeTime technologies and precision medicine in general, influenced by many factors. A number of authors point out what they consider the more relevant aspects in connection with public trust (some already mentioned in different parts of this report), indicating them as **areas which need to be properly addressed in public communication**:

- Capacity to avoid "black-box medicine" (Nicholson Price II, 2017), i.e., medicine overly dependent on the use of AI and learning machines (Van Staa, Goldacre, Buchan, & Smeeth, 2016), which tends to get out of the control of physicians and even researchers and technicians, creating diffidence in patients
- Adequate management, use and protection of personal data and biosamples in both research and clinical work (Australian Health Ministers' Council, 2017; Feiler, Gaitskell, Maughan, & Hordern, 2017; Salari & Larijani, 2017; Fangerau, Marx-Stölting, & Osterheider, 2019; Scarpato, Pieroni, Di Nunzio & Fallucchi, 2017)
- Appropriate management of private sector involvement in health research and healthcare, otherwise perceived as having interests which are incompatible with the public good (Yuan-Chuan Chen & Hui-Fang Li, 2018)
- Ability to demonstrate concrete and accessible benefits (Finkel, Wright, Pineda, & Williamson, 2018).

7.2. Inputs from the interviews

Among the many ethical issues reviewed in literature, those more strongly felt and addressed by interviewees have been the protection of personal data and the potentially discriminating effects of artificial intelligence algorithms (these were reported in Section 3, above), and the **management of incidental finding**. Other aspects – such as those relating to organoids – have not been particularly discussed. With respect to the connected issue of public trust in research, questions about **science-society relations and communication** have instead been frequently raised.

In general, **interviewees didn't seem to consider the specific LifeTime technologies particularly controversial** in ethical terms, even if regulations are certainly expected. In

addition, a sort of fatalistic attitude emerges, particularly from researchers. One interviewee calls for greater citizen inclusion in the decision-making process about ethical aspects.

> *Yes, I think that for new technologies there will need to be new regulations, (…) not to end up in a situation where things just happen. Well, there can always be some irresponsible people that's going in directions that the majority of others would consider unethical. In the case of single-cell technologies and organoids as such, I don't think that this is such a very problematic area at the moment. Of course, we don't know where we'll get. I think it's probably more at a level of R&D and product development that there can be more problematic aspects … At the moment, in terms of this LifeTime initiative, ethical concerns do not seem to be particularly serious.* (RE3)

> *Of course, genetic editing, chimeras, all that is regulated by governments. Then, the world is not a homogeneous place. There will always be countries where the regulations are not applied, or they don't exist. (…) If a crazy professor wants to test really unethical things, it will happen. We can't avoid it. Still, I think the governments should be well informed about and regulating those aspects. Again, I don't think that it will stop some dangerous experiments and some dangerous outcomes. (RE5)*

> *As with all scientific breakthroughs, there's going to be good things and bad things. I think artificial intelligence will play a huge part in changing clinical medicine. I don't think there's any question of that. (…) I can think of 100 ways that you could apply artificial intelligence to medicine. (…) Then you're going to say, well, what's the bad side of it? There's so many wicked people in the world.* [Laughs] (RE6)

Incidental findings, as anticipated, are instead a big concern for interviewees. New technologies and the kind and amount of information they deliver are making communication with patients and informed consent practices very difficult and sensitive, particularly when test results involve **family members**. These situations are so complex, that a solution is hard to identify.

> *The amount of information that you can get from individual samples can be really extensive and go really beyond the individual* [to encompass the family]*. (…) It is also very difficult to predict now and tell the patient what kind of implications there will be in the future, but I don't know if we have a very good solution here. I think the alternative would be don't tell anything, but I am not sure that's a good alternative. I think it's just that we need to be quite flexible.* (CL1)

> *That is a challenge. How we can overcome this, I don't have the answer, because it's very difficult to have an informed consent form filled and signed by several people, all the people affected, especially when it is related to children that are not even there.* (PG1)

The "right to know" and the "right not to know" are both evoked, by a clinician (full respect of the patient right to know) and by the representative of a patient association (respect of the choice of the patient).

> *We are for total transparency. We respect, of course, the feelings and emotions of the person, but we don't hide anything to anybody. It couldn't be any different.* (CL3)

> *The fact that one could predict that in 20 years, let's say, you will die, because you will develop a certain disease will impact what you would be able to do in that period. It's a philosophical issue. We are not only changing the concept of disease, but we are changing the whole concept of life. (…) I'm wondering whether people actually want to know. (…) Should we know? We have the potential to develop a technology so that we know, but do we want to know? Did they ask us whether we want to know? Everyone should have a choice about what they want to know. If you want to know, you can have it. If you don't want to know, you should not be obliged to know. (PG2)*

Those dealing with genetic diseases are well aware of the problem of incidental findings involving family members. With single-cell technologies, the problem risks spreading to other fields because, in an epigenetic perspective, the **consequences of individual behaviours** can be traced up to one's offspring, entailing complex ethical problems.

> *In a way, what you are anticipating for the use of single-cell biology is already there in our group of genetic diseases. (…) When one person is diagnosed for one particular disease, we know that the disease is in the family and we know that some relatives may be affected and they don't know, so what do you do? Some people say, 'No, I don't want to tell anyone'. If they do so, they can be blamed for not informing others that they have a specific risk. There is no quick answer to this. What we can do, and usually do about informed consent, is including some rules for the information of relatives if this is needed, but there is not a single way of dealing with that. Some geneticians, they don't want to go to this level and some others consider that they should.* (PG3)

Some sort of **guidance** would be needed.

> *You need to have a system to refer to, especially when you have genetic findings (…) that can affect the family as well. (…) There needs to be a lot of expertise, that usually the researchers and doctors don't have, about how to manage incidental findings. You need to have a referral and guidance system, so that patients and families will get the right information.* (CL1)

Public consultation and cooperation with **social scientists** are also called for in this respect.

> *I think that the scientific community would need to consult with the wider public. There should be a transparent public discussion about what is ethical and what should not be allowed.* (RE3)

> *I think there needs to be more social science research. Implementation research, ethical research, social perception research ... This is the hindrance at the moment, while I think that's the key to success. We know too little. (…) I have started to interact with social science people, and we need to work on understanding each other, because we know each other too little, but I'm super strong on that it's a collaborative effort that's going to make it happen. Definitely.* (RE4)

The **social acceptance of the new LifeTime technologies** is also a concern to interviewees, considering negative examples such as GMOs, or vaccines. Different explanations and attitudes have been expressed in this respect, attributing responsibilities to better manage science-society relationships either to scientists, citizens, or the state.

> *I think that scientists don't realise how much they can impact society. I think one mistake we scientists make is that perhaps we don't voice ourselves enough. We don't explain things in an easy way. The best example is vaccines, right? What happened with vaccines, I think mostly was because most people don't really understand a lot of what's beyond that. (…) Is it the people's fault or is it the scientist's fault? We need to learn how to talk to people.* (RE1)

> *I think it's happening in every country. I think informing society as correctly as possible and regulating the information flow carefully will help minimise these problems. Then, you can't educate everybody on science. That's not possible. There will be conspiracy theories all the time, and the same will happen with these other advancements in health. I mean, it is going to happen. I think the efforts should be for minimising that.* (RE5)

> *I think that diffidence is not against researchers or clinicians. I recently read that trust in clinicians is still very high. I think it's a sense of ill-concealed discontent with public institutions in general. Also with vaccines … I think it was not against scientists or clinicians, but because people thought that*

multination enterprises were behind that. And by the way, they got it really wrong, because if there's one thing you don't make money on, it's vaccines. (CL3)

Whether single-cell technologies will encounter this kind of bias, as with GMOs or vaccines, it's very difficult to actually say. I think there wouldn't really be a big reason for that, but it's also impossible to really rule it out. (RE3)

In my country, we have a strong movement against vaccinations and all these sorts of things. Opposition will be there. We will never have 100% of the population that is convinced that the new approach will be good for them. (PG3)

Carefully managing expectations becomes crucial in this framework, according to most interviewees, avoiding the temptation of raising them too high. It is mostly researchers who feel threatened by the mechanisms of public communication of scientific endeavours.

We need to keep our expectations not so high, because even with the advent of the genomics era, everybody said, 'Okay, once we get everything sequenced, we're going to have the answer to everything'. In fact, that didn't happen. In a way, when you move forward, you also move back, because you do want more and you go, 'This is still missing', and you realise that there's always a piece missing. (…) I think that even with all this technology, yes, we're going to move forward, but it's not going to happen immediately. We still have to learn how to incorporate all these data. (RE1)

I think the benefits of this project are clear and important, but we should be aware of not promising too much, as it was with the human genome project. We thought, even myself, that once we would have the entire sequence, we would understand the biology of any type of cancer, any type of disease, which is not true. We will advance for sure, but we will still have a lot of diseases that we will not be able to treat whatsoever. It's hard to communicate effectively and be realistic. (RE2)

I think that the most difficult part is that this kind of research, it's a very long-term investment. It's not very likely that we're going to get early breakthrough therapy within five years because we need to first learn even to understand those data that we generate and see what we can really do with that. The danger is creating a public perception that this will lead to an immediate change in medical practice. The expectation has to be managed in terms that it's not something that's certain and not something that's going to happen overnight. (RE3)

Well, surely the society will benefit from all that, (…) but people would need to be aware of what they should be expecting realistically. I hate newspapers and public relation officers. Universities and research institutes try to promote their work and they do it via the public relations officers. Those public relations officers, and then the newspapers' journalists, clearly exaggerate. What the general public then makes of it is completely different than the actual situation. For the scientists, it is just unacceptable, but it happens every day. (RE5)

There's a bit of a risk in communicating that. The idea is, of course, great and I fully support that, but we also need to make the formal studies to prove that it works. You can always be sceptical that even this is not enough, that this is not predictive enough … It's necessary to be realistic about that. (CL1)

A different perspective comes from a clinician, remarking how – after many announcements – people are already expecting that all medicine is personalised.

What would be important is that people managing scientific communication would be really qualified for this. There are so many fake news. What patients expect already now is that all medicine is precision medicine, and all medicine is personalised. Why should it be otherwise? (CL3)

A final comment is provided by a researcher, about the importance of **being fully aware of the progress** which has been achieved in the last decades, radically transforming medicine and the experience of all.

> *I think in terms of consenting advances in science, it's very, very important for people to acknowledge what we have rather than necessarily what we're going to get in the future. People are always much more interested in the future. Again, if you look at technology in clinical practice now, compared with even 40 or 50 years ago in my lifetime, it's so different, and I always think this is what I would like people to get. Nowadays, if you've got a bad hip, you get in, you have a hip replacement and you're walking like a 20-year-old. If you have a heart block, you go in and you get a pacemaker. Even when I was doing cardiology 30, 40 years ago, actually, pacemakers were a rare tool. If you wanted to present science, you'd say, look, don't expect this to happen in five or ten years, but actually, it's all going forward in a very positive and good way. That's getting better all the time. That would be my message, and you only have to look back over a very short period of time to realise just how much it's improved.* (RE6)

FURTHER FACTORS POTENTIALLY AFFECTING
PUBLIC CONFIDENCE IN LIFETIME TECHNOLOGIES

Key points to highlight from the interviews

- Among the aspects affecting public trust in LifeTime technologies, **ethical issues have not been particularly emphasised** by interviewees, partly because they generally do not consider the new technologies remarkably controversial from an ethical standpoint, and partly because, although new regulations are expected and even required, they are not considered effective enough to totally prevent unethical behaviours.
- An important exception is **incidental findings**, which is viewed by the interviewees as a highly problematic ethical issue. However, their opinions about incidental findings largely differ. Diverse aspects, sometimes contradictory to each other, are highlighted in this respect: the right to know; the right not to know; the right of concerned relatives and children to be informed; the need for doctors to adopt a flexible approach; the need to develop a guidance system; the need for public consultations and the involvement of social scientists to help manage these issues.
- Another crucial aspect is how to **manage public expectations** about LifeTime technologies. Interviewees take this issue seriously, also recalling some negative examples from the past such as GMOs or vaccines, although their opinions diverge about the factors and actors that play a major role in these dynamics. Beyond that, many respondents recognise the tendency of research institutions to over-emphasise future results, sometimes through their communication or public relation offices. The general and social media then reinforce the message, with the effect to feed false hopes or induce distorted perceptions of or expectations about the actual benefits of research.

PART THREE

DESIGN OF THE STAKEHOLDERS CONSULTATION

The third part of this report is intended to provide some methodological and substantive orientations for the development of a stakeholder consultation on expectations, as well as social and ethical issues, surrounding LifeTime technologies.

The aim is not to provide a ready-made design of the consultation, but to explore the options available and propose a general scheme.

With this aim in mind, we will start examining the relevant input from the interviews (Section 1). We will then consider the possible objectives the consultation could pursue (Section 2) and briefly review relevant methodological issues (Section 3). After that, a proposal for the consultation will be sketched (Section 4). Finally, we will examine the issues the consultation could primarily address (Section 5).

1. Relevant findings for consultation design

Some elements emerged from the interviews which can be relevant for identifying some of the main features of the consultation. In particular, the following elements deserve to be highlighted.

- **Clinicians and representatives of patient groups show limited knowledge of LifeTime technologies. Researchers display a selective knowledge**. The level of knowledge of LifeTime technologies (single-cell biology, AI applied to the data generated by single-cell analysis, and the development of organoid disease models) shown by health professionals and patient group representatives is limited (still with obvious differences). This led them, in some cases, not to distinguish single-cell technologies from genomic technologies. Researchers, instead, have a selective knowledge about LifeTime technologies: they know what they are, but they generally feel to be expert of or concerned with only one or two of them.

- **Respondents better understood LifeTime technologies when they associated them with personalised medicine**. Clinicians and – above all – representatives of patient groups tended to better frame LifeTime technologies when they grasp their link with personalised medicine. Personalised medicine has often been the main entry point for discussing LifeTime technologies. Indeed, personalised medicine is a topic which proved to be very well known by all the respondents. This was not the case with researchers.

- **Respondents barely distinguish the social and ethical implications of LifeTime technologies from those of genomics**. As a consequence of what highlighted above, respondents (including researchers) showed the tendency to see the social and ethical issues raised by LifeTime technologies as largely overlapped with those connected with the application of genomic technologies in general. This is particularly true for single-cell analysis and the use of AI in healthcare. As for the organoid models, the perception of social and ethical implications has been in general very limited, as this technology was poorly known by respondents.

- **This tendency to overlap the ethical and social issues of LifeTime technologies with those of genomics is due to the fact that the latter have long been the subject of public debate**. Indeed, as emerged from the literature review, many public consultations and surveys have been promoted in the past 20 years or so about the application of genetics and genomics by different organisations, including the World Health Organisation, the European Union, and other national and international organisations. Consultations have focused on specific issues like, e.g., the governance of genetic research and applications, the use of genetic tests, specific ethical issues related to genetic medicine, or the use of informed consent in the context of genomic applications in healthcare. Very few consultations have addressed the use of AI in healthcare provision, and apparently no public consultation included organoids-related issues so far.

- **The different groups of respondents share the expectations but less the worries**. It is worth observing that, beyond their divergent opinions on different issues, the three groups of respondents seem to share high expectations about all technologies contributing to the development of personalised medicine, although their worries appear to be different.
  - **Researchers** are the most aware of and show a positive attitude towards the current state of research and its possible future developments and benefits. They are also aware of their social and ethical implications, but do not seem overly concerned about them. They tend to resent excessive limitations regarding, e.g., the use of data or ethical issues, while expressing a deep concern about too high expectations in terms of short-term clinical application.
  - **Clinicians** are equally attracted by the potential opportunities opened by LifeTime technologies and personalised medicine. Their main worries concern the difficulties to make these opportunities really actionable (in both technical and organisational terms) and the existing problems which can be met to introduce them in clinical practice. They seem to be more concerned than researchers with the social and ethical implications of these technologies.
  - **Representatives of patient associations** are also very interested in the potential opportunities opened by LifeTime technologies and personalised medicine. Their worries mainly concern the personal condition of patients, their level of empowerment, and the issues related to the management of personal data, even if they don't want these problems to lead to a slowdown in the research process and the application of its results.

2. Objectives of the consultation

The aspects briefly presented above help to better define the possible objectives that the consultation on LifeTime technologies could pursue.

2.1. Assessing and increasing knowledge and awareness of LifeTime technologies

As highlighted above, a first issue to consider and address would be the **limited or very limited knowledge of LifeTime technologies** by part of the stakeholders. In particular, single-cell related technologies are not recognised in their specificity, while there is the tendency to fully

identify them with genetic or genomic technologies, or to view them as part of the large technological strand contributing to precision medicine.

This apparently low level of knowledge of LifeTime technologies **should be measured and assessed**, also in view of future possible actions aiming to favour their application in healthcare settings. It will be also important to measure how the level of knowledge of LifeTime technologies varies across European countries.

Moreover, promoting a consultation on LifeTime technologies may remarkably contribute to increase stakeholders' knowledge about them and to raise their awareness of their benefits and added value in comparison to genomic technologies, as well as their potential risks and controversial issues.

Thus, the **first objective** of the consultation would be twofold:

- Assessing to what extent stakeholders know and are aware of LifeTime technologies and, at the same time,
- Using the consultation for increasing stakeholders' knowledge and awareness of Lifetime technologies.

2.2. Assessing attitudes towards the social and ethical implications of LifeTime technologies

As we have seen above, also when it came to the social and ethical implications of LifeTime technologies, respondents showed the tendency not to distinguish them from those related to genetic and genomic technologies.

Indeed, they are largely overlapped, especially when we consider issues like, e.g., privacy breaches related to the management of personal data or biosamples, ethical issues concerning genetic screening or information about incidental findings, unequal access to healthcare or risks of social and ethnic profiling. Moreover, many polls, consultations and surveys have been conducted in the last twenty years on the social and ethical implications of genetic and genomic research and technologies, which indirectly provide useful data about the implications related to LifeTime technologies.

However, LifeTime technologies also have their specific implications on society which cannot be fully equated with those related to genetics and genomics.

Most of these implications are related to the capacity of single-cell analysis to detect changes in cellular phenotypes in a (phenotypically and possibly genetically) heterogeneous population of cells, providing more detailed information on epigenetic changes and an accurate snapshot of what happens to each cell in the transformation processes that occur during disease. This also implies producing more refined information about how personal behaviours and environmental factors play a role in the present and future of one's health state and that of one's own offspring. This has distinct potential impacts of social and ethical nature on issues such as:

- **Concept of illness and health** (thanks to early-testing of patients using single-cell analysis, the impact of personal behaviours and environmental conditions can be perceived more clearly than in the past, thus leading to a larger reconsideration of what being ill or healthy basically mean)
- **Personal responsibility for health** (single-cell technologies allow us to have a more specific view about how our lifestyle choices impact on our health and the health of our children, thus enlarging the scope of one's own responsibility; moreover, earlier disease detection, thanks to single-cell, analysis requires patients to be more proactive in both the elaboration of diagnoses and the implementation of therapies)
- **Security of data and biosamples** (single-cell technologies will generate immense amounts of sensitive data that can provide much more information about ourselves and our behaviours than other technologies; this inevitably increases the risk related to, e.g., data losses or privacy breaches)
- **Social and ethnic bias and profiling** (the risks of discrimination and stigmatisation of social groups may increase if also cultural behavioural patterns can be considered as a factor impacting on health)
- **Informed consent** (single-cell analyses produce a huge amount of complex information which is difficult to manage through traditional informed consent formulations, raising the question of how broad an informed consent can be; this is particularly true for research purposes, because the need may arise to use the data for experiments or questions that were not considered when patients accepted to be part of a research programme).

Other social and ethical issues are connected with the use of AI in healthcare and the development of personalised organoid disease models. As noticed above, the application of AI in healthcare services has been only rarely considered in a public consultation, while organoids have apparently never been the subject of public consultation.

These considerations lead us to identify a **second objective** for a future consultation: assessing the attitude of stakeholders and the public at large towards the specific social and ethical implications of LifeTime technologies.

2.3. Generating new knowledge on the conditions of application of LifeTime technologies

As noticed above, respondents share more or less the same level of expectations about the potentialities of LifeTime technologies, even though their worries are partly different. The latter are mainly related to the condition of applications of such technologies. They may concern, for example:

- The risk that ethical and privacy regulations may slow down or strongly limit research advancements
- The risk that different factors of economic, organisational or cultural nature may hinder the application of these technologies in the healthcare systems
- The risk that the application of these technologies could entail unintended negative consequences for patients and citizens.

All these worries do not only concern LifeTime technologies but also encompass all the technologies concurring in the shift to personalised medicine.

This kind of issues has been largely discussed in the literature and in some high-level policy documents produced by national or international bodies. However, they have been rarely considered in consultations involving stakeholders or the public at large.

Although including these issues in a stakeholder consultation may entail some methodological problems, understanding stakeholders' attitudes towards the conditions allowing precision medicine-related technologies to be appropriately applied could provide useful information for defining a future roadmap and anticipating obstacles and tensions.

Thus, the **third objective** of the consultation could be precisely: generating new knowledge on the conditions of application of all the technologies contributing to personalised medicine, including LifeTime technologies.

3. Methodological options

In this paragraph, we will briefly present the main methodological options related to the design of a stakeholder consultation on LifeTime technologies to be carried out in the future.

Very roughly, two main issues should be dealt with:

- Which are the stakeholder groups to be involved in the consultation
- Which are, in general, the main approaches available to implement a consultation exercise.

3.1. Stakeholder groups

The concept of "stakeholder" has been so largely used across disciplines and different contexts to become difficult to manage (Miles, 2017). In practical terms, the concept is mainly used for referring to all the individual, collective or institutional actors which may affect or can be affected by a given policy, project or measure and who, therefore, are able to influence its developments and results.

There are different possible categories of people who can be defined as stakeholders. A classification which is frequently used is the one from the European Commission (2017) distinguishes among six different kinds of stakeholders, i.e.:

- Those who will be involved in the implementation of the policy (we can refer to them as "implementers")
- Those affected by the policy ("affected actors")
- Those that have stated interest in the policy ("interested actors")
- Those that have knowledge and expertise about the issue ("experts")
- Those that support or can block solutions related to the issue ("supporting/antagonist actors).

According to the **types of stakeholders** they address, we can distinguish between public consultations and targeted consultations.

- **Public consultations** are consultations targeting the public at large and involving a wide spectrum of respondents, without, however, ensuring full statistical representativeness, which is instead expected in the case of a survey (EC, 2014)
- **Targeted consultations** are consultations reaching selected groups of stakeholders, thus tapping expertise more efficiently; in some cases, a single panel of experts is involved (this is the case, for example, of consultations based on the "Delphi method").

3.2. Consultation approaches and tools

There are different variables to take into consideration in designing a stakeholder consultation. Roughly, they refer to two main topics:

- The mode of consultation
- The tools used for the consultation.

The **mode** refers to the basic distinction between online/offline consultation. Mixed modes are often also used.

As for the **tools**, they can be characterised by the different degree of "openness" left to respondents to express their view. Among the tools, shifting from the closest to the more open ones, we can mention the followings:

- Structured questionnaire (questionnaire only including closed-ended questions)
- Semi-structured questionnaire (questionnaire including both closed-ended and open-ended questionnaire)
- Unstructured questionnaire (questionnaire including only or prevalently open-ended questions)
- Documents used as the basis for asking comments
- A wide range of tools in case of consultations implying direct interactions (e.g., world cafe, civic dialogue, focus group, etc.).

It is quite evident that the more the dialogue is open, the more respondents are allowed to qualify their opinions and to deal with specific questions. Consultations exercises often mix different tools

4. A scheme for the stakeholder consultation

On the basis of the options considered above, it is possible to define a scheme for the stakeholder consultation on LifeTime technologies.

As we have seen, three main groups of objectives of the consultation have been identified, as reported in Table 6, below.

Table 6 – Objectives of the stakeholder consultation

#	Description
Objective 1	– Assessing to what extent stakeholders know and are aware of LifeTime technologies – Using the consultation for increasing stakeholders' knowledge and awareness of LifeTime technologies
Objective 2	– Assessing the attitude of stakeholders and the public at large towards the specific social and ethical implications of LifeTime technologies
Objective 3	– Generating new knowledge on the conditions of application of all the technologies contributing to personalised medicine, including LifeTime technologies

As for the stakeholders, a first tentative list is proposed in Table 7, below.

Table 7 – Stakeholders to potentially involve in the consultation

Type of stakeholder	Description	Tentative list of stakeholders
Implementers	Those who will be involved in the implementation of the policy, project, or measure	Researchers/research institutes, Clinicians/ healthcare providers, Industry/Business, National governments, Local governments
Affected actors	Those affected by the policy, project, or measure	Public at large
Interested actors	Those that have stated interests in the policy, project, or measure	Industry/Business
Experts	Those that have knowledge and expertise about the issues involved	Social scientists, Ethicists, Public Health specialists
Supporting/ Antagonist actors	Those that support or can block solutions related to the issues involved	EU institutions, National/European medical associations, National/European Patient Groups, National/European associations representing industry/business

In order to pursue objectives 1 and 2, the involvement of the public at large (including citizens and patients) is necessary. As for objective 3, the issues to be considered are much more specific and mainly require the involvement of qualified stakeholders (implementers, experts, interested actors, supporting/antagonist actors).

All that considered, the strategy proposed here is that of splitting the consultation into two different branches, i.e.:

– A **targeted consultation**, involving all the key stakeholders, except the public at large
– A **public consultation** addressing the public at large.

The **targeted consultation** should be based on an invitation list including the different kinds of stakeholders mentioned above. Respondents can be invited as either representatives of an

institution or individual experts. The consultation should be conducted online adopting a semi-structured questionnaire (including closed questions complemented with comments or specifications). The targeted consultation should be only focused on the different issues pertaining to objective 3 (conditions of application of all the technologies contributing to personalised medicine, including LifeTime technologies). Since extracting data from open-ended questions or free comments is costly, it will be important to establish, for each type of stakeholder, a maximum number of respondents, in order to keep the total number of interviews as small as possible. Indicatively, the number of respondents should not exceed 200 units. The targeted consultation should be conducted in English only.

The **public consultation** should be conducted online and should be open to anyone. It could be based on a structured questionnaire, including only closed questions, focusing on the respondents' knowledge and awareness of LifeTime technologies (objective 1), as well as their attitudes towards their social and ethical implications (objective 2). Considering that in public consultations – differently from surveys –statistical representativeness is not required, the determination of a target number for respondents will depend on the aims of the consultation itself, and well as the available resources. In any case, it will be important to establish quantitative targets for each European country, while the questionnaire should be available in all the languages recognised by the EU.

In case both consultations are planned, it would be advisable to start with the targeted consultation and, also on the basis of the information collected, to launch the public consultation at a later time. In this way, it will be also possible to mobilise the stakeholders contacted during the targeted consultation for promoting the public consultation at European level or within their countries.

Both consultations should be open online for a given period of time (from 2 to 4 months). In case of need, a time extension can be decided later.

The main features of both the public and the targeted consultation are summarised in Table 8, below.

Table 8 – Main features of targeted vs. public consultations

	Targeted consultation	Public consultation
Stakeholders	Selected stakeholders	The public at large
Mode	Online	Online
Focus	Objective 3	Objectives 1 and 2
Tool	Semi-structured questionnaire	Structured questionnaire
Number of respondents	To be defined per type of stakeholder	To be defined per country
Language	English	All the languages recognised by the EU
Access to the consultation	By invitation only	No restrictions except that of being an EU citizen/residents

It is to highlight that the public consultation and the targeted consultation can also be run autonomously from each other. This will allow a flexible approach, especially in case the available funds are not sufficient for implementing both consultations.

5. Contents of the consultation and possible questionnaire structure

It is difficult at this stage to exactly identify the contents of the consultation, and therefore the questionnaires to be used, since they will also depend upon the features of the project the consultation will be part of. Therefore, the following orientations can be only understood as indicative of the possible structure of the questionnaires.

5.1. Targeted consultation

As mentioned above, the targeted consultation should be aimed at generating new knowledge on the conditions of application of all the technologies contributing to personalised medicine, including LifeTime technologies (objective 3).

To this aim, on the basis of the interviews and the literature review carried out, it is possible to identify **three main kinds of conditions** affecting the application of these technologies.

- **Conditions related to organisational arrangements**. Personalised medicine requires a change in the way healthcare systems are organised and managed. A set of issues could be highlighted in this regard:
  - The development of new healthcare provision models
  - The organisation of the research work
  - The relation between research and clinical work
  - The development and management of biodata infrastructures
  - The regulation of public-private relationships
  - The allocation of funds.

- **Conditions related to stakeholders' culture and relational practices**. Personalised medicine requires important changes in the cultural orientations of all the actors involved and in the way in which they cooperate with each other. A set of issues could be highlighted in this regard:
  - Changes in medical responsibility, practices and authority
  - Changes in doctor-patient relationships
  - Increased importance of interdisciplinary work and changes in the relationships between researchers and clinicians
  - Changes in the role of patients in the clinical and research context.

- **Conditions related to the management of the social impacts of personalised medicine**. Personalised medicine will have social impacts, related to public health, which should be appropriately managed. They concern both the availability of personalised medicine benefits to the entire population and the prevention of possible social risks. A set of issues could be highlighted in this regard:
  - Equitable access to care
  - Risks related to social bias and profiling deriving from the use of large datasets
  - Risk related to breaches of personal rights in the management of large datasets.

The semi-structured questionnaire could therefore be organised in five parts:

I. Information about the respondent (5 to 7 questions)
II. Conditions related to organisational arrangements (12 to 18 closed questions and request for comments for each question)
III. Conditions related to stakeholders' culture and relational practices (8 to 12 closed questions and request for comments for each question)
IV. Conditions related to the management of the social impacts of personalised medicine (6 to 9 closed questions and request for comments for each question)
V. Comments about the future development of precision medicine (1 to 2 comments).

Links could be included in the questionnaires to allow respondents to get additional information about the issues dealt with in the interview.

5.2. Public consultation

The public consultation should be aimed at:

- Measuring to what extent the public knowledgeable/aware of LifeTime technologies (Objective 1)
- Measuring the attitude of the public towards the specific social and ethical implications of LifeTime technologies (Objective 2).

Differently from the targeted consultation (which considers all the technologies contributing to the development of personalised medicine), the public consultation exercise is expected to be narrowly focused on LifeTime technologies, i.e.:

- Single-cell biology
- Artificial intelligence to interpret single-cell data
- Personalised organoid disease models.

As for Objective 1, the aim should be that of collecting information about:

- The respondent's perceived level of knowledge of the three LifeTime technologies
- The respondent's sources of information about the three LifeTime technologies
- The respondent's interest to get more information about the three LifeTime technologies.

As for Objective 2, different issues could be considered in the interview. For example, the interview could be aimed at collecting information on the respondents' attitude towards:

- The possibility to measure the impact of their behaviours on the health of their offspring and consequently the increase in personal responsibility on one's own health conditions
- The release of personal information for scientific reasons and for enhancing public health, even beyond the scope of the informed consent
- The security of personal data potentially concerning other persons (relatives and children)
- The possibility for patients to play a proactive role in healthcare provision
- The possibility that personal information could lead to forms of social profiling and social bias

- The possibility that diagnoses and treatments could be increasingly produced and managed by AI and learning machines
- The possibility of creating biological models made of one's own cells.

Therefore, the structured questionnaire could be organised in four parts:

I. Information about the respondent (5/7 questions)
II. Knowledge and general attitudes towards LifeTime technologies (4/6 closed questions)
III. Attitudes towards specific social and ethical implications of LifeTime technologies (8/12 closed questions)
VI. Opinion of the respondents about the interview (1/2 questions and a space for comments).

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ANNEX 1

QUALITATIVE INTERVIEW GRID FOR RESEARCHERS

LIFETIME

INTERVIEW GRID

Researchers

The LifeTime Initiative

LifeTime is an EC-funded initiative aimed at developing a Roadmap to take a major step beyond the genomic revolution through quantifying, modelling, and predicting cell trajectories in tissues and whole organisms. This process is expected to fundamentally transform current understandings of life and the practice of medicine. Ultimately, LifeTime's long-term vision is to make it possible for physicians to assess the molecular state of patient tissues in real-time, leading to early diagnosis and effective interception of disease.

LifeTime is based on the development, integration and application of three key technologies:

- The methods of **single-cell biology** to map the gene activity of cells during disease, with the possibility to intercept a wide-range of diseases well in advance of the onset of symptoms and to further develop personalised medicine approaches
- The use of **artificial intelligence (AI)** on a large scale to interpret the data generated by single-cell analysis
- The development of **organoids** (mini-organs) obtained from the cells of patients which allows developing personalised cellular models of human diseases, and thus to better understand the causes of disease and identify possible treatments.

The objective of the interview

We are currently conducting a set of 15 preliminary interviews with researchers, clinicians and representatives of patients' associations, in preparation of a larger stakeholder consultation aimed at collecting information about expectations and concerns, but also practical obstacles and constraints, related to the diffusion and use of single-cell technologies, as the ones mentioned before.

The aim of these preliminary interviews is that of **identifying and framing** – through the perspective of qualified informants like you – **the more important and sensitive issues** to be considered in this larger stakeholder consultation. We will now bring up some broad issues connected to LifeTime, and we will ask you to tell us about your views about them, based on your professional experience and viewpoint.

After briefly asking a few questions about you, the interview is organised in two parts.

- The first part concerns long-term perspectives and visions connected to the advancements in personalised medicine and single-cell research and technologies
- The second part is focused on the short-term impacts of these advancements on current clinical research and practice.

Privacy conditions

All information and opinions you will provide during this interview are strictly confidential and will be exclusively used in the framework of this research study. Anonymity will be ensured in all phases of data processing and reporting.

The interview will be recorded as this increases accuracy in recording your responses and speeds up the process. Recordings will be destroyed at the end of the study.

RESPONDENT PROFILE

Note: Only ask missing information

1. Gender
2. Age
3. Country of residence
4. Nationality
5. Present professional role
6. Research field
7. Professional experience of LifeTime research areas and technologies
   Ask specifically if they have research experience/knowledge about
   - *Single-cell biology/personalised medicine*
   - *Artificial intelligence to interpret single-cell data*
   - *Personalised organoid disease models*

PART ONE
LONG-TERM PERSPECTIVES

In this first part, we would like to focus on the **future perspectives**. We would like to address foreseeable **societal** advancements, **clinical** advancements, and **knowledge** advancements.

Note: DO select questions to ask about single-cell biology, AI and organoids based on the experience of the interviewee as emerged in the respondent profile

A. KNOWLEDGE ADVANCEMENTS

A.1. According to you, in terms of scientific progress, what are the main advancements that can be reasonably expected from the present rapid development of single-cell biology research and technologies even beyond current genomic approaches?

A.2. … And what are the main scientific advancements that can be reasonably expected from the application of artificial intelligence in the biosciences?

A.3. … And what about the scientific advancements that can be reasonably expected from the development of personalised organoid disease models?

B. CLINICAL ADVANCEMENTS

B.1. According to you, what are the main – desirable – impacts the advancements in single-cell biology and personalised medicine – will have in terms of clinical practices (e.g., improvements in diagnosis, prevention, therapies, public health)? *(Including AI applications and the development of personalised organoids)*

C. SOCIETAL ADVANCEMENTS

C.1. According to you, what broader impacts can personalised medicine based on single-cell research and technologies have on society?
(e.g., transformed medical systems, extended healthier lifetime, healthcare cost savings, improved health policies, increased health culture and awareness, modification of health-related personal behaviours, increased role of citizens and patients in healthcare, growth of technological economic sectors)

PART TWO
SHORT-TERM IMPACTS

The second part of the interview is about the short-term and most challenging issues related to the development of personalised medicine based on single-cell biology and related technologies, from the perspective of researchers and research institutions. In your answers, please consider both positive and negative aspects, both potential benefits and risks.

A. IMPLICATIONS FOR RESEARCHERS AND RESEARCH INSTITUTIONS

We would like to start with issues focusing on the impact of the new single-cell technologies on **current research practices and arrangements**.

1. ORGANISATION OF THE RESEARCH WORK

The first issue is how the **organisation of the research work** is expected to change with the further development of these research technologies *(single-cell biology, application of AI in biosciences, personalised organoid disease models)*, for example in terms of interdisciplinary work, access to and use of research technologies, research practices, or access to research funds.

What are the implications for the work of researchers? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*
- *Growing interaction between nanotechnology, biotechnology, information and cognitive technology*
- *New education and training needs*
- *New job opportunities for researchers*
- *Access to research infrastructures*
- *Impact of increasing competition for funds and scientific recognition*

2. DATA/BIOSAMPLES SECURITY

The availability of increasingly larger datasets and biobanks is both a key and promising result and a potentially controversial area. Indeed, issues related to the **management and security of data and bio-samples** arise, e.g., data collection procedures, preventing data/samples loss and protecting personal data.

What are the implications for the work of researchers? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*
- *Access to and sharing of datasets*
- *Legal and ethical issues related to data/samples ownership (does it belong to researchers or patients/test subjects?)*
- *The possibility to apply informed consent rules, given the complexity of the information that is obtained as a result of genomic and single-cell analysis*
- *Management of privacy and confidentiality (e.g., access of the third party; use of data in patenting; data/sample exchange; access of patients to their data)*
- *Use, storage, and sharing of medical data impacted by AI (for example, capacity to identify harms caused by algorithmic activity)*
- *Bias and incompleteness of data used to train healthcare algorithms*

3. ETHICS AND RESEARCH

There are also relevant **ethical implications of research** connected to the use of these new research technologies *(single-cell biology, application of AI in biosciences, personalised organoid disease models)*. Regulations and codes of practice are already in place and cover some aspects. However, new ethical questions arise as research advances, modifying the responsibility profile of researchers and resulting in new procedures, committees, etc.

What are the implications for the work of researchers? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*

- *Need of continuous examination of research objectives by ethics, law and communication experts*
- *Adequacy of present practices (e.g., ethical boards, current regulatory frameworks)*
- *New ethical, social and legal issues affecting research, connected with, e.g.,*
  - *gene-editing technologies (how and to what extent they can be used, how they can be used for germline-based interventions and enhancement)*
  - *creation and use of organoids (which is their legal and ethical status)*
  - *creation of chimeras, i.e., structures of human origin introduced into non-human animals (which is their moral and ethical status, how and for which aims they can be used)*

4. TRUST IN RESEARCH INSTITUTIONS AND RESEARCHERS

Another issue concerns **people's trust in research**. Both ethical and privacy/data management issues could lead to suspect and diffidence, and the new technologies could be rejected in whole or in part by some, as it happened, for instance, to vaccines or GMO research. **Private sector involvement** can also have a negative impact on public trust, in turn affecting public research.

What are the implications for the work of researchers?

***Issues to be proposed**: (if needed)*

- *The capacity, willingness and possibility of researchers to communicate their research or be involved in public engagement initiatives*
- *The development of effective measures and mechanisms ensuring transparency and accountability in genetic research and data management*
- *Trust/distrust in the capacity of public authorities to effectively regulate the contribution of the private sector in the development of research and innovation*
- *Trust/distrust in the capacity of private companies to be accountable and transparent in their research and innovation activities*
- *Trust/distrust in the capacity of patients and citizens to have a voice and to dialogue with private companies in orienting genomic and single-cell research (for example, towards specific pathologies)*
- *The capacity of ensuring human control over AI applications*

5. RESEARCH-CLINICAL WORK RELATIONSHIPS

The development of genomics and single-cell multi-omics is destined to **blur the lines between basic and translational research and clinical work**, about, e.g., the interaction between researchers and clinicians, data management and communication (since patients provide data for clinical and research purposes at the same time), publication and funding schemes.

What are the implications for the work of researchers? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*

- *Innovation of outdated professional models, publication patterns and research funding schemes*
- *Disciplinary culture resistance and lack of competencies for developing new cooperation schemes between researchers and clinicians*
- *Diagnoses related to machine learning methods ("black-box medicine") making it difficult to have a recognisable person taking responsibility*
- *Technical, economic and organisational implications related to a different organisation of healthcare provision*

6. PUBLIC-PRIVATE RESEARCH RELATIONSHIPS

The development of genomic and single-cell research and technologies is fuelled by the involvement of the private sector, in terms of both funding and the development of marketable innovation from public research. **New regulations and practices** to harmonise private interest, innovation and the protection of health as a public good are often claimed.

From your perspective, how is private sector involvement impacting research in positive (e.g. acceleration of research and innovation) and negative terms (e.g., the possible "merchandisation" of research outputs, management of sensitive individual data, etc.)?

***Issues to be proposed**: (if needed)*

- *Regulation and practices related to patenting (e.g., of human gene sequences, of transgenic organisms) and their impact on research*
- *Modes of collaboration and Material Transfer Agreements*
- *Regulations and practices related to the collection, storage, management, and availability of personal data by private companies and their impact on research*
- *Regulations and practices in the development of drugs and their impact on research*
- *The capacity of public authorities to keep control over the quality and reliability of the algorithms used in genomics and single-cell research and technologies*

B. OTHER EMERGING ISSUES

A second, broad area concerns broader societal issues which do not directly impact your work as a researcher, but which are still connected to single-cell biology, applications of AI in the biosciences, personalised organoid disease models and more generally to personalised medicine. We are interested in your qualified point of view about them.

7. EQUITABLE ACCESS TO CARE

Personalised and single-cell research and therapies are costly, and ensuring **fair access** could be difficult. This issue primarily concerns health policies and systems. However, researchers and research systems are increasingly expected to be involved with healthcare delivery and in finding sustainable, innovative solutions.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (If needed)*

- *Cost of drug development which could be problematic for low and middle-income classes and low and middle-income countries*
- *The risk that genomic and cell-based medicine could exacerbate the existing health variations because of unfair access to the cure*
- *The allocation of research funds*

8. BIAS AND PROFILING

Another issue is the risk of social, ethnic, and gender profiling (or profiling according to other categories). Genomic and single-cell research may lead to forms of **discrimination and stigmatisation** of large groups and subgroups. This problem could be even more acute in the case of AI in healthcare, since bias and profiling may be much more difficult to detect and rectify.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *Under-representation of specific ethnic minorities and groups in clinical trials and research data, leading to biased scientific results and therapies*
- *The quality and representativeness of data used to train machine learning algorithms (for example, adult males of Caucasian origin being strongly overrepresented)*
- *Cultural and ethnic identification which could lead to stigmatisation if the group is found to have a genetic disposition to particular diseases*

9. MANAGING EXPECTATIONS ABOUT NEW TECHNOLOGIES

The advancements in this sector are evident and hopes and expectations are high. However, there could be the risk of overpromising about the **practical relevance of research outputs for patient care**, at least in the short to medium term, and it could be difficult to make a realistic cost/benefit assessment of new applications.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *Connection with funding dynamics and possible distortions*

10. OTHER ISSUES

Are there any other relevant issues which you think did not emerge in our interview?

Thank you for your kind cooperation …

ANNEX 2

QUALITATIVE INTERVIEW GRID FOR CLINICIANS

LIFETIME

INTERVIEW GRID

Clinicians

The LifeTime Initiative

LifeTime is an EC-funded initiative aimed at developing a Roadmap to take a major step beyond the genomic revolution through quantifying, modelling, and predicting cell trajectories in tissues and whole organisms. LifeTime's long-term vision is to make it possible for physicians to assess the molecular state of patient tissues in real-time, leading to early diagnosis and effective interception of disease.

LifeTime is based on the development, integration and application of three key technologies:

- The methods of **single-cell biology** to map the gene activity of cells during disease, with the possibility to intercept a wide-range of diseases well in advance of the onset of symptoms and to further develop personalised medicine approaches
- The use of **artificial intelligence** (AI) on a large scale to interpret the data generated by single-cell analysis
- The development of **organoids** (mini-organs) obtained from the cells of patients which allows developing personalised cellular models of human diseases, and thus to better understand the causes of disease and identify possible treatments.

The objective of the interview

We are currently conducting a set of 15 preliminary interviews with researchers, clinicians and representatives of patients' associations, in preparation of a larger stakeholder consultation aimed at collecting information about expectations and concerns, but also practical obstacles and constraints, related to the diffusion and use of single-cell technologies, as the ones mentioned before.

The aim of these preliminary interviews is that of **identifying and framing** – through the perspective of qualified informants like you – **the more important and sensitive issues** to be considered in this larger stakeholder consultation. We will now bring up some broad issues connected to LifeTime, and we will ask you to tell us about your views about them, based on your professional experience and viewpoint.

After briefly asking a few questions about you, the interview is organised in two parts.

- The first part concerns long-term perspectives and visions connected to the advancements in personalised medicine and single-cell research and technologies
- The second part is focused on the short-term impacts of these advancements on current clinical research and practice.

Privacy conditions

All information and opinions you will provide during this interview are strictly confidential and will be exclusively used in the framework of this research study. Anonymity will be ensured in all phases of data processing and reporting.

The interview will be recorded as this increases accuracy in recording your responses and speeds up the process. Recordings will be destroyed at the end of the study.

RESPONDENT PROFILE

Note: Only ask missing information

1. Gender
2. Age
3. Country of residence
4. Nationality
5. Present professional role
6. Research field
7. Professional experience with LifeTime research areas and technologies

Ask specifically if they have research or clinical experience/knowledge about

- *Single-cell biology/personalised medicine*
- *Artificial intelligence to interpret single-cell data*
- *Personalised organoid disease models*

PART ONE
LONG-TERM PERSPECTIVES

In this first part, we would like to focus on the **future perspectives**. We would like to address foreseeable **societal** advancements, **clinical** advancements, and **knowledge** advancements.

Note: DO select questions to ask about single-cell biology, AI and organoids based on the experience of the interviewee as emerged in the respondent profile

A. CLINICAL ADVANCEMENTS

A.1. According to you, what are the main – desirable – impacts the advancements in single-cell biology and personalised medicine – will have in terms of clinical practices (e.g., improvements in diagnosis, prevention, therapies, public health)?

A.2. … And what are the main – desirable – impacts which can be reasonably expected on clinical practice from the application of artificial intelligence in the biosciences?

A.3. … And what could realistically be the impacts of the developments of personalised organoid disease models in clinical practice?

B. KNOWLEDGE ADVANCEMENTS

B.1. According to you, in terms of scientific progress, what are the main advancements that can be reasonably expected from the present rapid development of single-cell biology research and technologies even beyond current genomic approaches*? (Including AI applications and the development of personalised organoids)*

C. SOCIETAL ADVANCEMENTS

C.1. According to you, what broader impacts can personalised medicine based on single-cell research and technologies have on society?
(e.g., transformed medical systems, extended healthier lifetime, healthcare cost savings, improved health policies, increased health culture and awareness, modification of health-related personal behaviours, increased role of citizens and patients in healthcare, growth of technological economic sectors).

PART TWO
SHORT-TERM IMPACTS

The second part of the interview is about the short-term and most challenging issues related to the development of personalised medicine based on single-cell biology and related technologies, from the perspective of clinicians, healthcare providers and public health in general. In your answers, please consider both positive and negative aspects, both potential benefits and risks.

A. IMPLICATIONS FOR CLINICIANS AND HEALTHCARE PROVIDERS

We would like to start with issues focusing on the impact of the new single-cell technologies on **current clinical practices and arrangements** as concerns, e.g., diagnoses, therapies, and relations with patients.

1. EVALUATION OF BENEFITS AND RISKS

A relevant issue, in this regard, concerns the evaluation, for individual patients, of the benefits and risks of therapies related to single-cell technologies having to consider, e.g., safety issues, high costs, the risk of overpromising about their effects.

What are the consequences for clinical work? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*
- *Improved and enlarged set of personalised alternatives*
- *Criteria to use for assessing safety and utilities of therapies related to single-cell technology approaches and the extended use of AI*
- *Risk of overdiagnosis (for example, when the diagnosis is strongly dependent on the use of algorithms)*
- *Overpromises about the potential of new therapies based on single-cell technology approaches*
- *High cost of diagnosis and therapies based on genomic and single-cell technologies and consequent need for clinicians to make difficult decisions on whether to opt for them or for less-costly traditional approaches*

2. MEDICAL RESPONSIBILITY AND AUTHORITY

Another related aspect concerns the **responsibility and authority of healthcare professionals**. Developments in personalised medicine are making medicine more complex and dependent on the use of increasingly advanced technologies and large datasets. In this frame, the responsibility of physicians increases, while their direct control over medical data and their interpretation risks decreasing.

What are the consequences for clinical work? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*
- *Increased set of competencies of medical doctors*
- *Need for training to keep control over the diagnostic and therapeutic processes*
- *Tendency to shift medical authority from clinicians to technicians, because of the increased use of algorithms and models in defining diagnosis and therapies*
- *Need for processes supporting clinical decision-making for integrating patient biomarker information*

3. DATA/BIOSAMPLES SECURITY

The availability of increasingly larger datasets and biobanks is both an opportunity and a potentially controversial area. Indeed, issues related to the **management and security of data and bio-samples** arise, e.g., in data collection procedures, preventing data/samples loss and protecting personal data. This aspect is particularly serious considering the dual use of patients' clinical data, i.e., for clinical and research purposes.

What are the consequences for clinical work? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*

- *Access to and sharing of datasets*
- *Legal and ethical issues related to data/samples ownership (who is the owner of data; how patients can access their personal data)*
- *Management of privacy and confidentiality (for example, access of the third party; use of data in patenting; data/sample exchange; access of patients to their data)*

4. INFORMED CONSENT

Another important question concerns how **informed consent** could be applied in the context of personalised medicine, given the complexity of the information that is obtained as a result of genomic and single-cell analysis and also considering that sensitive results may involve other people (e.g., children and relatives).

What are the consequences for clinical work? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*

- *The need for a greater level of genomic literacy of patients to make them aware of the contents of the informed consent*
- *The need to involve in the process, besides healthcare providers, additional actors (including researchers and pharmaceutical companies)*
- *The need to clarify the scope and validity over time of the informed consent, given that personal data may provide sensitive information on other people (for example, children and relatives) and may be used in the future for other purposes which are not predictable*
- *The need to inform patients and citizens about the location and use of their data*

5. DOCTOR-PATIENT RELATIONSHIP

The development of single-cell research and personalised medicine poses new questions about doctor-patient relationship. Genome and single-cell analyses increases the amount of information available, implying the need to identify **what information is to be provided to patients**, while also widening the group of stakeholders involved (e.g., with the increased role of technicians in diagnoses and therapies), potentially weakening the doctor-patient bilateral relationship. The use of Artificial Intelligence in defining diagnosis and therapies – with all its benefits and risks – may also profoundly change the role of physicians and affect doctor-patient relationships.

What are the consequences for clinical work? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*

- *Patients having to deal with multiple professional figures (e.g., technicians, AI specialists, geneticists)*
- *More active involvement of patients in the clinical process*
- *Need to decide which is the right level of information to pass on*
- *The variable attitude of patients towards knowing or not knowing about testing procedures and their outputs*
- *Information of patients about incidental findings*
- *Management of information about patient's relatives deriving from genome and single-cell analysis*
- *Management of screenings such as newborn screenings, screening involving patients' relatives (cascade screenings) or screening for reproductive purposes*
- *Regime of confidentiality and privacy about patient's genome and single-cell analysis information*

B. OTHER EMERGING ISSUES

A second, broad area concerns broader societal issues which might impact more indirectly your work as a clinician, but which are still connected to single-cell biology, applications of AI in the biosciences, personalised organoid disease models and more generally to personalised medicine. We are interested in your qualified point of view about them

6. EQUITABLE ACCESS TO CARE

Personalised and single-cell research and therapies and personalised medicine are costly, and ensuring **fair access** could be difficult. There is the risk that, in the next future, only wealthier patients will be able to take advantage of these advancements.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *Cost of drug development which could be problematic for low and middle-income classes and low and middle-income countries*
- *The risk that personalised medicine could exacerbate the existing health variations because of unfair access to healthcare*
- *The introduction of new criteria in the allocation of resources*

7. BIAS AND PROFILING

Another issue is the risk of social, ethnic, and gender profiling (or profiling according to other categories). Genomic and single-cell research may lead to forms of **discrimination and stigmatisation** of large groups and subgroups. This problem could be even more acute in the case of AI in healthcare, since bias and profiling may be much more difficult to detect and rectify.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *Under-representation of specific ethnic minorities and groups in clinical trials and research data, leading to biased scientific results and therapies*
- *Cultural and ethnic identification which could lead to stigmatization if the group is found to have a genetic disposition to particular diseases*

8. FUTURE HEATHCARE PROVISION MODELS

The development of personalised medicine is going to change **healthcare provision models**, which are expected to be increasingly delivered in out-patient settings, based on coordinated, multidisciplinary care involving expert centres, clinical labs, and researchers.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *Less invasive, personalised and sustainable healthcare models for patients*
- *Resistance to modify consolidated practices from different professional groups*
- *Bureaucratic obstacles*
- *Technical, economic and organisational implications related to a different organisation of healthcare provisions*

9. INCREASED INVOLVEMENT OF THE PRIVATE SECTOR IN HEALTHCARE DELIVERY

The development of genomic and single-cell research and technologies is fuelled by the **involvement of the private sector**. This also concerns healthcare provisions, since private actors will be involved in providing technology allowing and managing DNA sequencing, in collecting and managing personal data and biosamples or in designing and producing personalised drugs and therapies.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *The need to define new regulations and practices related to patenting (e.g., of human gene sequences, of transgenic organisms), patients' data management, development of drugs*
- *Impact of the greater involvement of the private sector on people's trust/distrust in healthcare providers and public health authorities*

10. OTHER ISSUES

Are there any other relevant issues which you think did not emerge in our interview?

Thanks for your kind cooperation …

ANNEX 3

QUALITATIVE INTERVIEW GRID FOR
REPRESENTATIVES OF PATIENT ASSOCIATIONS

LIFETIME

INTERVIEW GRID

Patient groups

The LifeTime Initiative

LifeTime is an EC-funded initiative aimed at developing a Roadmap to take a major step beyond the genomic revolution through quantifying, modelling, and predicting cell trajectories in tissues and whole organisms. Ultimately, LifeTime's long-term vision is to make it possible for physicians to assess the molecular state of patient tissues in real-time, leading to early diagnosis and effective interception of disease.

LifeTime is based on the development, integration and application of three key technologies:

- The methods of **single-cell biology** to map the gene activity of cells during disease, with the possibility to intercept a wide-range of diseases well in advance of the onset of symptoms and to further develop personalised medicine approaches
- The use of **artificial intelligence** (AI) on a large scale to interpret the data generated by single-cell analysis
- The development of **organoids** (mini-organs) obtained from the cells of patients which allows developing personalised cellular models of human diseases, and thus to better understand the causes of disease and identify possible treatments.

The objective of the interview

We are currently conducting a set of 15 preliminary interviews with researchers, clinicians and representatives of patients' associations, in preparation of a larger stakeholder consultation aimed at collecting information about expectations and concerns, but also practical obstacles and constraints, related to the diffusion and use of single-cell technologies, as the ones mentioned before.

The aim of these preliminary interviews is that of **identifying and framing** – through the perspective of qualified informants like you – **the more important and sensitive issues** to be considered in this larger stakeholder consultation. We will now bring up some broad issues connected to LifeTime, and we will ask you to tell us about your views about them, based on your professional experience and viewpoint.

After briefly asking a few questions about you, the interview is organised in two parts.

- The first part concerns long-term perspectives and visions connected to the advancements in personalised medicine and single-cell research and technologies
- The second part is focused on the short-term impacts of these advancements on current clinical research and practice.

Privacy conditions

All information and opinions you will provide during this interview are strictly confidential and will be exclusively used in the framework of this research study. Anonymity will be ensured in all phases of data processing and reporting.

The interview will be recorded as this increases accuracy in recording your responses and speeds up the process. Recordings will be destroyed at the end of the study.

RESPONDENT PROFILE

Note: Only ask missing information

1. Gender
2. Age
3. Country of residence
4. Nationality
5. Core professional qualifications
6. Employment position
7. Patient organisations
8. Role in the patient organisation
9. Disease area (Cancer, Neurodegenerative diseases, Inflammation and autoimmune, Infectious diseases, cardiovascular and metabolic diseases)
10. Experience with/knowledge of LifeTime research areas and technologies
    Ask specifically if they have personal experience/knowledge about
    - *Single-cell biology/personalised medicine*
    - *Artificial intelligence to interpret single-cell data*
    - *Personalised organoid disease models*

PART ONE
LONG-TERM PERSPECTIVES

In the second part of this interview, we will go into the practical challenges in current research, clinical practice, healthcare provision and patient experience connected to further developments in personalised medicine based on the analysis of single cells and connected technologies.

In this first part, we would like to focus on the **future perspectives**. We would like to address foreseeable **societal** advancements, **clinical** advancements, and **knowledge** advancements.

Note: DO select questions to ask about single-cell biology, AI and organoids based on the experience of the interviewee as emerged in the respondent profile

A. SOCIETAL ADVANCEMENTS

A.1. According to you, what are the main promises of personalised medicine based on single-cell research and technologies for health and healthcare?
(e.g., transformed medical systems, increased role of citizens and patients in healthcare, extended healthier lifetime, healthcare cost savings, improved health policies, increased health culture and awareness, modification of health-related personal behaviours, growth of technological economic sectors).

A.2. How do you expect these technologies to impact [the disease of concern of the organisation] in terms of prevention, therapies, care arrangements, patient role and responsibility?

B. CLINICAL ADVANCEMENTS

B.1. According to you, what are the main – desirable – impacts the advancements in single-cell biology and personalised medicine – will have in terms of clinical practices (e.g., improvements in diagnosis, prevention, therapies, public health)? *(Including AI applications and the development of personalised organoids)*

C. KNOWLEDGE ADVANCEMENTS

C.1. According to you, in terms of scientific progress, what are the main advancements that can be reasonably expected from the present rapid development of single-cell biology and personalised medicine?

PART TWO
SHORT-TERM IMPACTS

The second part of the interview is about the short-term and most challenging issues related to the development of personalised medicine based on single-cell biology, especially in the perspective of patients and public health. In your answers, please consider both positive and negative aspects, both potential benefits and risks.

1. CHANGES IN THE CONCEPTS OF HEALTH, ILLNESS AND IDENTITY

Advancements in single-cell biology may have an impact on the very **concept of health and illness**. Today, illness is defined clinically. In the future, disease will be more and more intercepted before the symptoms appear, hence the boundaries between being sick and being healthy will increasingly blur. Moreover, the very perception of personal identity can be influenced by the possibility to access one's genome and its information on current and prospective conditions.

What are the consequences for citizens and patients, on the one hand, and public healthcare systems, on the other? Are there also opportunities opening up?

***Issues to be proposed**: (if needed)*
- *Emotional and practical impacts of genetic testing and single-cell technologies on patients*
- *Changes in the way people see their future or their identity*
- *Risk to overburden public healthcare systems*

2. PERSONAL RESPONSIBILITY FOR HEALTH

In this framework, new technologies are now empowering patients to know, not only genetic predisposition to a specific illness, but also how aspects of their lifestyle or their environment have an impact on their health, including on their offspring. This may affect the sense of personal responsibility for health. Taken to the extremes, this attitude can potentially lead to blaming the sick for their illness, but in general, it loads people with responsibilities while risking excessive medicalisation of life.

What are the consequences for citizens and patients? Does this development also have positive aspects?

***Issues to be proposed**: (if needed)*
- *Changes in the concept of compliance to therapies and in connected practices*
- *Risk of medicalising increasingly large parts of human life*
- *New expectations to be closely monitored and screened in a prevention setting*

3. DOCTOR-PATIENT RELATIONSHIPS

The development of single-cell research and personalised medicine poses new questions about doctor-patient relationship. Genome and single-cell analyses increases the amount of information available, implying the need to identify **what information is to be provided to patients**, while also widening the group of stakeholders involved (e.g., with the increased role of technicians in diagnoses and therapies), potentially weakening the doctor-patient bilateral relationship. The use of Artificial Intelligence in defining

diagnosis and therapies – with all its benefits and risks – may also profoundly change the role of physicians and affect doctor-patient relationships.
From your vantage point, what are the consequences for patients?

***Issues to be proposed**: (if needed)*
- *Patients having to deal with multiple professional figures (e.g., technicians, AI specialists, geneticists)*
- *More active involvement of patients in the clinical process*
- *Need to decide which is the right level of information to pass on*
- *The variable attitude of patients towards knowing or not knowing about testing procedures and their outputs*
- *Information of patients about incidental findings*
- *Management of information about patient's relatives deriving from genome and single-cell analysis*
- *Management of screenings such as newborn screenings, screening involving patients' relatives (cascade screenings) or screening for reproductive purposes*
- *Regime of confidentiality and privacy about patient's genome and single-cell analysis information*

4. INFORMED CONSENT

Another important question concerns how **informed consent** could be applied in the context of personalised medicine, given the complexity of the information that is obtained as a result of genomic and single-cell analysis and also considering that sensitive results may involve other people (e.g., children and relatives).

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*
- *The need for a greater level of genomic literacy of patients to make them aware of the contents of the informed consent*
- *The need to involve in the process, besides healthcare providers, additional actors (including researchers and pharmaceutical companies)*
- *The need to clarify the scope and validity over time of the informed consent, given that personal data may provide sensitive information on other people (for example, children and relatives) and may be used in the future for other purposes which are not predictable*
- *The need to inform patients and citizens about the location and use of their data*

5. EQUITABLE ACCESS TO CARE

Personalised and single-cell research and therapies and personalised medicine are costly, and ensuring **fair access** could be difficult. There is the risk that, in the next future, only wealthier patients will be able to take advantage of these advancements.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*
- *Cost of drug development which could be problematic for low and middle-income classes and low and middle-income countries*
- *The risk that personalised medicine could exacerbate the existing health variations because of unfair access to healthcare*
- *The introduction of new criteria in the allocation of resources*

6. DATA/BIOSAMPLES SECURITY

Personalised medicine also brings to the fore security problems of **patients' data and biosamples**. This aspect is particularly serious considering the dual use of patients' clinical data, i.e., for clinical and research purposes.

From your vantage point, what are the main issues to highlight in this domain?

Issues to be proposed: *(if needed)*

- *Needed tools and procedures for patients' data protection*
- *Legal and ethical issues related to data/samples ownership (who is the owner of data; how patients can access their personal data)*
- *The need to find a balance between data protection and the opportunity to broaden the scope and length of analysis so as to increase the possibility to prevent serious diseases*
- *Management of privacy and confidentiality (for example, access of the third party, like insurers or private companies; use of data in patenting; data/sample exchange; access of patients to their data)*

7. BIAS AND PROFILING

Another issue is the risk of social, ethnic, and gender profiling (or profiling according to other categories). Genomic and single-cell research may lead to forms of **discrimination and stigmatisation** of large groups and subgroups. This problem could be even more acute in the case of AI in healthcare, since bias and profiling may be much more difficult to detect and rectify.

From your vantage point, what are the main issues to highlight in this domain?

Issues to be proposed*: (if needed)*

- *Under-representation of specific ethnic minorities and groups in clinical trials and research data, leading to biased scientific results and therapies*
- *Cultural and ethnic identification which could lead to stigmatization if the group is found to have a genetic disposition to particular diseases*

8. PATIENT AND CITIZEN ENGAGEMENT

Personalised medicine is based on a **proactive role of patients**, for example in providing information, deciding about their personal data and taking clinical decisions. Similarly, the development of personalised medicine also requires a **higher engagement of citizens** in the research endeavour and health policies (e.g., as members of ethics committees or joint policy groups). The question is, therefore, how to support this process in cultural and organisational terms.

From your vantage point, what are the main issues to highlight in this domain?

Issues to be proposed*: (if needed)*

- *Mechanisms and tools for citizens' surveillance over the new technologies and their application*
- *Empowerment of patients in terms of information, health literacy, health self-management, use of personal health-related technological devices*
- *Procedures to promote the involvement of patients' or citizens' association in healthcare provisions*
- *Involvement of patients and citizens in health research programmes (Citizen science)*

9. TRUST IN THE INVOLVEMENT OF THE PRIVATE SECTOR IN RESEARCH AND INNOVATION

A more general, connected issue concerns **people's trust** in research and clinical advancements in genomics and single-cell research. Both ethical and privacy/data management issues could lead to suspect and diffidence, and the new technologies could be rejected in whole or in part by some sectors of society, as it happened, for instance, to GMO research. **Private sector involvement** – so relevant in the field – can also have a negative impact on public trust, leading people to think that technologies are not being developed in the interest of patients.

From your vantage point, what are the main issues to highlight in this domain?

***Issues to be proposed**: (if needed)*

- *Needed transparency and accountability mechanisms, communication and public engagement strategies*
- *Trust/distrust in the capacity of patients and citizens to have a voice and to dialogue with private companies in orienting genomic and single-cell research (for example, towards specific pathologies)*
- *Trust/distrust in the capacity of public authorities to effectively regulate the contribution of the private sector in the development of research and innovation*
- *Trust/distrust in the capacity of private companies to be accountable and transparent in their research and innovation activities*

10. FUTURE HEATHCARE PROVISION MODELS

The development of personalised medicine is going to change **healthcare provision models**, which are expected to be increasingly delivered in out-patient settings, based on coordinated, multidisciplinary care involving expert centres, clinical labs, and researchers.

What are the consequences for citizens and patients? What opportunities are opening up?

***Issues to be proposed**: (if needed)*

- *Less invasive, personalised and sustainable healthcare models for patients*
- *Resistance to modify consolidated practices from different professional groups*
- *Bureaucratic obstacles*
- *Technical, economic and organisational implications related to a different organisation of healthcare provisions*

11. OTHER ISSUES

Are there any other relevant issues which you think did not emerge in our interview?

Thank you for your kind cooperation …