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D2.4: Ethical Analysis
of Human Genetics and Genomics

[WP2 – Genomics]

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Abstract

This report is prepared within the context of a European project called SIENNA (http://sienna-project.eu/), which was selected to fulfil the grant call SWAFS-18-2016[1]. The aims are to identify and present ELSI in human genetics and genomics, both present and emerging issues with a relatively short time horizon. First, we report a presentation of the SIENNA approach to ethical analysis, situated in the landscape of other existing frameworks developed for studying ELSI of genomics. We discuss the merits and challenges of different types of investigations pursued in SIENNA: foresight analysis; overview of ELSI of genomics in 11 countries; public survey in 11 countries; and focus-groups in 5 countries. Secondly, we provide an extensive ethical analysis of human genomics[2]. In particular, we focus on the ethical issues pertaining to two areas of human genomics: 1) the study of the genome as currently performed through high throughput sequencing (e.g. with tools such as next generation sequencers); and 2) gene editing (or genome editing: for example, as performed with tools such as CRISPR-Cas9 and other gene editing technologies). The aim of the report is not to make recommendations or present solutions, but only to identify and present ELSI pertaining to genomic technologies within their context of application. The report is based on a description of such technologies in previous deliverable D.2.1 and intends to provide a basis for our next report D.2.7, in which we aim to discuss an ethical framework for human genomics.

While the sheer amount of work outlined in, and conducted for, the formal SIENNA approach is laudable, we question whether it is a requirement to use it to obtain the results herein (i.e. could any other ELSI approach have resulted in the same results); we also question whether it is well adapted for the analysis of the ELSI of human genomics in particular. Moreover, we present some difficulties with attempting to include empirical work into normative analyses; beyond the theoretical reasons, we have also experienced logistical issues relating to the specific types of expertise needed to carry out this work and the challenges raised by trying to obtain such expertise via sub-contracting with a for-profit social and policy research company outside of the consortium. Finally, we remain sceptical of too much unwarranted emphasis on technologies as oppose to their uses, since in genomics, the technologies are constantly changing (from PCR machines to next-generation sequencers etc.) and it is how these technologies affect practice (e.g. clinical testing, research, and other areas) that tends to be the heart of the ethical tension.

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[1] https://ec.europa.eu/info/fundingtenders/opportunities/portal/screen/opportunities/topic-details/swafs-18-%202016

[2] Many of which are also applicable to human genetics. We use human genetics and genomics in the title to be inclusive and because some authors have more strict definitions of each term. Also, it is debatable what category to place gene editing; some would say it is not genomics, nor classical human genetics, yet others would classify it in the both, or one or the other.

Document history

Version	Date	Description	Reason for change	Distribution
V0.1	5 August 2019	First Draft	Comments from the authors	Authors
V0.2	16 August 2019	Version for quality assurance and consortium wide comments	Comments from quality assurance reviewers and all partners	Quality assurance reviewers
V0.3	30 August 2019	Final Version		

Information in this report that may influence other SIENNA tasks

Linked task	Points of relevance
Task 2.7	The proposal for an ethical framework for human genomics will follow-up on the current report as the framework will be based on important issues identified in this task.
Task 5.2	The code of responsible conduct relating to human genomics will require consideration of the issues identified in this task.
Task 6.1	The report on adapting methods for ethical analysis of emerging technologies will require contemplation about the successes and challenges in the methodology used to complete this task.
Task 6.3	The step-by-step guidance from ethical analysis to ethical codes and operational guidelines task will require reflection about the successes and challenges in completing this task.

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Executive summary

What the reader should know about the general context behind the development of this report

This report is delivered in the context of a European Commission (EC) funded SWAFS[3] project called SIENNA, which began in October 2017 (http://www.sienna-project.eu). In the SWAFS-18-2016[4] call, that the SIENNA project has been developed to respond to, three areas of technologies have been defined: Human Genomics, AI/Robotics, and Human Enhancement.

This report is the fourth deliverable completed for Work Package (WP) 2, which addresses the ELSI of Human Genomics. Specifically, this report fulfils the task described in the description of action of the project by the following:

> *"Task 2.4: Analysis of current and future ethical issues: This task will review existing ethical theories and approaches regarding genomics technologies. We will perform an ethical impact assessment of current and future ethical issues. We will use the review and assessment to identify major ethical issues and approaches to them regarding the technology in general, and regarding different domains and applications. The ethical impact assessment will engage stakeholders and experts, and is therefore connected to Tasks 2.5 and 2.6."*

The term "ethical impact assessment" in this context can be replaced by the term "ethical analysis".

All main authors (HCH, EN, AS) of this report are employed as academic researchers at the Centre for Research Ethics and Bioethics at Uppsala University (Uppsala, Sweden) with main expertise in Genomics and Bioethics (HCH and EN) and in Philosophy and Bioethics (AS). All authors declare having no conflicts of interest regarding the material covered in this report.

Both WP3 (ELSI Human Enhancement) and WP4 (ELSI AI/Robotics) lead by S.K. Nagel (UAachen, De, and UTwente, NL) and P. Brey (UTwente, NL) and respectively, have also produced reports with similar aims, however given the different technology areas and related ethical aspects, the organisation of the reports may differ.

What are the aims and use of this report?

This report engages in a critical presentation of SIENNA approach and in an extensive ethical analysis

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[3] SWAFS = Science with and for Society
[4] https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/swafs-18-2016.html

of human genomics. It aims to identify and present ELSI in genomics, both present and emerging ones with a relatively short time horizon. The aim of the report is not to make recommendations or present solutions, but only to identify and present ELSI pertaining genomic technologies within their context of application. The report is based on a description of such technologies in previous deliverable D.2.1 and intends to provide a basis for our next report D.2.7, in which we aim to discuss an ethical framework for human genomics.

What is the content of this report?

In this deliverable, we report on both a critical presentation of the SIENNA approach and an analysis of current and future ethical issues emerging in the context of human genomics.

Section 1 introduces to the topic of the deliverables while presenting the different methods that SIENNA aims to merge in ethical analysis.

Section 2 provides context to the ethical analysis that is to come by providing a brief history of ethics of human genetics and ethical, legal and social issues (ELSI) of genomics. Indeed, the ELSI approaches to study the ethics of human genetics and genomics have predominated in the last three decades since the human genome project. While many early activities related to this approach may have originated primarily in the USA, it is widely used around the world today, including in Europe.

Section 3 presents SIENNA approach for ethical analysis of human genomics and discusses its positioning in the current landscape of frameworks adressing ELSI of genomics. The SIENNA approach can be considered as falling within or overlapping with ELSI approaches. The use of foresight and stakeholder input are certainly interesting but not necessarily novel (for ELSI studies). That said, the formal way in which the steps are described and should be perfomed tend to be more rigid or laboured as compared to the generally very open ELSI approaches. Furthermore, there remains a lot of debate on if and how empirical data could or should be used in normative frameworks. Beyond this, the logistical factors including the generally unrobust (academically) foresight methods and the need for specific expertise to conduct valid empirical studies are challenges to the SIENNA approach. Within the current project, many limitations were encountered with the empirical approaches.

Section 4 provides an overview of what ethical issues in human genomics have been debated in different countries, both in the EU and non-EU countries. This exploratory study, provided a variety of ELSI perspectives, none of which were novel, but which gave an idea of the different preoccupations per country. The content of these reports is not easily summarised and is considered as a resource to be used as we go forward with task 2.7 addressing ethical framework in human genomics.

Section 5 discusses the notion of stakeholder input into (bio)ethical analysis, and in particular provides and overview of two empirical investigations that were performed for SIENNA in the first semester of 2019 and aimed at investigating publics' attitudes towards human genomics. There remains much debate about whether and how empirical studies should be used in normative frameworks. Furthermore, the experience in the SIENNA project of empirical studies has raised many

challenges regarding expertise of methodology and content, as well as logistical and temporal challenges around partnering with a commercial social research company.

Section 6 presents and discusses the foresight approach in SIENNA. The idea of looking towards the future is not new in ethics, however the formal use of foresight notions is not often mentioned in the ELSI approaches. This may be due to the fact that foresight is often considered to lack academically robust methodology. Nonetheless, we conducted a few foresight activities (survey, interview, and workshop) which resulted in valuable information.

Section 7 contains the actual ethical analysis. We briefly summarize the approach for ethical analysis used within SIENNA and in this report. This is followed by an extensive review of ELSI based on the descriptions of technologies developed in a previous deliverable D.2.1 (march 2018) and based on interactions with experts and updated literature. In line with previous deliverables in SIENNA, the ELSI addressed herein focus on two main approaches in genomics: 1) the study of the genome as performed through high throughput sequencing (e.g. with tools such as next generation sequencers); and 2) gene editing (or genome editing, for example, as performed with tools such as CRISPR-Cas9 and other editing technologies). In the first part, we consider ethical issues raised by genome sequencing in particular application domains of human genomics (research; clinics; security and democracy; infrastructures; companionship. In the second part, we address the ELSI of gene editing with a focusing on germline gene editing in research and in the clinic; we also include a brief section on CRISPR-based gene drive approaches in animals.

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List of acronyms/abbreviations

Abbreviation	Explanation
AI	Artificial Intelligence
AIDS	Acquired immune deficiency syndrome
BTWC	Biological and Toxin Weapons Convention
BW	Biological Warfare
DNA	Deoxyribonucleic Acid
DTC	Direct-To-Consumer Genetic Testing
ELSI	Ethical Legal Social Implications/Issues
ELSA	Ethical Legal Social Aspects
EMA	European Medicine Agency
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GE	Gene editing
GLGE	Germline gene editing
HGP	Human Genome Project
HIV	Human immunodeficiency virus
IVF	*In vitro fertilization*
ML	Machine Learning
NGO	Non-governmental organization
NGS	Next-generation Sequencing
NIPT	Non Invasive Prenatal Testing
NT	NanoTechnology
PCR	Polymerase Chain Reaction
PGD	Pre-Implementation Genetic Diagnosis
REC	Research Ethics Committee
RRI	Responsible Research and Innovation
RNA	Ribonucleic Acid
SSH	Social Science and Humanities
STS	Science and Technology Studies

Table 1: List of acronyms/abbreviations

Glossary of terms

Term	Explanation
Allele	A variant of a gene or a DNA locus. A human organism has two alleles of each locus/gene; one allele is inherited from the mother, the other allele by the father. A pair of alleles of a given gene can be called a genotype of that gene.
Bioethics	An interdisciplinary field of study which focuses on, for example, philosophical, ethical, legal, and social issues that arise in medicine and in the life sciences.
Biological warfare	Deliberate launching of outbreaks of a disease through the manipulation and distribution of pathogens with the intention of disrupting economic and societal infrastructures; employed by armed groups (states, terrorist groups or criminal organizations).
Carrier testing/screening	Genetic testing or screening aiming to determine if a person carries a gene variant, which may cause a (recessive) disease in their offspring if the same gene variants is present in the second parent.
Chromosome	A chromosome is a structural subset of the genome. As a structural unit, it allows genetic material (DNA) to be organized in a (more or less) compact fashion within the cell's nucleus. Proteins such as histones help to organize (e.g. fold) the DNA.
Clinical genetics	A medical speciality within which genetic testing and genetic counselling (to support patients who take a genetic test) are offered to individuals and families with, or at risk of, genetic disorders.
Confidentiality	The duty of anyone entrusted with secret/private information not to share that information.
CRISPR-Cas9	A site-specific gene editing technology, which is used to introduce precise modifications in genomes. It is the tool that has sparked this recent renewed work and ethical and legal debate into genetic modification. There are other tools that can also be used for gene editing.
Direct-to-consumer genetic testing	A commercial offer of genetic testing in which tests are advertised and/or sold directly to consumers without necessarily having a health care professional as an intermediary.
Dominant disorder	A disorder caused by a gene that is expressed in a hereditary pattern in families referred to as "dominant". Only one copy of such a pathogenic gene is needed for a patient to express the disease.
DNA	A molecule which contains genetic information. It is made of nucleotides, each of which contains a deoxyribose sugar, a phosphate and one of four bases (adenine, guanine, thymine, or cytosine). The order of the nucleotides is a DNA sequence.
DNA sequencing	The approach or technology of 'reading' DNA, that is, obtaining the DNA sequence (order of nucleotides in a given DNA molecule).
Ethical, legal, and,	Ethical, legal, and social implications (ELSI) programme was a research

social issues/implications (ELSI) of genetics and genomics	project established to address issues and impacts of Human Genome Project. Over time ELSI has become an interdisciplinary research field which focuses on implications of genetics and genomics.
Ethics	The branch of philosophy that deals with good and bad behaviours, moral duty and obligations
Exome	Protein-coding part of the genome.
Gene	A gene is a sequence of nucleotides, a fragment of DNA or RNA, which is a functional unit of inheritance. A gene usually contains information about the sequence of amino acids in a protein or polypeptide, however, it may have a function of controlling expression of other genetic material.
Gene editing (also called genome editing)	A type of genome modification used to add, remove, or change particular sequences in the genome. CRISPR-Cas9 is one of many tools which can be used to achieve gene editing (see the definition of CRISPR-Cas 9 above).
Gene therapy	A therapeutic approach involving introducing and/or altering DNA in an organism in order to provide treatment or cure for a disease; traditionally, gene therapy used viral vectors to deliver extraneous DNA to cells. Gene editing, as the currently popular term, using updated tools, can also be considered a form of gene therapy if used for treating a disease (see the definition of gene editing).
Genome	All the DNA of a given organism.
Genome modification	Approaches to introduce changes to the genome, including gene editing, mitochondrial replacement, and gene therapy approaches which use viral vectors to deliver extraneous DNA to cells (see the definitions of these approaches).
Genomic sequencing	Analysis of the order of DNA nucleotides in part of or in an entire genome (See Whole Genome Sequencing).
Genomics	A field of biology focused on studying genomes. It uses high-throughput technologies, which produce large quantities of data, mainly sequencing data. Traditional genetics focuses on studying a few genes at a time; genomics meanwhile, provides insights into whole genomes thanks to advanced technologies, such as next generation sequencing. Some authors, however, use the terms genomics and genetics interchangeably. These terms are distinguished in this report where relevant.
Genotype	The genetic makeup of an organism, DNA sequences which determine a given trait.
Germline	Concerning the population of cells that may pass on their genetic material to the progeny; examples are: gametes, zygote and embryonic cells.
Heterozygous individual	An individual with different alleles of a given gene.
Homozygous individual	An individual with two identical alleles of a given gene.
Human Genome Project	An international endeavour, originally initiated by the US government. The HGP started in 1990 with the aim to sequence the human genome.

	Eventually it grew to include an international consortium including researchers in the UK, France, Germany, Japan, China, as well as the USA.
Human genetics	The study of human heredity. More precisely, the study of human genes, including how they are transmitted from parents to offspring and the ways in which they act in the cells. In medicine, the understanding of human genetics helps with the prediction, diagnosis and treatment of diseases that have a genetic component. This term historically, predates genomics, and can be seen as the "precursor" to genomics. Some authors, however, use the terms genomics and genetics interchangeably. These terms are distinguished in this report where relevant.
In vitro **fertilization**	The process of fertilizing an egg by sperm conducted outside of an organism, in a laboratory.
Mitochondrial replacement (also called nuclear genome transfer)	A technique in which the nucleus is transferred from one embryo (or oocyte before fertilization) that have mutated DNA in its mitochondria to an embryo (or oocyte before fertilization) with healthy DNA in the mitochondria.
Mosaicism	The occurrence of cells with different genotypes in one organism. For example, where a given gene is modified in some cells, but not in all of them.
Next generation sequencing	Technologies of DNA/RNA sequencing characterized by high-throughput massively parallel approach, whereby millions of DNA strands are sequenced in parallel in a relatively short time period
Non-invasive prenatal testing	A technique allowing for analysis of foetus DNA using blood sample of the mother
Oocyte (egg)	A female reproductive cell which can be fertilized by sperm (male reproductive cells); fertilization initiate development of a new organism
Polymerase chain reaction	A technology used in molecular biology to amplify selected fragments of DNA (aka PCR machine).
Phenotype	Observable characteristics of an organism, such as morphology, physiology, development, resulting from the organism's genotype and the influence of the environment.
Polymorphism	In genetics, an occurrence of more than one DNA sequences in a given locus in a given population. Some authors only use the word polymorphism if the sequence exists above a certain frequency (as to not be rare, for example, over 1% or 5% of the population).
Preimplantation genetic diagnosis and screening	An approach allowing for evaluation of genetic make-up of embryos *in vitro* before they are implanted in the uterus to establish a pregnancy.
Privacy	The right of an individual to keep his or her health information secret.
Recessive disorder	A disorder caused by having two pathogenic alleles (usually at one gene). Two copies of pathogenic alleles are needed to be affected by such type a recessive disease.
Somatic	Referring to the cells of the body that are not germline cells/gametes. Somatic cells are not inherited to future generations.
Targeted sequencing	Sequencing of selected genes or fragments of a genome.

Technology transfer	Sharing of information about a technology, its manufacturing, and related skills between disciplines or economy sectors.
Tripronuclear zygote/embryo	A zygote or an embryo which has three pronulei, instead of the normal number of two pronuclei. Pronucleus is a nucleus (structure in a cell containing DNA) in both sperm and eggs during fertilization. Presence of two pronuclei is a sign of a successful fertilization; occurrence of three pronuclei in zygotes is an abnormality and is associated with spontaneous abortions.
Value	Any principle or quality that reflects a sense of right and wrong and what ought to be.
Vulnerability (in the context of technologies)	A state of lesser ability to withstand adverse impacts from technological developments to which they are exposed.
Whole exome sequencing	An approach where high throughput sequencing is applied in which the protein-coding parts of a genome are sequenced.
Whole genome sequencing	An approach where high throughput sequencing is applied in which nearly the entire genome sequence is obtained.
Zygote	A fertilized egg, the first developmental stage of an organism.

Table 2: Glossary of terms (includes definitions provided in D.2.1)

1. Introduction
1.1 Introduction to the topic of the deliverable

This report is delivered in the context of a European Commission (EC) funded SWAFS[5] project called SIENNA (Stakeholder-informed ethics for new technologies with high socio-economic and human rights impact), which began in October 2017 (http://www.sienna-project.eu). In the SWAFS-18-2016[6] call, that the SIENNA project has been developed to respond to, three areas of technologies have been defined: Human Genomics, AI/Robotics, and Human Enhancement. SIENNA is a three-and-a-half-year (October 2017 – March 2021) project that has received funding under the European Union's Horizon 2020 Research and Innovation programme. The project received total amount of approximately 4 million euro and has 13 partners (including 2 associate partners who do not receive funding).

SIENNA tackles important issues of ethical, legal and social implications (ELSI) of new technologies and has as one of the main aims to develop ethical frameworks for three technological areas: human genomics, human enhancement, artificial intelligence and robotics. The tasks and sub-tasks which will feed into the development of the ethical frameworks include, among others, the following: state of art review of the technological field (deliverables 2.1, 3.1, 4.1, each deliverable focuses on different technology area); analysis of professional codes of conduct and guidelines (deliverables 2.3, 3.3, 4.3); survey of publics' on awareness and acceptability of the technologies (deliverables 2.5, 3.5, 4.5); citizens panels (deliverables 2.6, 3.6, 4.6) focusing on the same issues as the survey; foresight approaches (reported here in section 6 for human genomics); and "countries studies" reporting on the debate on ethical issues of the three areas of technologies in different countries (reported here in section 4 for human genomics). This report is the fourth deliverable completed for Work Package (WP) 2, which addresses the ELSI of Human Genomics. Specifically, this report fulfils the task described in the description of action of the project by the following:

> *"Task 2.4: Analysis of current and future ethical issues: This task will review existing ethical theories and approaches regarding genomics technologies. We will perform an ethical impact assessment of current and future ethical issues. We will use the review and assessment to identify major ethical issues and approaches to them regarding the technology in general, and regarding different domains and applications. The ethical impact assessment will engage stakeholders and experts, and is therefore connected to Tasks 2.5 and 2.6."*

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[5] SWAFS = Science with and for Society
[6] https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/swafs-18-2016.html

The term "ethical impact assessment" in this context can be replaced by the term "ethical analysis".

1.2 Objectives, Scope and Limitations

This report engages in a critical presentation of SIENNA approach and in an extensive ethical analysis of human genomics. It aims to identify and present ELSI in genomics, both current and emerging issues with a relatively short time horizon. The aim of the report is not to make recommendations or present solutions, but rather to provide an overview of ELSI pertaining to genomic technologies within their context of application. The report is based on a description of such technologies in previous deliverable D.2.1 and intends to provide a basis for our next report D.2.7, in which we aim to discuss an ethical framework for human genomics. In particular, the analyses presented herein may help in identifying issues that can be considered when developing ethical framework.

Although we provide a comprehensive overview of ELSI of human genomics, due to time and space constrains we were not able to address all ELSI in depth. Furthermore, the SIENNA approach has its methodological limitations, which are detailed in relevant sections, especially where empirical approaches are discussed. The limitations include, among others, limited time allocated for the tasks to each partner (e.g. for "country studies", see section 4) and various expertise of the partners who contributed to the tasks.

1.3 Methodology

This section describes the methodology followed for the ethical analysis of genomic technologies herein. It is adapted from the methodological approach developed in *SIENNA D1.1 – The consortium's methodological handbook*[7]. The SIENNA approach consists of a six-step process:
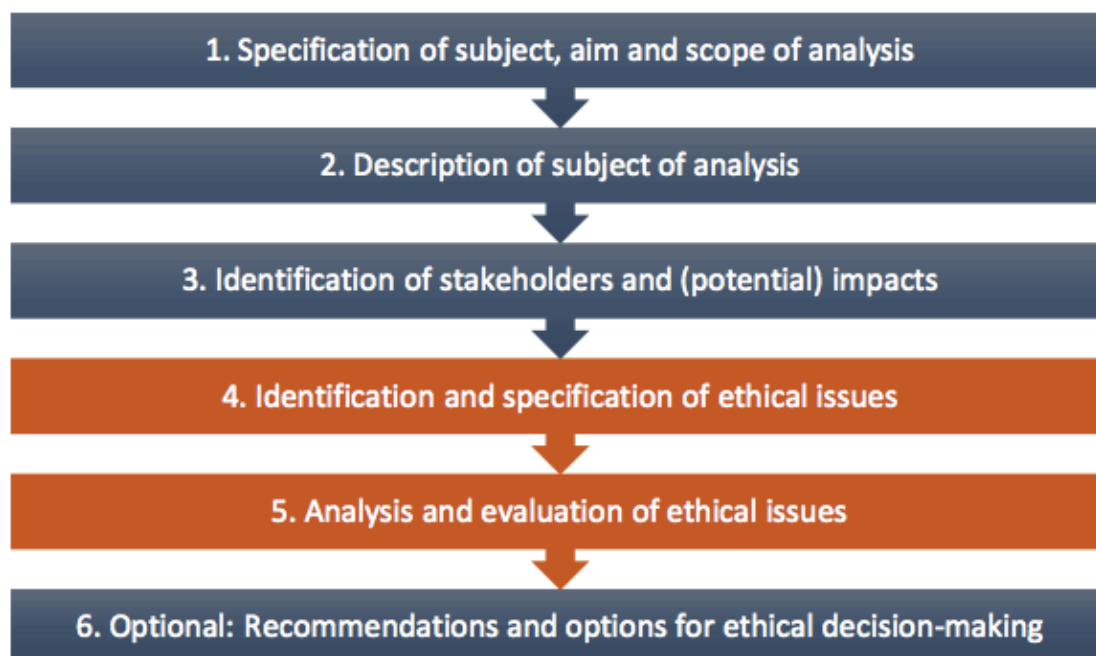
Figure 1: Overview of the 6-step process for SIENNA approach of ethical analysis

Previous deliverables, entitled *SIENNA D2.1 - State of the art review of human genomics*, address steps 1, 2 and 3 ; deliverable D1.1 addresses step 3 of this process. This report includes steps 4 and 5 of this process:

- **Identification and specification of ethical issues**

The identification of ethical issues is partly based on the emerging and potential applications and emerging and potential social and economic impact of genomic technologies, described in the SIENNA D2.1 report. It is also based on a survey proposed to experts in genomics in january 2019 (cf. "Experts' survey on foresight of genomic technologies", p. 91) and review of the literature concerning recent developments in gene editing (cf. section 7.4).

Emerging and potential future ethical issues were thus identified through: (1) literature review of prior ethics studies related to genomic developments; and (2) stakeholder and expert consultation through informal interviews, a survey and two workshops. Workshops were used to both reflect on

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[7] Rodrigues, Rowena, et. al., *D1.1: The consortium's methodological handbook*, WP1, 2018, Public deliverable report from the SIENNA project.

parts of the SIENNA approach and collect emerging and potential future ethical issues of genomic development:

- In January of 2019, we held a workshop in London on foresight approach in ethical analysis of genomics that was attended by around 20 stakeholders, ethicists and genomics experts. Description of the activities and list of the participants can be found in Annex 1.Discussions that took place during this workshop about the benefits and limitations of foresight in ethical analysis are reflected in this report (p.92).

- In June of 2019, we held a workshop with 20 academic experts in (bio)ethics, ELSI studies, social science, law, genetic counselling, as well as genetics and genomics from 10 countries, including 7 European countries, Turkey, Australia, and the USA. Description of the activities and list of the participants can be found in Annex 2. The aim of the workshop was to discuss the benefits and limitations of SIENNA approach and to brain storm on 3 particular domains of genomic development that had not been addressed in the previous D2.1 deliverable: genomics and human enhancement; genomics and artificial intelligence; the military uses of genomics.

Considering "future" issues, we put special emphasis on issues that have a reasonable likelihood of occurring within five to ten years from now. We thus tried to capture emerging developments and trends while avoiding the pitfalls for guessing too far in the future and sink into pure speculation.

In the SIENNA approach, the ethical analysis of emerging technologies is suggested to include 3 levels of analysis:

- the *technology level*, the most general level of description, which specifies the technology in general, its subfields, and its fundamental techniques, methods and approaches;
- the *artefact level* or *product level*, which provides a systematic description of the technological artefacts (physical entities) and procedures (for achieving practical aims) that are being developed on the basis of the technology;
- the *application level*, which defines particular uses of these artefacts and procedures in particular contexts by particular users.

This approach developed by philosopher and coordinator of SIENNA Philip Brey[8] in the context of the ethics of Artificial Intelligence and Robotics (AIR) was, however, not deemed productive for the ethical analysis of human genomic technologies. First, unlike the areas of AIR and Human Enhancement (HE), human genetics and genomics already had specific areas of focus identified in the call (i.e. genetic testing and screening, patents, pharmacogenomics etc…) and in these were mirrored in the grant agreement along with gene editing, which we added, knowing it was a crucial area to study. Importantly, these areas of focus are not technologies but rather ways in which technologies are used to provide genetic information and/or manage genetic information. Hence the technology level was already bypassed to some extent, and uses were already identified. Moreover, in task 2.1, it became apparent that a plethora of ELSI work had already been done in the areas outlined and using very specific situations such as genetic testing in adults for a specific disease like Huntington disease (and not just the study of genetic testing in general), so we choose to focus on two current

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[8] Brey, "Anticipatory Ethics for Emerging Technologies".

approaches – high throughput sequencing, and gene editing- which are the most likely approaches (using latest technologies) to impact patients and society in the future (see below). So when compared to AIR and HET we have a relatively smaller or more focussed area to analyse, which reflects the current relatively advance state of ELSI studies of genetics and genomics, and this makes the approach described by Brey at the technology level less useful or informative for human genetics and genomics.

Secondly, there were problems with using the "artefact" level for analysis as well. Let us illustrate this point with the example of the DNA sequencer, which is an artefact, and more precisely an instrument developed to automate the DNA sequencing process. As such, this could fit within the level of "artefact" or "product". However, it is the application of sequencing in a certain context that raises ethical issues, not the existing DNA sequencer. Ethical issues indeed differ greatly whether this instrument is used for the diagnosis of an adult, a child, a foetus in a clinical setting; for an ancestry test provided by a commercial company; in the context of research or for surveillance purposes etc. We thus chose to address two main types application domains of genomic technology - high throughput sequencing used to **study the genome** and gene editing used to **modify the genome** – and to focus on their fields of applications. Next generation sequencing is currently applied in research on human genomes, in clinical care, in direct-to-consumer setting as well as for forensic purposes. Current and potential clinical uses include to facilitate diagnosis, guide treatment, assess predisposition for diseases, screen newborns, test foetuses and in carrier screening. Meanwhile, gene editing is currently primarily used only in the research context (including clinical trials for somatic gene editing).

This necessary adaptation from the suggested SIENNA approach may highlight how all new technologies with deep, wide societal impact should not necessarily be apprehended with the same ethical framework.

- **Analysis of ethical issues** (SIENNA handbook step 5)

Having had identified the ethical issues in relation to genomic technologies, the second phase in writing this report was to further clarify, provide details about nuances, and contextualise the ethical issues that were identified.

As described in Deliverable 2.1- SIENNA's handbook- step 5 involves ethical analyses to help us better understand the ethical issues. While such a better understanding may be used to eventually resolve the issues, as outlined in the description of action, making moral evaluations and identifying solutions are not the goal of this task. This means that we have not, per se, made moral judgments regarding the goodness or rightness of particular actions, persons, things and events, and the rightness or wrongness of possible courses of action in relation to the ethical issues that have been identified. In the upcoming SIENNA report D2.7, moral judgments will be considered for the ethical issues analysed here so as to provide guidance.

Methods for the analysis of identified current and potential future ethical issues include: (1) application of instruments from the field of ethics (i.e., ethical concepts, theories, frameworks and/or arguments), (2) literature review of studies discussing ethical issues of genomics, and (3) expert consultation through aforementioned workshops.

1.4 Outline of the remainder of the deliverable

In this deliverable, we report both a critical presentation of SIENNA approach and an analysis of current and future ethical issues emerging in the context of human genomics.

The report consists of seven sections, including an introduction to SIENNA approach of ethical analysis (section 1), a brief history of ethics of human genetics and genomics (section 2), a discussion of SIENNA approach in the landscape of current frameworks developed to address ELSI of genetics/genomics (section 3), a review of how ELSI of genomics have been debated in eleven countries (section 4), a critical presentation of the two empirical investigations about publics' attitudes towards human genomics that took place in SIENNA (section 5), a discussion of foresight approach in SIENNA (section 6) and finally the ethical analysis of current and emerging ELSI in two areas of technology development in genomics (section 7): 1) the study of the genome as performed through high throughput sequencing (e.g. with tools such as next generation sequencers); and 2) gene editing (or genome editing, for example, as performed with tools such as CRISPR-Cas9 and other editing technologies) .

2. Historical overview of ethical analyses of Human Genomics

In the following section, the focus of our discussion is on ethical discourse rather than on practice and on conceptual analysis rather than on empirical research. We outline the different ways in which ethical issues in human genetics and genomics have been addressed in the last three decades with a focus on the approach used in "ethical, legal and social issues" (ELSI) research. We highlight similarities and contrasts between approaches, as well as strengths and weaknesses. We also briefly address the SIENNA approach suggested by the philosopher and coordinator of SIENNA Philip Brey, and situate this approach within the wider context of the diverse ethical approaches proposed to study innovative technology. The reason it is important to understand the different approaches used to study ethical (legal and social issues) of a subject is that the frameworks used influence the type of results obtained. For example, an approach with very specific questions gives different results than an approach with a more general or global perspective. Different approaches may be more useful for ethical reflection rather than practical guidance etc.

2.1 History of the ethical study of human genomics
While the coining of the term genomics is traced back to the mid 1980's, the beginning of the field of human genomics in practical terms can be identified in 1990 with the launch of the Human Genome

Project (HGP)[9]. The achievements of this international scientific research project allowed for, among others, the completion of a high-quality version of the human genome sequence. The HGP included as an integral part of the project a multi-disciplinary ethical, legal and social implications[10] (ELSI) group which was tasked with addressing potential (ELSI) consequences of the work including privacy, discrimination, clinical translation of new technologies, informed consent and education of different stakeholders. As such, the ethical study of human genomics thus traces back to this scientific development. Before the HGP, the ethical study of human genetics was understood as the ethics of clinical genetics and genetic research ethics.

2.1.1   The ethics of clinical genetics

Clinical ethics is a discipline that provides a structured approach to assist health care professionals in identifying, analysing and resolving ethical issues that arise in clinical practice. Ethical problems in clinical genetics include inequitable access to services, voluntary versus mandatory testing and screening, safeguarding of individual and parental choice, full disclosure of information, confidentiality versus duties to relatives at genetic risk, privacy of genetic information, directive versus non-directive counselling, non-medical use of prenatal diagnosis (including sex selection) and gene therapy.

The following issues, for which we provide a brief description are particularly salient since they question the foundations of medical ethics:

- **Informed consent**

As will be seen below, ethical violations in research on humans in the first half of the twentieth century brought informed consent into sharp focus, but within the clinical landscape, the concept took more time to take hold, particularly through developments in case law during the 1950s and 1960s[11]. In the clinical setting, the conditions of informed consent are similar to those outlined in the Belmont Report[12] on ethics and health care research: the patient must be apprised of all relevant information, have the capacity to reason soundly, and have the ability to exercise decision making freely. Only when disclosure, capacity, and voluntariness are present can informed consent be obtained.

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[9] A succession of developments led to the study of the human genome as a whole, and not only of single genetic markers or genes (e.g. Sanger sequencing in the 70s, polymerase chain reaction as well as the study of DNA repeated sequences [mini and microsatellites]) in the 80s and the creation of institutes dedicated to the study of human genome globally such as CEPH (Centre d'études du polymorphisme humain) in France in 1984, one usually considers that the field of human genomics started in 1990 with the HGP.

[10] Often referred to as ethical, legal and social issues (not implications)

[11] Faden and L, *A History & Theory of Informed Consent*.

[12] Published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, this report laid out ethical Principles and guidelines for the research of Human Subjects. It is available: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

In clinical genetics, the question to be asked is: to what exactly are patients consenting when they agree to undergo genetic tests? As with other types of medical tests, patients may fully expect the return of primary results but they might not anticipate certain findings generated by the tests as well as the fact that many detected variants have uncertain significance. Although this information may be harmless, the possibility exists that the genetic testing could reveal embarrassing, stigmatising, or unsettling medical information.

Within this context, predictive testing of minors for genetic conditions raises specific ethical questions. *Predictive testing* is defined as genetic testing of a presymptomatic individual (that is, before any symptoms appear). Members of the ethics and genetics communities broadly support predictive testing of adults for adult-onset diseases and minors for childhood-onset disorders for which medically beneficial interventions are available. However, there exists an ethical grey zone when it comes to predictive testing of minors for late-onset diseases or carrier status, particularly when there are no clear medical treatment or prevention options available. The procedure of informed consent complicates even further this practice: under current law in many Western countries, clinicians are required to secure parental consent for medical treatment of patients younger than 18 years. That being said, although minors are legally presumed to lack capacity—and thus are unable to grant consent—the threshold of a legal age for medical decision that corresponds to legal majority is considered arbitrary by some ethicists and psychologists [13].

- **Return of results**

As stated above, genetic tests involve the possibility of generating unexpected findings, also called secondary or incidental findings, and thus challenges physicians to determine what should be communicated to the patient. There is a robust bioethical debate on the disclosure of such findings in clinical practice[14]. There is consensus in the medical community that secondary findings with actionable clinical significance should be returned[15]. However, there is a spectrum of opinion about which conditions and genetic variants meet these criteria, and the extent to which patient preferences should be taken into account[16].

- **Confidentiality**

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[13] Mand et al., "Predictive Genetic Testing in Minors for Late-Onset Conditions: A Chronological and Analytical Review of the Ethical Arguments".

[14] Bennette et al., "Return of Incidental Findings in Genomic Medicine: Measuring What Patients Value—Development of an Instrument to Measure Preferences for Information from next-Generation Testing (IMPRINT)"; Roche and Berg, "Incidental Findings with Genomic Testing: Implications for Genetic Counseling Practice"; Burke, Evans, and Jarvik, "Return of Results: Ethical and Legal Distinctions between Research and Clinical Care".

[15] Evans and Rothschild, "Return of Results: Not That Complicated?"

[16] Jacob et al., "Genomics in Clinical Practice: Lessons from the Front Lines".

Although physician-patient privilege forms a cornerstone of medical practice, confidentiality in this relationship is not inviolable. Reporting otherwise confidential information by a physician can be required to protect third parties in the cases of infectious diseases, impaired drivers, injuries from weapons, intended violent crimes, child abuse, elder abuse, and intimate partner violence. Given the familial nature of genetic conditions, there arises an ethical and legal question when a physician learns the results of a patient's genetic testing: is there an obligation for the physician to warn the patient's family members of their genetic risk?

Although the regulations differ between countries, professional societies have largely agreed that disclosure discretion should be left to the provider[17]. Overall, however, clinicians should inform patients about the familial implications of results, both before and after testing, and encourage disclosure to at-risk relatives. In some jurisdictions, physicians have the discretion to inform family members when attempts at encouraging voluntary disclosure by the patient have failed and the risk of harm is likely.

2.1.2 Genetic research ethics

Research ethics is an academic domain that ideally provides a structured approach to assist researchers in identifying, analysing and resolving ethical issues that arise in their research practices. At the heart of the distinction between research and clinical practice is a divergence of purpose and of (legal) duties. While clinical practice seeks to optimize health outcomes for an individual and has a duty to care, research pursues generalizable knowledge in order to eventually optimize health outcomes without the same duties to care as clinicians. Emerging from these differences are separate sets of legal obligations, ethical duties, and governing regulations covering clinicians and researchers, as well as separate sets of rights and protections owed to patients and research subjects.

- **Informed consent**

As introduced above, informed consent is entrenched in both an ethical and legal doctrine. Its formal origins can be traced to the 1947 Nuremberg Code which was drafted in the wake of the "Doctors' Trial," which scrutinized the human experimentation conducted under the Nazi regime[18]. The code sought to establish a set of conditions defining ethical research involving human subjects, and crucially included voluntary consent as 1 of its 10 critical points.

In the United States, after revelations of egregious misconduct in the 40-year Tuskegee Syphilis Study[19], the National Commission for the Protection of Human Services of Biomedical and Behavioral

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[17] Parker, "Confidentiality in Genetic Testing".

[18] Germany (territory Under, Zone) 1945-1955: U. S. Trials of War Criminals Before the Nuernberg Military Tribunals Under Control Council Law No. 10, Nuremberg, October 1946-April, 1949: Case 6: U.S. v. Krauch (I.G. Farben case). Washington, DC: U.S. G.P.O.; 1949.

[19] Decker et al., "Homologous Mutation to Human BRAF V600E Is Common in Naturally Occurring Canine Bladder Cancer--Evidence for a Relevant Model System and Urine-Based Diagnostic Test"; Schiffman and Breen,

Research was established in 1974. In 1979, this Commission published its first set of principles and guidelines to protect the rights of research subjects. Known as the Belmont Report, the document outlines 3 basic tenets in the conduct of ethical research: respect for persons, beneficence, and justice. Furthermore, the Belmont Report elaborates practices to safeguard these principles: informed consent, risk/benefit assessments, and the selection of subjects, respectively. Ethically acceptable conduct of human genetic (and/or genomics) research has also traditionally been based on these notions. Recently, however, with the imperative to use as much data for research as possible, the primacy of informed consent seems to have been eroded in genomics.

Informed consent in research is defined as the right of subjects to decide whether to participate in research, provided they are furnished with adequate information, possess the full capacities for comprehension, and enjoy voluntariness of decision-making. Its implementation is often difficult to achieve given the complexity and uncertainty of some research projects, especially when it involves samples or data for future research projects, which may or may not be known at the time of obtaining the initial informed consent. This is certainly the case with genomic research using biobanks[20] and increasingly the case for large genome projects like those in the UK, France and Sweden The data obtained could be deposited into scientific databases which are accessible to many different researchers and/or even publicly accessible. The privacy of the subject and autonomy pose many challenges under these, and other, circumstances. Meanwhile, ideally, all of these issues need to be incorporated into the consent process, which is always limited in time.

One of the most promising approaches to be introduced recently is "dynamic consent", which is based on different modalities of conveying information including film, and/or webpages and often involves digital communication interfaces (e.g. a website) that connects researchers and participants (through a participant-specific account) so that research participants can tailor and manage their own consent preferences[21] over time instead of in one static moment during recruitment. While this offers many new options and time for participants, there are also, ethical and political consequences to turning research participants into users of Internet enabled communication technologies[22].

- **Returning of results**

Although researchers must protect subjects from harm, and in interventional clinical trials, they must also provide the basic standard of care, in genetic research researchers have no duty to provide

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"Comparative Oncology: What Dogs and Other Species Can Teach Us about Humans with Cancer"; Davis and Ostrander, "Domestic Dogs and Cancer Research: A Breed-Based Genomics Approach".

[20] Cambon-Thomsen, "The Social and Ethical Issues of Post-Genomic Human Biobanks".

[21] Steinsbekk, Kåre Myskja, and Solberg, "Broad Consent versus Dynamic Consent in Biobank Research: Is Passive Participation an Ethical Problem?"; Budin-Ljøsne et al., "Dynamic Consent: A Potential Solution to Some of the Challenges of Modern Biomedical Research"; Kaye et al., "Dynamic Consent: A Patient Interface for Twenty-First Century Research Networks".

[22] Soulier, "Reconsidering Dynamic Consent in Biobanking: Ethical and Political Consequences of Transforming Research Participants Into ICT Users".

clinical benefit per se. However, a number of consensus statements, guidelines, and committees have used clinical relevance and actionability as the benchmarks for returning individual results to study participants[23]. Albeit this would not have to be done by researchers themselves but researchers would have the responsibility to initiate a chain of events to contact a responsible clinician who then would take over communication with the individual (i.e. research participant) in question. If results are to be returned, the possibility of disclosing such findings must be discussed during the informed consent phase, and the subject should have, ideally, indicated a willingness to receive this information.

- **Privacy**

Informational privacy is the right of being free from intrusive or illegitimate third party access to personal information, and within the health care sphere, confidentiality—the duty of entrusted professionals to safeguard an individual's data—is a closely associated concept[24]. The values to safeguard privacy and support confidentiality, however, seem to increasingly run up against the direction of research in genomics. Here the trend is leaning towards increased collaboration, data sharing, and large-scale research networks at the expense of informing and trying to obtain specific consent from participants. Although data sharing in genomic research has enabled genome-wide association studies and research on rare conditions, such practices make the guarantee of subject anonymity harder to secure[25].

2.1.3 Important international over-aching guidance documents in medicine and genetics: codes and declarations

Herein we provide a brief list of international over-arching (i.e. very general and encompassing and meant for different contexts) documents that have been important in shaping the ethics context in biomedicine, including genetics. Unfortunately we do not have the space to go into very much detail on each, but the list should serve as a good anchoring point for the history of ethical sources in biomedicine for the reader. It is also important to note that we do not include specific guidance documents from professional organisations such as the European Society of Human Genetics or the American College of Human Genetics and Genomics, which also publish recommendations; these are specific to genetics and/or genomics and usually address only very narrow areas in the field per guideline and while ELSI in nature are also very practical. These have been included in deliverable 2.3.

Name of code/declaration	Description

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[23] Mathijs, Vandenbussche, and Van, "Using Genomics for Surveillance of Veterinary Infectious Agents."
[24] Laurie, *Genetic Privacy: A Challenge to Medico-Legal Norms*.
[25] Denholm, "Genotype Disclosure in the Genomics Era: Roles and Responsibilities".

Name of code/declaration	Description
The Nuremberg Code[26]	The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects, including voluntary consent, avoidance of unnecessary suffering and injury.
Universal Declaration of Human Rights[27]	The Universal Declaration of Human Rights (1948) was adopted by the United Nations General Assembly on 10 December 1948 setting out, for the first time, the fundamental human rights to be universally protected. While not directly addressing issues of medical treatment or research, more general articles would have indirect influence, such as protections of freedoms, dignity and privacy.
International Code of Medical Ethics[28]	Adopted by the 1949 General Assembly of the World Medical Association (amended 1968, 1983 and 2006), the International Code of Medical Ethics establishes the global ethical principles of the physicians, in terms of their overall duties to their patients and their colleagues.
Helsinki Declaration[29]	The World Medical Association has also developed the Declaration of Helsinki (adopted 1964, last revision 2013) as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Notably, medical research involving human subjects includes research on identifiable human material or identifiable data. Interestingly this declaration is continuously revised with some important changes with each revision, so it is always important to note the year of the document to which you are referring.
The Belmont Report[30]	Published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, this report laid out ethical Principles and guidelines for the research of Human Subjects.
Convention for the protection of Human	Ratified in 1997, the Convention is the first legally-binding international text (for those states who sign and ratify it) designed to preserve human

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[26] https://history.nih.gov/research/downloads/nuremberg.pdf
[27] https://www.un.org/en/universal-declaration-human-rights/index.html
[28] https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/
[29] https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf
[30] https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Name of code/declaration	Description
Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine[31]	dignity, rights and freedoms, specifically in the context of biological and medical fields through a series of principles and prohibitions against misuse and abuse. The Convention's starting point is that the interests of human beings must come before the interests of science or society. It lays down a series of principles and prohibitions concerning bioethics, medical research, consent, rights to private life and information, organ transplantation, public debate etc.
Universal Declaration on the Human Genome and Human Rights[32]	This document issued by the United Nations Educational, Scientific and Cultural Organization (UNESCO) at its 29th session in 1997 was unanimously passed by the seventy-seven national delegations in attendance. It is probably best known for its statement against human cloning and abuse of human genome against human dignity.
Universal Declaration on Bioethics and Human Rights[33]	With this document, for the first time in the history of bioethics in 2005, Member States committed themselves and the international community to respect and apply the fundamental principles of bioethics set forth within a single text. In dealing with ethical issues raised by medicine, life sciences and associated technologies as applied to human beings, the Declaration anchors the principles it endorses in the rules that govern respect for human dignity, human rights and fundamental freedoms and recognizes the interrelation between ethics and human rights in the specific field of bioethics.
WMA Statement on Genetics and Medicine[34]	The World Medical Association adopted this statement to assist physicians with the ethical and professional issues that arise from scientific advances in the field of genetics. It specifically addresses genetic diagnosis, genetic counselling and genetic engineering.

Table 3: List of the main international codes and declarations in medicine and genetics

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[31] https://rm.coe.int/168007cf98
[32] https://unesdoc.unesco.org/ark:/48223/pf0000122990
[33] http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html
[34] https://www.wma.net/policies-post/wma-statement-on-genetics-and-medicine/

2.2 What is ELSI?

Since the Human Genome Project (HGP), one type of bioethical study of human genomics in particular has taken up much of the ethical studies landscape: the Ethical Legal and Social Issues/Implications (ELSI) framework[35]. Stemming from the HGP, this approach focuses very much on consequences, policies and rather specific contexts (i.e. minors vs adults, or prenatal vs postnatal or diagnostic versus pre-symptomatic testing or screening), as opposed to creating very general ethical approaches that could be used with any genomic context. This practical ELSI type of research in bioethics is now expanding outside of the realm of genomics.

- **ELSI Programme**

While ELSI is used as a field of research, it also designates in its narrow sense research programmes, such as that led first by the National Center for Human Genome Research, and then by the National Human Genome Research Institute (NHGRI), which is one of the first National Institutes of Health (NIH) in the United States devoted to genomic research.

The first ELSI programme was founded as an integral part of the HGP in 1990. Genomic research practices and the expanding knowledge of the genome were expected to have a profound impact on the individual and broader society. Accordingly, the leaders of the HGP recognised the importance of addressing the wide range of ethical, legal and social issues related to the acquisition and use of genomic information, in order to balance the potential risks and benefits of incorporating this new knowledge into research and clinical care. Key questions revolved around how this new genetic information should be interpreted and used and who should have access to it. Important questions also arose about how people can be protected from the harm that might result from its improper disclosure or use. HGP's leaders thus proposed that a percentage of the Human Genome Project budget at the National Institutes of Health and the U.S. Department of Energy (DOE) would be devoted to ELSI research.

> "*ELSI, in its modern incarnation, was born in a last minute revision of a 1988 James Watson speech, where Watson set aside funds specifically for the study of the ethical, legal, and social implications of the massive US government funded Human Genome Project*"[36].

The initial ELSI programme was thus an outcome of the HGP, developed as an afterthought by the project leaders. In 1989, the Program Advisory Committee on the Human Genome established a working group on ethics to develop a plan for the ELSI component of the human genome program[37].

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[35] As will be further distinguished below, ELSI is sometimes referred to as ELSA (Ethical, Legal and Social Aspects).

[36] Greenbaum, "Grand Challenge: ELSI in a Changing Global Environment".

[37] Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome*.

One year later, the ELSI Working Group issued its first report and defined the function and purpose of the ELSI programme as follows:

- "*To anticipate and address the implications for individuals and society of mapping and sequencing the human genome.*
- *To examine the ethical, legal and social consequences of mapping and sequencing the human genome.*
- *To stimulate public discussion of the issues.*
- *To develop policy options that would assure that the information be used to benefit individuals and society*" [38].

The ELSI Working Group, later renamed the ELSI Research Program, envisioned the anticipation of problems and identification of possible solutions, and suggested a number of means to accomplish these goals. Specifically, it encouraged the research community to explore and gather data on a wide range of issues (i.e. ethical, legal, societal) pertinent to the HGP that could be used to develop education programmes, policy recommendations or possible legislative solutions[39]. Along the duration of the HGP, the mission of the ELSI programme was to support empirical and conceptual research to anticipate and address the ethical, legal, and social implications of the HGP itself as well its broader impact, that is to say issues raised by genomic research that would affect individuals, families, and society.

Importantly, the ELSI programme of the HGP provided a new approach to scientific research by identifying, analysing and addressing the ethical, legal and social implications of human genetics research at the same time that the basic science is being studied. In this way, problem areas could be identified and solutions developed before scientific information is integrated into health care practice.

Since the end of the HGP in 2003, the United States Congress has mandated that no less than five percent of the annual NHGRI budget would be dedicated to studying the ethical, legal and social implications of human genome research, as well as recommending policy solutions and stimulating public discussion[40]. Then, the current NHGRI Division of Genomics and Society has identified the following three overlapping research domains (addressing issues that also cut across domains) to be considered for support by the ELSI programme[41].

- Genetic and Genomic Research. These projects investigate and address the ethical, legal, social, and policy issues that arise in connection with the design and conduct of genetic and genomic research.
- Genetic and Genomic Health Care. These projects investigate and address the ethical, legal, social, and policy issues that arise in connection with the translation of genetic and genomic research into clinical medicine and health care in a variety of healthcare settings.

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[38] https://www.genome.gov/human-genome-project
[39] Moses, Niemi, and Karlsson, "Pet Genomics Medicine Runs Wild".
[40] Ibid.
[41] https://www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program/domains

- Broader Legal, Policy and Societal Issues. These projects investigate and address a range of broader ethical, legal, policy and societal issues raised by the use of genetic and genomic technologies and information in research, clinical or non-medical settings

The ELSI program at NHGRI, unprecedented in biomedical science in terms of scope and level of priority, provides an effective basis from which to assess the implications of genome research [42].

Since its inception, the ELSI program at NHGRI has made several notable contributions to the genomics field. Among these are major changes to the way investigators and institutional review boards handle the consent process for studies in genomics. Another contribution is crucial guidance on the NIH's genomic data sharing policy, notably the need to balance open science with personal privacy and autonomy. The ELSI program has been particularly effective in promoting dialogue about the implications of genomics, and shaping the culture around the approach to genomics in research, medical, and community settings.

- **ELSI and ELSA**

While the term ELSI is used in the US and much of Europe, the term ELSA is also used in Europe and they both refer to research and interaction activities that aim to anticipate and address ethical, legal and social implications (ELSI) or aspects (ELSA) of emerging life sciences, notably genetics and genomics. For the purposes of this report we use the term ELSI throughout regardless of if we address the North American or European context.

Interestingly, both neologisms have been introduced by science policy makers and funding agencies – notably the European Commission for ELSA[43]. On the one hand, the shift in signifiers, from I (implications) to A (aspects) might be seen as an effort to broaden the scope of the research, particularly to avoid the flawed linearity implied by 'implications'[44] (which is also achieved by using the word "issues" instead of implications) and to perhaps to also avoid undesirable connotations connected with the original ELSI label (such as the reproach of being too supportive of genomics research as such[45]). On the other hand, the shift can also be seen as an effort to launch a European alternative to the American counterpart.

In the United Kingdom, this led to a network of ELSI centres funded by the Economic and Social Research Council: the ESRC Genomics Network (– that is now no longer in existence). In the Netherlands, 5% of the budget of the Netherlands' Genomics Initiative (NGI) has been devoted to ELSI activities, organized through trans-university collaborations, from 2002 to 2013. As stated by Hub Zwart, "*in purely quantitative terms, ELSA could be regarded as the Social Sciences and Humanities version of 'Big Science'*"[46]. Through these and similar initiatives, a European ELSI/ELSA

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[42] Ioannidis, Tarone, and McLaughlin, "The False-Positive to False-Negative Ratio in Epidemiologic Studies".

[43] Zwart, Landeweerd, and Rooij, "Adapt or Perish ? Assessing the Recent Shift in the European Research Funding Arena from ' ELSA ' to ' RRI '".

[44] Wickson, Strand, and Kjølberg, "The Walkshop Approach to Science and Technology Ethics".

[45] Zwart and Nelis, "What Is ELSA Genomics?"

[46] Zwart, Landeweerd, and Rooij, "Adapt or Perish ? Assessing the Recent Shift in the European Research Funding Arena from ' ELSA ' to ' RRI '".

research community developed as the European equivalent of the US ELSI community [47]. These similarities should not hide the fact that US ELSI researchers, with their large-scale ELSI programme, find themselves in a rather different position to European counterparts. In Europe, there is no centralised funding like that at the NHGRI, so it could be considered more uneven and must be sought through a wide variety of sources and often involving smaller projects, sometimes linked to technical research projects and laboratories. However, in this way, perhaps this makes the ELSI work in Europe more independent and less at the mercy of having to bend to scientists' wills?

- **ELSI as a research field**

The ELSI research programme, which originated with the HGP and was institutionalised within the NHGRI, has led to the creation of analogous ELSI/ELSA research programs throughout the world (See the list of major organizations contributing to the ethical study of human genomics, p.39). These research programmes have instilled a global culture of study – and to some a sceptical scrutiny" [48]. of human genomics The terms ELSI (Ethical, Legal and Social Implications/Issues) – coined initially simply as bureaucratic shorthand for a particular NIH funding program – and ELSA (Ethical, Legal and Social Aspects) have become included in the lexicon of bioethics as research initiatives expected to produce advanced practical assessments of the impacts of technological developments. Accordingly, they are frequently attached to major science programmes.

An ELSI/ELSA model has thus emerged with deliberative commissions and academic scholarship progressing in parallel with scientific and technical advances, not only for genomics but also other fields (for example, the field of stem cell research often integrates ELSI/ELSA work [49]). Stemming from practice, there was no abstract ethical–legal–social–implication object of analysis preceding its formal emergence as a field, but rather that ELSI/ELSA emerged as "*a desideratum for an object of knowledge that has yet to be defined, a seemingly empty knowledge space*"[50]. ELSI/ELSA produces a type of knowledge that is supposed to steer science and technology but whose form and content are unknown in advance.

It is thus very difficult to define a proper agenda, a set of methods or a core theoretical background for this research field. This absence of cohesion comes from the sheer interdisciplinary nature of the field, which makes ELSI/ELSA exist at the intersection of competing conceptual definitions, methodological approaches, institutional settings and sanctioned forms of expertise. Scholars in

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[47] Stegmaier, "The Rock 'n' Roll of Knowledge Co-Production"; Wickson, Strand, and Kjølberg, "The Walkshop Approach to Science and Technology Ethics".

[48] Mattocks et al., "A Standardized Framework for the Validation and Verification of Clinical Molecular Genetic Tests".

[49] Richards et al., "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology"; Harrison et al., "Clinical Laboratories Collaborate to Resolve Differences in Variant Interpretations Submitted to ClinVar".

[50] López and Lunau, "ELSIfication in Canada : Legal Modes of Reasoning ELSIfication in Canada : Legal Modes of Reasoning".

medical science, in social sciences or in humanities may perform ELSI/ELSA studies. The choice of methods and approaches are often a result of ad-hoc decisions depending on the issues addressed and the type of expertise required. ELSI/ELSA analysis can thus be exploratory or hypothesis-driven or policy-oriented; conceptual and/or empirical; performed through corpus analysis or resulting from quantitative, qualitative or mixed methods.

Therefore, ELSI/ELSA should not be seen as a new discipline but as a "*style of doing research*" that may apply to all disciplines involved and which possesses the following features[51]:

- Proximity to life science research
- An anticipatory, forward-looking approach; a focus on the agenda-setting and design stages of innovation trajectories, rather than on the product stage
- Interaction with a broad range of societal stakeholders (media, policy, NGO, industry) as an integral part of the research
- Interdisciplinarity: the ELSI/A research field involves a broad range of disciplines (philosophy of science, bioethics, social science, Technology Assessment, Science and Technology Studies, innovation studies, science communication etc.)
- A focus on micro-analysis (case studies) rather than on macro analysis (socio-economic studies), however, the latter have been increasing in recent years.
- A tendency to draw on a wide variety of sources, from academic philosophy to policy reports, media coverage of public debates and genres of the imagination.

If there is an ELSI/ELSA research approach, it may be best understood by its practice of collaboration between researchers in basic or natural science (e.g. laboratory geneticists) and social science researchers. Proximity of ELSI/ELSA researchers with life scientists can make ethical reflections, observations and criticisms more precise, up-to-date, targeted, and relevant. Scientists involved in ELSI/ELSA research do not merely function as objects of research, as is the case in more traditional types of research, but are invited and allowed to comment on (preliminary versions of) ELSI/ELSA analyses and assessments. Thus, preliminary assessments are developed and tested in the context of critical dialogue and mutual learning within specific projects or in a cooperative mode. This does not only lead to benefits in terms of research ethics but also might make ELSI/ELSA analyses and assessments more robust.

As such, ELSI/ELSA holds its specificity from its integration within scientific practice and science governance. This is why Stegmaier explains that "*ELSA programs tend to fund activities that are geographically and organizationally close to the life sciences research programs with which they interact, serving as public and academic forums for addressing urgent societal issues arising in this context*"[52].

However, given its sheer positioning at the intersection of different interests and types of research ELSI/ELSA also faces serious challenges:

- Research agendas of ELSI/ELSA studies may be pre-formatted by the scientific research programs they intend to study and hence lack the expertise or foundation needed for

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[51] Zwart and Nelis, "What Is ELSA Genomics?"
[52] Stegmaier, "The Rock 'n' Roll of Knowledge Co-Production".

coherent or truly interesting research.

- Given the dominance of medical ethics in the field of human genetics, ELSI/ELSA may focus on a limited set of issues, notably individual autonomy (and related items such as privacy) and harm or risk. Yet as genomic applications develop and exceed the biomedical realm, they move far beyond the areas of health applications. Thus, whereas ELSI/ELSA-expertise tends to remain associated with medical ethics, stressing issues of health risks and patient autonomy, other concerns and issues related to human genomics (naturalness, identity, global justice etc.) may be neglected.

- Although the complexities of interdisciplinary practices between life sciences and social sciences and humanities are addressed, the complexities of the collaborations and the various forms of rivalries between different strands of ELSI/ELSA research may create tensions in the field. Bioethicists, philosophers, STS scholars, lawyers, sociologists, anthropologists and others may disagree, not only over methods, but also over chairs, journals, program committees, funding opportunities and the like.

- Due to the recent creation of it's own interdisciplinary research culture and researchers needing to use different methods in which they may not be formally trained and/or experts means that the level of quality of some studies (especially empirical work conducted without formally trained academics) may lack coherence and meaning. For example, qualitative studies produced by bioethicists are often not of a high enough "quality" to be accepted in social science journals.

- Because the academics conducting ELSI studies usually work closely with scientists and often will be part of the grants written and/or conceived by scientists (i.e. ELSI researchers will often have a work package in a larger science grant), scientists will usually choose ELSI researchers who: 1) have a lot of exposure either in meetings or on social media, regardless of the quality of their work per se; 2) are not so critical of the science. The trickle down effect of this may be ELSI studies that are superficial, more or less a "rubber" stamp of the science, and that offer no serious reflection or challenge of the science under study.

Thus, the question that ELSI communities must continuously address is how to combine proximity to the science and scientists with intellectual autonomy and academic credibility and integrity while still being able to receive funding.

Although, there are differing nuances between ELSI and ELSA, for simplification purposes, we will adopt the more generally used ELSI terminology in the rest of this report.

- **Critiques of ELSI of genomics**.

i. **ELSI: the superficial communication branch of genomic research?**

Because ELSI developments stem from a concern with genomics, it has mainly focussed on genomic innovation and while a "hot" subject, it may have deprived other research fields from ethical attention for a time.

"One potentially adverse effect of the ELSI genome program was the concentration of resources in a relatively narrow field of biomedical research. As support for bioethics related to the genome project grew, and with few resources available for other lines of bioethical analysis, many bioethics programs developed modules on genetics. This may have helped achieve the goals of the genome office, but it also skewed concern with bioethics toward the genome

research. Where cash went, ethics followed"[53](p.241)

This being said, like most academic fields, different subjects appear to cycle into being more interesting or "hot topics" and currently we can see that the ethics of artificial intelligence is receiving a lot of attention and funding.

Another critique pertaining to the origins of ELSI relates to its embedded modality, within scientific projects. Some scholars in bioethics wonder if ELSI serves as an institutionalized, in-house covering excuse for life scientists in genomics who can thus claim that ELSI is responsible for the ethics side of their practice. ELSI should be used, some advocate, to educate the public about human genomics and to train genetic counsellors [54]. If so, ELSI may not be more than a promotional, public relations tool for the life sciences agenda [55].

The above critiques are particularly prominent from the field of science and technology studies, where ELSI is considered to be more or less a box-ticking exercise [56]. They argue that the integration of ELSI into scientific and governance practices in order to address funders' and government's requirements to anticipate the positive and negative impact of genomic research prevents from radical critical thinking and places too much emphasis on the promises surrounding sociotechnical innovation rather than on its practices [57], resulting in 'speculative ethics', with the risk of being so disconnected from the reality that ethical discussions may be useless. Interestingly, this was also seen as the problem with ethics from the philosophy field; a problem ELSI research was supposedly going to remedy. The integration of ELSI within the overall governance of science may constrain opportunities for bringing about changes in practice but also for productive relations between natural and social scientists who, through ELSI, are turned into 'foretellers' [58] and 'nay-sayers' [59].

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[53] Woliver, *The Political Geographies of Pregnancy*.

[54] Fullerton et al., "Return of Individual Research Results from Genome-Wide Association Studies: Experience of the Electronic Medical Records and Genomics (EMERGE) Network"; Fabsitz et al., "Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group"; Knoppers et al., "The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives"; Evans and Rothschild, "Return of Results: Not That Complicated?"

[55] Association, "Disclosure of Familial Risk in Genetic Testing"; Hamilton, Bowers, and Williams, "Disclosing Genetic Test Results to Family Members"; Hallowell et al., "Balancing Autonomy and Responsibility: The Ethics of Generating and Disclosing Genetic Information"; Offit et al., "The Duty to Warn a Patient's Family Members about Hereditary Disease Risks".

[56] Brandt, "Racism and Research: The Case of the Tuskegee Syphilis Study".

[57] Faden and L, *A History & Theory of Informed Consent*.

[58] Lunshof et al., "From Genetic Privacy to Open Consent."

[59] Kaye, "The Tension Between Data Sharing and the Protection of Privacy in Genomics Research".

ii. ELSI, a case of hype?

With the announcement of the Human Genome Project came speculation about a host of profound social challenges. Indeed, no scientific program has so systematically fostered the study of ethical, legal and social implications in parallel to the science. This ELSI literature has led to a great deal of public debate, policymaking and the enactment of national legislation and international declarations. However, is the field of genomics really causing social issues worthy of a formal policy response? Ironically, genomic research has been critiqued by ELSI scholars for its hype, specifically its tendency to entirely overestimate its near- or medium-term potential[60]. One could wonder if the anticipation of the ethical, legal and social harms associated with genomics would also be a by-product of this hype.

> "*The nature and magnitude of ELSI concerns are closely tied to the relevant scientific developments. Given that the conclusions of genetic research have proven to be less definitive than previously anticipated, it should be no surprise that the same trend is found in the context of ELSI*"[61].

For instance, many ethical issues are related to the predictive nature of genomic information. However, even though some genetic risk information is highly predictive, this is not the case of most forms of genetic information, particularly regarding common, chronic diseases[62]. If genetic information is not generally highly predictive, then the value of most gene patents may not as high as anticipated and genetic testing may, in various circumstances, also appear as less deterministic than expected. In this sense, some effects of our newly gained knowledge of the genome may be less of a concern than expected, or in a different way than expected. Indeed, if stakeholders erroneously believe that genetic information is more predictive than it really is, and make decisions based on this, then there are other types of ethical issues around harm and lack of informed consent.

Another aspect of this discussion relates to the relatively slow pace of clinical adoption of genomic technologies in some countries or regions. Research on inequalities in terms of access to genomic care either between countries[63] or within developed countries[64] indicates that the integration of genomics in healthcare is far from being a reality for the majority of the population. Here again the hype related to the "genomic revolution" and its potential for dramatically altering our perception of healthcare, nationally or globally, has to give way to a much more nuanced reality.

The ELSI community, in its anticipation of a hyperbolised social harm, would thus have been a collateral victim of genomics hype.

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[60] Greenbaum, "Grand Challenge: ELSI in a Changing Global Environment".

[61] Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome*.

[62] Ibid.

[63] McEwen et al., "The Ethical, Legal, and Social Implications Program of the National Human Genome Research Institute: Reflections on an Ongoing Experiment".

[64] Ibid.

iii. ELSI, a cause for harm and/or confusion?

Are non-medically trained ELSI researchers legitimate to intervene in the medical realm?
In 2018, two geneticists[65] expressed their concerns towards the academic work of researchers from social sciences and humanities (SSH), Solbrække et al., (YEAR) investigating the social implications of breast cancer genetic testing[66]. More precisely, these SSH researchers used qualitative methods to explore the rise of "the breast cancer gene" as a field of medical, cultural and personal knowledge"[67]. The critics address both the scientific validity of this work and its impact on the patients interviewed during the process. According to Møller and Hovig (2018), this research based on interviews with cancer patients should be considered harmful:

> "*Having personally discussed these matters with some thousand patients, we can confirm that the selection of arguments brought forward by Solbrække et al. are disease-creating, by telling the patients how dreadfully difficult their lives are, and overlooking all the rest. The patients feel harmed by their position. Solbrække et al. are violating the philosophical rule of not doing harm (…)*"[68]

This argument is highly questionable. In their response to these critiques, Gripsrud and Solbrække refute in particular the idea that "*providing a nuanced account of mediated representations and narratives of lived experience*" could jeopardize patients' safety [69]. However, the position of Møller and Hovig refers to a much older and entrenched debate about the legitimacy of non-medically trained professionals to address medical issues and to enter the medical realm. As the interdisciplinary claim pertaining ELSI entails, ELSI researchers come from diverse background. They are not necessarily medically trained and are not bound by an ethical obligation to do no harm. Their presence on a medical settings and their legitimacy in interacting with patients might thus be questioned on an ethical ground.
Furthermore, the argument from medical doctors or laboratory scientists regarding the meaning and/or "validity" and/or good/harm of ELSI research may also stem from a confusion as to what the studies may or may not conclude. For example, qualitative research and its results are often misunderstood. Qualitative research is often conducted with rather small sample sizes, and with the aim of exploring themes in depth instead of generalising or testing hypotheses yet those not familiar with this approach may falsely think that the results are generalizable or replicable. Moreover, in fields where decisions need to be made and these decisions must be defended with (seemingly)

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[65] Macpherson and Segarra, "Commentary: Grand Challenge: ELSI in a Changing Global Environment".
[66] Solbrække et al., "Our Genes, Our Selves: Hereditary Breast Cancer and Biological Citizenship in Norway".
[67] Ibid.
[68] Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome*.
[69] Andrews et al., *Assessing Genetic Risks: Implications for Health and Social Policy*.

coherent reasons/arguments, studies (in ELSI/bioethics) that offer ways of reflecting and offering new perspective on technology may not be fully appreciated or understood.

2.3 Overview of recent approaches for the ethical study of human genomics

Besides the frameworks already presented of clinical ethics, ethics of genetic research and ELSI, other ethical approaches have been developed and may be applied to genomics; these are listed below. However, the main approach to study ethical issues in genomics currently remains ELSI.

i.   **Responsible research and innovation** (RRI) is a political program that intends to nudge the trajectories of new knowledge and technologies toward desirable futures, based on social and/or ethical tools such as, public dialogue, constructive technology assessment, foresight or codes of conduct [70]. The aims of the RRI approach consists of [71] :
     - considering societal needs and ethical aspects in research funding programs, e.g. through public and stakeholder dialogue;
     - developing criteria for the early appraisal of research and innovation, e.g. technology assessments;
     - establishing processes to better integrate societal needs in research and innovation, e.g. trans-disciplinary approaches in sustainability science;
     - setting up advisory bodies such as councils on ethical aspects of new technologies.

RRI does not seem a radical departure from ELSI, however the differences are important enough to keep many ELSI researchers from identifying as RRI researchers and/or from using the approach. In particular, RRI has a large emphasis on furthering socio-economic goals through partnerships with industry and private companies. In its report on the state of art on responsible research and innovation in Europe[72], the expert group refers to "*the ambition of the European Union to ensure that research and innovative ideas can be turned into products and services that create jobs and prosperity, as well as help preserve the environment and meet the societal needs of Europe and the world*" (p. 11). The point of RRI is to help achieve this ambition by having the "*potential to make research and innovation investments more efficient, while at the same time focusing on global societal challenges.*" (p.16) Inclusion of ethics from the start, it seems, will lead to less contestation of innovations afterwards.

The difference between RRI and ELSI is thus not in the methods or approaches used as such, but rather in the finality of RRI, namely, ensuring that the EU economy remains internationally competitive and robust.

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[70] Brown, "Hope against Hype--Accountability in Biopasts, Presents and Futures"; Kerr, Cunningham-Burley, and Tutton, "Exploring Ambivalence about Genetic Research and Its Social Context"; Caulfield et al., "Harm, Hype and Evidence: ELSI Research and Policy Guidance".

[71] van den Hoven et al., *Options for Strengthening Responsible Research and Innovation, p. 12*.

[72] Ibid.

This focus on innovation has at least two important consequences:

- Micro-level case studies of knowledge production and innovation processes (dominant in ELSI) are potentially not conducted with as much depth as in ELSI studies and are complemented by mid- and macro-level studies of transformations and transitions, to bring the broader socio-economic context into view. Substantive normative questions also come into play at this level, particularly the question what kind of society and economy we want (which, of course, includes issues of sustainability and fairness).
- Private companies are involved in RRI (being less prominent in ELSI), which entails a shift of focus from analysing knowledge production to processes of co-design in innovation and public-private interaction. Ethicists involved in RRI become increasingly co-responsible for the innovations they help to develop.

RRI approach differs from ELSI in the sense that this approach may lead to ensuring market accountability through standards, certification, accreditation and labels as a new form of governance to manage the potentially sizable number of products coming to the market.

ii. **Research ethics by design**: A typical feature of RRI is an attempt to use ethics as a design principle for technology. Following the template of the privacy by design framework, which requires privacy concerns to be embedded into the design and architecture of IT systems and business practices[73], research ethics by design encourages ethical issues to be considered in a bottom-up fashion during the design phase of research studies[74]. This approach would ideally allow research ethic committees (RECs) to point out to researchers at an early stage, the need to accommodate ethical concerns pre-emptively in order to foster collaborations, diminish frustration towards RECs procedures on the part of the researchers and ensure maximal protection for research participants. At the moment, the application of ethics by design to human genomics is mainly restricted to the research use of genomics and focuses on privacy concerns[75].

iii. **Upstream public engagement**: Public engagement emphasizes a shift away from an expert model of delivering academic knowledge to the public, toward a more collaborative model where stakeholders play a significant role in creating and sharing knowledge to meet needs of institutions and society alike[76]. Moving public engagement upstream means that the only way to ensure that science contributes to the common good is to open up innovation

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[73] Cavoukian, "Privacy by Design in Law , Policy and Practice A White Paper for Regulators."; Shaar, "Privacy by Design"; Langheinrich, "Privacy by Design—Principles of Privacy-Aware Ubiquitous Systems".

[74] Borrett, Sampson, and Cavoukian, "Research Ethics by Design: A Collaborative Research Design Proposal".

[75] Ibid.

[76] Woliver, *The Political Geographies of Pregnancy*.

processes at the earliest stage. Answers to key (ethical) questions should be debated publicly: Who owns socio-technological innovation? Who benefits from it? To what purposes will it be directed?[77]

iv. **Constructive technology assessment**: CTA has been developed primarily by social actors (consumers, producers) other than the governments. It "*shifts the focus away from assessing impacts of new technologies to broadening design, development, and implementation processes*"[78]. The social problems surrounding technology are thus addressed through the inclusion of a large diversity of actors in technological design and implementation processes.

v. **Anticipatory governance and real time technology assessment** are attempts to integrate social science and policy research with research in the natural sciences from the outset[79]. Their ambition is to inform and support natural scientific research, and to provide a framework for observing, critiquing, and influencing social values as they become embedded in innovations[80].

2.4 Overview of actors in the field of ethics in genetics and genomics

Above and beyond the academic teams that conduct academic research and/or policy studies on human genetics and genomics, there are organisations including professional societies, academic journals, governmental organisations, non-governmental organisations which contribute to the ELSI landscape of human genomics. We list a non-exhaustive list here, to show the reader a sampling of these types of organisations throughout the world. We do not include law-making and regulatory bodies as these are addressed in depth in deliverable 2.2.

i. **Major organizations contributing to the ethical landscape of human genetics and genomics**

Name of organization	Description
The American College of Medical Genetics and Genomics[81] (ACMG)	Established in 1991, the ACMG states that "*(as) the voice of experience and reason in medical genetics and genomics, ACMG will achieve its vision by developing and sustaining initiatives in the following areas that support the professional needs of its members: Clinical & Laboratory Practice, Education, and Advocacy.*" Especially in the last decade, the ACMG's recommendations regarding whole genome

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[77] Jasanoff, *Designs on Nature: Science and Democracy in Europe and the United States*.
[78] Nordmann and Rip, "Mind the Gap Revisited".
[79] Balmer et al., "Taking Roles in Interdisciplinary Collaborations : Re Fl Ections on Working in Post-ELSI Spaces in the UK Synthetic Biology Community".
[80] Fortun, "For an Ethics of Promising, or: A Few Kind Words about James Watson".
[81] https://www.acmg.net/

Name of organization	Description
	sequencing have been particularly impactful internationally (e.g. opportunistic screening).
Bioethics, Council of Europe[82]	Founded in 1949, Council of Europe's aim in the field of bioethics is to protect the individual's dignity and fundamental rights with regard to the application of traditional medicine and new medical techniques (genetics, medically assisted procreation, etc.).
BBMRI-ERIC common service ELSI[83]	BBMRI-ERIC supports the biobanking community by facilitating compliance with regulatory requirements and best practice standards. Given that the proper consideration of ethical, legal and social issues (ELSI) is key to any biobanking activity, they provide services and tools for researchers who would like to be informed of ELSI matters or have specific ELSI questions.
Eubios Ethics Institute[84] (Japan)	The Eubios Ethics Institute is a non-profit group that aims to stimulate the international discussion of ethical issues, including how technology can be used in ways consistent with "good life" (eu-bios). It aims at an integrated and cross-cultural approach to bioethics, and at building up an international network.
Eubios Journal of Asian and International Bioethics (EJAIB)[85]	EJAIB is the official journal of the Asian Bioethics Association (ABA) and the International Union of Biological Sciences (IUBS) Bioethics Program.
Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)[86]	The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) is a network of independently established regional forums for ethical review committees, health researchers and invited partner organizations with an interest in the development of the ethical review process. The regional fora are composed of Asia and Western Pacific (FERCAP), former Russian states (FECCIS), Latin America (FLACEIS), Africa (PABIN) and North America (FOCUS). SIDCER formally began through the formation of these forums.

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[82] https://www.coe.int/en/web/bioethics/home
[83] http://www.bbmri-eric.eu/services/common-service-elsi/
[84] https://www.eubios.info/
[85] https://www.eubios.info/EJAIB.htm
[86] https://www.who.int/sidcer/en/

Name of organization	Description
Nuffield Council on Bioethics (United Kingdom)[87]	The Nuffield Council on Bioethics is an independent body established by the Trustees of the Nuffield Foundation in 1991 to consider the ethical issues arising from developments in medicine and biology. The Council is funded jointly by the Nuffield Foundation, The Wellcome Trust and the Medical Research Council.
The National Human Genome Institute (USA)[88]	The National Human Genome Research Institute's (NHGRI) Ethical, Legal and Social Implications (ELSI) Program was established in 1990 as an integral part of the Human Genome Project (HGP) to foster basic and applied research, and support education and outreach.
UNESCO IBC (France)[89]	UNESCO's Programme on the Ethics of Science and Technology reflects its concern for the ethical issues raised by scientific progress today. The organisation aims to place such progress in a context of ethical reflection rooted in the cultural, legal, philosophical and religious heritage of the various human communities. Created in 1993 UNESCO's Bioethics Programme addresses the ethical, legal and social concerns stemming from advances in the life sciences, particularly in genetics.
Wellcome Trust (United Kingdom)[90]	The Wellcome Trust programme in Biomedical Ethics aims to provide evidence and thinking to inform decision making, public debate and public policy making.
The National Academies of Sciences, Engineering, and Medicine[91]	The National Academies of Sciences (founded 1863), Engineering (founded 1964), and Medicine (founded 1970) are established (as a private, non-profit) to provide expert advice on the most pressing challenges facing the US and the world, including in genomics. Their work helps to shape public policy and to inform public opinion.
European Academies'	Formed by the national science academies of the EU Member States,

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[87] http://nuffieldbioethics.org/
[88] https://www.genome.gov/
[89] http://www.unesco.org/new/fr/social-and-human-sciences/themes/bioethics/international-bioethics-committee/
[90] https://wellcome.ac.uk/
[91] http://www.nationalacademies.org/

Name of organization	Description
Science Advisory Council (EASAC)[92]	Norway and Switzerland to enable collaboration and the provision of independent science advice to European policy-makers. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.
Public Population Project in Genomics and Society[93]	A not-for-profit consortium that encourages collaborations between researchers and biobankers and/or databases curators, promotes harmonization of data, works towards the development of health and social research infrastructures.
The European Society of Human Genetics[94]	A non-profit organisation which aims to promote research in basic and applied human and medical genetics, to ensure high standards in clinical practice and to facilitate contacts between all persons who share these aims, particularly those working in Europe. The public and professional policy

Table 4: List of the main organizations in the field of ELSI of genomics

ii.   Online resources on ELSI of human genomics

We list below a non-exhaustive selection of different online resources (beyond those associated with the organisations listed above) to show the reader the different scope of existing resources for the b ELSI of genetics and genomics.

Online resources	Description
Bioethics Today	Bioethics Today is a web-based resource on the ethical, medical, legal, social science and lay perspectives on biomedical research and biotechnology related to animals, humans and agriculture. It is developed by the Universities of Sheffield, Lancaster and Oxford, funded by The Wellcome Trust.
International Bioethics Exchange Project (USA)	The International Bioethics Exchange Project (IBEP), a program of the Institute's Library and Information Services area, promotes research and education in bioethics in the developing world. Through IBEP, multiple volumes of the Bibliography of Bioethics, an annual compilation of citations and abstracts to English-

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[92] https://www.easac.eu/
[93] http://www.p3gconsortium.org/
[94] https://www.eshg.org/index.php?id=home

Online resources	Description
	language literature, are donated to libraries abroad in order to encourage the development of bioethics reference resources in those countries.
Science and Development Network (UK)	The Science and Development Network (SciDev.Net) aims to enhance the provision of reliable and authoritative information on science- and technology-related issues that impact on the economic and social development of developing countries. Their goal is to ensure that both individuals and organisations in the developing world are better placed to make informed decisions on these issues. This site includes information on medical ethics, intellectual property as well GM foods and related areas.
The Hastings Centre - Genetics and biotechnology	The Hastings Center addresses social and ethical issues in health care, science, and technology. Founded in 1969 by philosopher Daniel Callahan and psychoanalyst Willard Gaylin, The Hastings Center is the oldest independent, nonpartisan, interdisciplinary research institute of its kind in the world.
National Human Genome Research Institute's ELSI Research Program	This program fosters basic and applied research on the ethical, legal and social implications of genetic and genomic research for individuals, families and communities.
ELSI2.0 initiative	This website provides an overview of ELSI2.0 activity, and aims to advertise globally the community of ELSI about research in the Life Sciences.
Humgen (Canada)	The University of Montreal "Humgen" website gives policy makers and lay people alike access to a comprehensive database on the legal, ethical and social aspects of human genetics. The purpose of this website is to connect visitors of this site to credible and readily accessible policy information on human genetics.

Table 5: List of online resources on ELSI of genomics

iii.   Main journals publishing ELSI of human genomics

We present below a non-exhaustive list of journals in which ELSI studies of human genetics and

genomics are published. This list of the top 20 journals has been generated using Google Scholar, following Eriksson and Helgelsson[95] criteria: impact factor over one over a five year period, and a good reputation (i.e. not identified as a predatory journal)[96].

1. *The American Journal of Bioethics*
2. *Bioethics*
3. *Biology & Philosophy*
4. *BMC Medical Ethics*
5. *Developing World Bioethics*
6. *Ethics*
7. *Ethics and Information Technology*
8. *Hastings Center Report*
9. *Health Care Analysis*
10. *Indian Journal of Medical Ethics*
11. *Journal of Clinical Ethics*
12. *Journal of Empirical Research on Human Research Ethics*
13. *Journal of Law, Medicine and Ethics*
14. *Journal of Medical Ethics*
15. *Kennedy Institute of Ethics Journal*
16. *Medicine, Healthcare and Philosophy*
17. *Public Health Ethics*
18. *Science & Engineering Ethics*

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[95] https://ethicsblog.crb.uu.se/2016/04/19/where-to-publish-and-not-to-publish-in-bioethics/

[96] https://predatoryjournals.com/ This community-based website provides a blacklist of journals that publish work without proper peer review, in continuity with the work of Jeffrey Beall, scholarly communications librarian at the University of Colorado at Denver, who started a blacklist in 2008 but had to stop in 2017 because of harassment and threats. This list is established based on 10 criteria:

1. Charging exorbitant rates for publication of articles in conjunction with a lack of peer-review or editorial oversight.
2. Notifying authors of fees only after acceptance.
3. Targeting scholars through mass-email spamming in attempts to get them to publish or serve on editorial boards.
4. Quick acceptance of low-quality papers, including hoax papers.
5. Listing scholars as members of editorial boards without their permission or not allowing them to resign.
6. Listing fake scholars as members of editorial boards or authors.
7. Copying the visual design and language of the marketing materials and websites of legitimate, established journals.
8. Fraudulent or improper use of ISSNs.
9. Giving false information about the location of the publishing operation.
10. Fake, non-existent, or mis-represented impact factors.

19. *Science, Technology and Human Values*

Beyond these primarily (bio)ethics journals, genetics/genomics journals also publish ELSI studies, these include, among others: the *European Journal of Human Genetics*, the *American Journal of Human Genetics,* the *Journal of Genetic Counselling*, *EMBO Journal*, *Nature Bioetechnology*, *Nature Reviews in Genetics*, *Human Molecular Genetics*, *CRISPR journal*, *New Genetics and Society*.

3. SIENNA approach for ethical analysis of human genomics: methods and approach

SIENNA is a three-and-a-half-year project focussing on the ethical, legal and social challenges posed by human genomics, human enhancement and human-machine interactions (i.e. AI and robotics). Human genomics, like the other areas of technologies, is an innovative field that promises benefits to individuals and society, but also presents significant ethical challenges, e.g. in relation to autonomy, equality, liberty, privacy, and accountability. The purpose of SIENNA is to identify and assess these issues, in collaboration with a variety of stakeholders.

In the following section, we present SIENNA approach in order to question its legitimacy in providing a framework adapted to the ethical analysis of human genomics and to compare the results brought by SIENNA with approaches relying on different methods. This reflection on the strength and weaknesses of SIENNA approach is necessary to contextualise and weigh the results presented in this and in other SIENNA deliverables.

3.1 Stakeholder involvement in SIENNA: Why and how?

vi.   Stakeholder engagement and consultation play a crucial role in ethical analysis envisaged by SIENNA. This approach is thus in line with recent developments in bioethics, such as

Constructive technology assessment and **Responsible research and innovation** which insist on involving stakeholders and enhancing public engagement throughout the process of science and socio-technological innovation.

Stakeholders are broadly defined in the SIENNA project as anyone with a vested interest in, personal stake in, or involvement with the (impact of) the technologies. The term originates from business where stakeholders may be designated as shareholders, employees, customers, suppliers, financiers, families of employees and the community in which the corporation is located. This could also potentially include taxpayers who may need to fund a government rescue of a distressed company or those suffering the effects of corporate pollution. Stakeholders' interests thus encompass specific views and public considerations. Stakeholders in genomics include diverse groups of patients,

research participants, public and private providers of services and technologies involving genomics, researchers, advocacy groups, tax payers, policy makers, and general publics.[97]

Public engagement can serve to educate the lay publics on genomics and can also pave the way to include the different interests of multiple stakeholders so as to provide direction in science and technology and consider how genomics may best be regulated. Many issues raised by the development of genomics may benefit from the involvement of diverse stakeholders. DNA patenting for instance is increasingly polarized and would greatly benefit from such procedures that help the development of a mutually acceptable balance between private incentives for innovators and the public interest of maximising access to the fruits of innovation.

As such, the development of genomic technologies in public health cannot happen without well-developed plans to educate and engage the public in general but also the wide range of professions that that would have specific interactions with, and duties to, patients or research subjects or persons with results – from local general physician, to social workers, to dietician, etc[98].

As stated in SIENNA 's handbook (p. 29):

> "*Getting stakeholder input early in the ethical impact assessment process will help make the recommendations, frameworks and codes developed in SIENNA useful and actionable. Stakeholder input will be one of the primary sources of information that enhances the SIENNA ethical impact assessment.*"

Stakeholders with whom SIENNA engages are (p. 30):

Ethics committees	Field experts (natural and life sciences, medicine, social sciences and humanities, engineering and information sciences)	Human rights organisations	Consumer rights organisations
Patient advocacy organisations	Policy-makers	Regulators	Professional organisations or associations
Industry	The public (including non-experts)		

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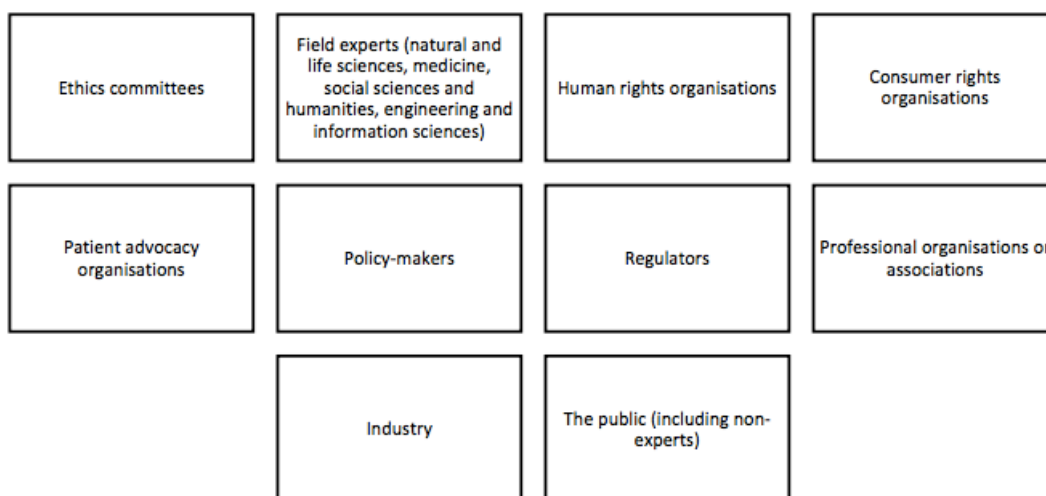
[97] Lemke and Harris-Wai, "Stakeholder Engagement in Policy Development: Challenges and Opportunities for Human Genomics".
[98] See for instance https://www.primarycaregenetics.org/?page_id=109&lang=en, a website aiming to enable health professionals who are working in primary care to update their knowledge and skills in genetics.

Figure 2: Overview of stakeholders in SIENNA

As mentioned above, SIENNA collects views of experts and lay public groups on recent and future developments of human genomics in four ways: (1) a major survey of citizens in 11 countries within and outside the EU; (2) focus groups involving citizens in five countries; (3) (informal) interviews with experts and stakeholders; and (4) workshops with stakeholders including scientists, ethicists, and various individuals involved in research ethics. More precisely:

- Lay public groups are engaged primarily through focus groups (task 2.6) and public opinion surveys (task: 2.5) designed to gain the public's views on genomics. Here, the focus groups function as a space for discussion and deliberation of complex, sensitive and/or contentious topics. They help explore the general awareness and public concerns about the applications of genomic technologies and related ethical issues, including the perspective of vulnerable populations. Although the term "panels" has been used in SIENNA, we are using the terminology "focus group with lay people" because in research, "panels" engage the same group of respondents for an ongoing set of interviews (as it is the case for Delphi panels[99] or citizen panels[100]) which was not the case of the investigation led by Kantar research group. The results will provide additional insight into publics' views of genomics and lay the ground work for future (empirical) studies; the results will also be used, in as far as qualitative results can be used, to inform the development of the ethical framework (task 2.7).

- SIENNA's engagement activities also include stakeholder consultations (interviews and surveys) and stakeholder events (e.g. legal analysis workshops, foresight workshops, and workshops on operational codes and guidelines). To date, for human genetics and genomics, consultations have been held to find out stakeholder opinions about the technologies and their socio-economic, ethical and human rights aspects (see deliverable Deliverable 2.1 for methods and results). An explorative survey on foresight of genomics was also conducted with experts to obtain their opinions on genomic developments expected in the near future. It targeted scientists involved in genetics and/or genomics, including genomic research, clinical genetics and genetic counselling. It was done in February 2019 and thirteen complete responses have been obtained (See Methods and preliminary results of the survey p.94).

These different procedures were set up to enhance our knowledge about different visions of genomics, so as to further inform the ethical analysis.

3.2 Why is there a foresight approach - and how is it conceived?

Foresight analysis is used in SIENNA to identify potential future impacts associated with projected future developments and uses of the technology.

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[99] Avella, "Delphi Panels: Research Design, Procedures, Advantages, and Challenges".
[100] Kathlene and Martin, "Enhancing Citizen Participation: Panel Designs, Perspectives, and Policy Formation".

Historically, foresight analyses have been used primarily for political or commercial uses in order to anticipate change and future needs of either consumers or citizens[101]. It is the "*practice of making studies of future possibilities*"[102]. Professor in political science B. Martin provided an early definition of foresight as:

> "*the process involved in systematically attempting to look into the longer-term future of science, technology, the economy, environment and society with the aim of identifying the areas of strategic research and the emerging generic technologies likely to yield the greatest economic and social benefits.*"[103](p.158)

Foresight analyses have been used heavily in policy-making where actors elaborate on the type of research that they would like to see over a given period, and what actions are required in order to realise their vision[104]. It relies on qualitative and quantitative methods to monitor clues and indicators of evolving trends in research and technology. However, these methods may sometimes lack the academic rigour usually associated with social science empirical research and therefore the interpretation of results must be done with caution. Moreover, foresight is not forecast. Whereas forecasting is an attempt (often using numerical calculation) to predict the single most likely future in periods characterized by rapid and stable growth, foresight considers multiple possible futures in situations characterized by complexity, turbulence and ambiguity[105].

Although there is a growth of academic interest in the foresight approach, it remains less common than in in the political and corporate fields, since the methodologies used lack a firm theoretical basis, do not lend themselves easily to rigorous systematic analyses, nor are there current ways to validate these[106]. Given the weaknesses of foresight as an academic approach, explorative research dominates. As a form of explorative research, foresight endeavours can be grouped into two broad categories: conceptual[107] and empirical[108]. Conceptual research refers to studies that formulate concepts, models, and frameworks, including literature reviews. Empirical research refers to research with some form of empirical data collection and analysis and includes surveys, interviews, case

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[101] Wilhelmer, "Society in Need of Future: Complementary Foresight as a Method to Co-Create Transition BT - Handbook of Cyber-Development, Cyber-Democracy, and Cyber-Defense".

[102] Hideg, "Theory and Practice in the Field of Foresight".

[103] Martin, "Technology Foresight: Capturing the Benefits from Science-Related Technologies".

[104] Da Costa et al., "The Impact of Foresight on Policy-Making: Insights from the FORLEARN Mutual Learning Process".

[105] Andreescu et al., "Technological Forecasting & Social Change Understanding Normative Foresight Outcomes : Scenario Development and the ' Veil of Ignorance ' Effect".

[106] Iden, Methlie, and Christensen, "The Nature of Strategic Foresight Research: A Systematic Literature Review".

[107] Andreescu et al., "Technological Forecasting & Social Change Understanding Normative Foresight Outcomes : Scenario Development and the ' Veil of Ignorance ' Effect".

[108] Kayser and Bierwisch, "Using Twitter for Foresight : An Opportunity ?"

studies, and experiments[109].

To study the ethical and social impact of human genomics within SIENNA, the Foresight approach has been developed in different ways:

i. **Horizon Scanning**: a policy tool usually used in government and business to identify future threats or opportunities in relation with future developments[110]. This step was accomplished through an overview of the literature, formal and informal interviews with genomics' experts about technologies to be developed for the sequencing and editing of the genome (See Deliverable 2.1 for methods and results) and a survey filled out by thirteen genomics experts (See Methods and preliminary results of the survey p.94).

ii. **Speculative ethics**: the foresight approach has also been adapted to the ethical analysis of future issues in human genomics through consultations with experts during a workshop specifically dedicated to this task (See p.91 for presentation of the workshop, methods and preliminary results). This workshop was developed primarily to facilitate conceptual analysis through thought experiments via various exercises involving group discussions and brief presentations on genomic technologies and related impacts in possible futures. The various methods presented included, brainstorming, scenario building and a discussion of a science fiction literary text. In a reflexive perspective, the utility of the foresight approach and its ability to gain new insights in the ethics of human genomics have also been questioned and discussed. Ultimately, the use of foresight in speculative ethics aimed to gain enhanced perception of potential ethical issues raised by human genomics in different envisioned futures.

iii. **Public engagement**: in some ways, the 11 country survey to collect laypeople's opinions on future developments on humans genomics (task/deliverable 2.5) and the one-day focus groups conducted in five EU countries (task/deliverable 2.6) also used some aspects of foresight. The purpose of the survey was to assess publics' views regarding specific topics posed in close-ended questions (see p. 88 for details). The purpose of the focus-groups was explore citizen awareness, understanding, views and concerns raised by genome sequencing and genome editing – both fields are expected to develop increasingly with time. Result from focus-groups and surveys will inform the ethical analysis by exploring public awareness and concerns about the applications of human genomics, including from the perspective of vulnerable populations.

In summary, the foresight approach in SIENNA has been developed and used from an explorative

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[109] Iden, Methlie, and Christensen, "The Nature of Strategic Foresight Research: A Systematic Literature Review".
[110] Brown et al., "A Horizon Scan of Future Threats and Opportunities for Pollinators and Pollination".

perspective. It has been used for conceptual and empirical purposes:
- to collect empirical data from experts about anticipated developments in human genomics and their socio-economic impact;
- to develop future scenarios and discuss ethical issues in a speculative fashion about these developments and their impact;
- to collect empirical data about public awareness and discuss laypeople's concerns about these developments and related ethical issues.

The foresight approach, as developed in the ethical analysis of human genomics in SIENNA, aligns with the key features of the Foresight framework (see p.91) since it embraces uncertainty and explores near futures through scenario methodology, while grounded in empirical work and committed to gathering the perspectives of various stakeholders.

3.3 Discussing Foresight and ELSI in SIENNA approach

ELSI, as a research field, embraces a wide variety of disciplines and methods (cf. p.10). Given its openness to various approaches and its lack of explicit theoretical basis, there is no *a priori* contradiction for ELSI to adopt a foresight approach as a tool to address the concerns raised by developments in human genomics. In fact, the foresight approach and ELSI share common features and interests:
- Shared temporality of ELSI and the foresight approach: ELSI may either refer to the ethical issues raised by genomics, the socio-economic impact of developments in genomics or the implications of specific projects. At least two of these meanings invite ethicists to disconnect genomic activities from their particular applications and to project their analysis in a forthcoming or future context. According to some ethicists[111], these features have propelled ELSI analysis into a speculative form of ethics disconnected from today's activities and focussing to future applications. The foresight approach shares the same sense of anticipation, based on various modes of future thinking, primarily cultivated through future scenario practices.

- Common interest for conceptual and empirical analysis: the array of methods developed in ELSI encompasses quantitative and qualitative empirical methods as well as conceptual work (p.10). Foresight analysis involves empirical data to develop future scenarios and identify key drivers of change, and thus integrates horizon scanning tasks such as literature review and consultations with experts. It also involves reflexive inquiry in order to interpret and respond to future situations.

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[111] Guchet, "L'éthique Des Techniques, Entre Réflexivité et Instrumentalisation"; van der Burg and Swierstra, *Ethics on the Laboratory Floor*; Guston and Sarewitz, "Real-Time Technology Assessment".

- Common lack of theory: since the foresight approach lacks theoretical background and validation[112], it falls under some critiques addressed to ELSI for being merely an explorative framework and contributing to overly speculative forms of ethical reasoning.

These common traits indicate proximity between ELSI and the foresight approach. This was already underlined in the critique of ELSI as a "compressed foresight"[113]. Indeed, the requirement of ELSI to produce pragmatic and advanced assessments of a developing technology encourages such scholars to consider the future as a calculable and manageable extension of the present. This framing of ethical implications and social impacts as being inherent in the technologies themselves relies on a mechanistic and linear understanding of technological development compressing all technological possibilities and possible uses of technologies into the present stage of development.

> "*The desire to resolve from the outset debates about the future prospects and implications of new technology motivates our attempts to anticipate the future and map the technical and social outcomes in a higher level of detail than previously. In attempting such a mapping, the future may be presented as if it were here today (or at least visible and already known) in a way that can make these futures appear as largely determinate and imminent; in this process, the gap between imagined and actual futures is foreshortened; our attempts at foresight, at anticipation of the future, are thus compacted and compressed*"[114].

The notion of "compressed foresight" holds two critiques against ELSI:
- ELSI analyses may rely on simplified models of the innovation process, which stands in contrast to the empirically grounded studies of historical scientific and technological developments, which point to the unpredictability of social and technical outcomes. These studies show that innovation pathways often deviate from their initially expected trajectory – in many cases falling short of their initial promise but occasionally far exceeding expectations – and include unanticipated costs and benefits as well as those intended[115]. Indeed, studies of historical experiences show that initial conceptions of the implications of a technology are often so far removed from ultimate outcomes as to be uninformative[116]. The consequent critique of deterministic accounts of innovation outcomes has led most

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[112] Iden, Methlie, and Christensen, "The Nature of Strategic Foresight Research: A Systematic Literature Review".

[113] Williams, "Compressed Foresight and Narrative Bias : Pitfalls in Assessing High Technology Futures"; López and Lunau, "ELSIfication in Canada : Legal Modes of Reasoning ELSIfication in Canada : Legal Modes of Reasoning".

[114] Williams, "Compressed Foresight and Narrative Bias : Pitfalls in Assessing High Technology Futures"p. 329.

[115] Hughes, *American Genesis. A Century of Invention Technological Enthusiasm*; Hughes, *Networks of Power*.

[116] Williams, Stewart, and Slack, *Social Learning in Technological Innovation: Experimenting with Information and Communication Technologies*.

contemporary Science and Technology Studies to reject the terminology of the 'impacts' of technology, and the simplistic 'linear' innovation models that underpin them, in favour of concepts such as the co-production of a technology and its societal outcomes[117]. The presumption, for example, that ethically conducted research will have ethically desirable outcomes (and vice-versa) brings us back to essentialist analyses of the relationship between social values and innovation outcomes that have long been rejected by STS.

- When ELSI analysis relies on determinate projections of technological development and exploitation and definite predictions of the related societal and ethical implications, the scope of ethical enquiry may be overly narrowed. Open-ended and less expedient questions may for instance be displaced, fuelling a notion of control over technology that does not correspond with our experience of handling past technologies [118].

Far from being new to ELSI, the foresight approach can be seen as a component of ELSI itself, in the sense that the analysis of new technologies' implications involves a "compressed foresight". This trait of ELSI has already been criticized because it may be based on an essentialist understanding of the technology-society relationship and suggests a simple relationship between the values surrounding technological development, the artefacts developed and the resulting social outcomes. Based on foresight, ELSI accounts may even encourage a narrowed scope of enquiry.

Within these limits, the foresight approach may still bring interesting tools to ELSI. Key to the foresight approach, scenario methodology is a creative instrument that is not systematically conducted in ELSI analysis but could enhance the capacity of ethicists to perceive possible developments in genomics, to interpret them and to respond to these developments. The practice of integrating a wide variety of stakeholders and integrating diverse perspectives into multiple futures may also widen the ELSI enquiry – thus bringing up new ethical issues or new insights on already identified ethical issues. This is particularly important when ethicists are "embedded" in specific genomic projects (which was the case of the first ELSI program) in order to widen ethical analysis to outsiders' concerns and partially prevent ELSI from being the communicative branch of genomic researchers.

This analysis of SIENNA approach and the appreciation of its limitations are necessary in order to question its legitimacy as an appropriate framework for genomic technologies and to compare its results with the results provided by other methods, whether labelled as ELSI or other approaches. According to the methods they display, different approaches have different objectives, scopes and limitations and will bring different results to be interpreted in different ways. Since ethical analysis deals with sensitive issues, we cannot emphasize enough the importance of reflecting on the

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[117] Jasanoff, *States of Knowledge. The Co-Production of Science and Social Order*; Sørensen and Williams, *Shaping Technology, Guiding Policy: Concepts, Spaces and Tools*.
[118] Jasanoff, "Technologies of Humility".

strengths and weaknesses of the approach developed and of being cautious with the results provided.

4. Country-based approach: ethical issues raised by human genomics in 11 different countries

In order to help us consider as many ethical, legal and social issues (ELSI) in human genomics as possible, and in parallel obtaining a snap-shot of what is currently salient in different countries, we asked all SIENNA partners to conduct a small-scale study of ELSI in the country where they work. The short time allotted to this task for human genomics (0.3 person months, hence roughly 6-7 days) was delimited by the budgets agreed to in the grant agreement[119] and this meant the methods needed to be adapted for such a short time and swift study (see below). It also means the results should be contextualised in light of this timing and results should be considered preliminary.

That being said, the results of the studies nonetheless help us ensure that we have considered a broad scope of ELSI of human genomics in different regions in Europe. They also give us a glimpse of ELSI outside of Europe, albeit in only three countries. Globally, the results will feed into tasks 2.7 on establishing an ethical framework for human genomics and into task 5.2 into codes of conducts for human genomics.

This sub-task should be considered very much like task 2.3 (deliverable D2.3) on the gathering of guidelines and views from ethics committees in that it is a resource in itself, from which no large conclusions can be reached at this point. Rather the information will be useful in going further in different tasks, and certainly will help partners in identifying preliminary gaps and needs for their countries with respect to addressing ELSI of human genomics in further research.

4.1 Aims and methods

In order to gain insight into the discourses on ethical issues in partner countries (as specified in the Description of Action), we asked the partners to conduct a search and preliminary analysis of relevant academic and media articles with goals of:

1. providing overview of academic discourse on ELSI aspects of human genomics & genetics in a partner's country,

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[119] We are more than aware that more time would have resulted in more robust results and in a greater depth of analysis, however, in order to respect the grant agreement on the one hand and the work and time of our partners, we could not expect them to work for free and/or to charge this time to other funding they may have. This would have not been responsible or respectful.

2. providing overview of academic media studies on human genomics and genetics in partner's country,

3. providing overview of ELSI of genomics and genetics addressed by organisations and institutions in partner's country.

Specific instructions were provided to fulfil each of these aims, including suggested key terms and databases to use for the search (for full details please refer to the complete instructions prepared for the partners in Annex 3). Partners were also provided with reporting documents which contained tables to fill in and questions to guide the summaries that they were asked to write based on their search results. As mentioned earlier, each partner had 6-7 days to complete the search and write the report for each technological area. The instructions were shared with the partners in early December 2018 and preliminary results of their searches were collected in February 2019. Questions which appeared at that stage were discussed and clarified. In April 2019, the Uppsala University team proposed a summary table to be filled in by the partners, which was used to facilitate the analysis. The summaries of the findings provided by each partner are presented in the section below. Complete reports from each partner are available upon request.

4.2 Summaries of preliminary results from ELSI searches in 8 European countries and 3 non-European countries

We provide below the summaries written by each SIENNA partner. To ensure accuracy of the information and due to the time allotted for this task, only minimal editing for language was conducted. This would explain any lack of uniformity of language, and represents and contextualises very well the complexity and challenges of working on large multi-partner European projects with limited funds to answer the tasks requested in project calls. We also include the specific methods used as reported by each partner in order for readers to be contextualise the summaries. In the section 4.3 we included the summary tables which provide overview of the most important results for each country and contextualize them with the results of SIENNA task 2.3.

4.2.1 Brazil

Important ELSI issues in Brazil

Three ELSI issues stood out in the research conducted: namely 1. "'Genomics in general', 2. 'Genetic Testing and Genetic Screening', and 3. 'Gene Editing'. The report covered about twenty years of academic research in the field of human genetics and human genomics in Brazil. A number of general trends were observable over this period of time. Some trends, though, overlap with each other so that a clear-cut timeline limiting one from the other could not be drawn. The most relevant trends for the purpose of the present report corresponded, in broad chronological order, to the three ELSI categories mentioned above.

Genomics in general
In the research conducted, the earliest academic article included "Projeto genoma humano e ética" (*The Human Genome Project and ethics*) by Mayana Zatz (2000), a well-known Brazilian geneticist.

The article focuses mainly on the ethical relevance of the Human Genome Project. The early 2000s saw the publication of a significant number of academic articles (and academic media articles) on that grand-scale project and its ethical implications, for instance, for the understanding of genetic diseases.[120]

More recently, Zatz (2011) has published a book (not included in the search results as it could not be adequately reviewed and assessed in the 6-7 days allotted for this task) in which she analyses the importance of the Human Genome Project. She also identifies different aspects of the ethics of human genomics to the Brazilian general public. As far as was ascertained, this is the only book-length study on the relationship between ethics and genetics for the general public in Brazil.[121] The book is often mentioned in the press coverage of topics related to human genomics in Brazil.

Genetic Testing and Genetic Screening

Most academic articles on the ethics of human genetics and human genomics published in Brazil focus on issues related to genetic testing and genetic screening. Brazil pursued state-sponsored **eugenic** policies in the past. For this reason, eugenics is an issue often addressed in the academic literature on the ethics of human genomics in Brazil.[122] Genetic testing and genetic screening have been addressed in several academic articles also because of the miscegenational profile of the Brazilian population.[123] A further reason for the academic interest in genetic testing and genetic screening is the growing demand for IVF in Brazil.

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[120] Further relevant contributions in this regard are "Saúde pública e ética na era da medicina genômica: Rastreamentos genéticos" (*Public health and ethics in the age of genomic medicine: Genetic screening*) by Bandeira et al. (2006), and "Manipulação do genoma humano: Ética e direito" (*Manipulation of the human genome: Ethics and law*) by Goulart et al. (2010).

[121] Zatz, Mayana. 2011. *Genética: Escolhas que nossos avós não faziam [Translation: Genetics: The choices our grandparents did not have to face]*. São Paulo: Globus. http://globolivros.globo.com/livros/genetica-escolhas-que-nossos-avos-nao-faziam

[122] See for instance "The path of eugenics in Brazil: Dilemmas of miscegenation" by Hochman et al. (2010), and "Pre-genetic Diagnosis (PGD): Diagnóstico genético pré-implantação (DGPI): Uma eugenia mascarada? " (*Pre-genetic Diagnosis (PGD): Disguised eugenics?*) by Eler et al. (2019).

[123] As one study points out, "The population admixture has always posed a challenge to the gene mapping studies of complex traits in Brazil" ("Genetics and genomics in Brazil: a promising future" by Passos-Bueno et al., 2014). Although it does not qualify as academic literature, it is worth mentioning here a documentary film produced by the Instituto Nacional de Ciência e Tecnologia de Genética Médica Populacional (*Brazilian National Institute for Science and Technology for Medical and Population Genetics,* also known as *INAGEMP*). The film deals with the occurrence of rare genetic diseases that are now reported to be prevalent in some regions of Brazil. This occurs, mainly, due to interbreeding. The INAGEMP proposed public policies to make vulnerable populations aware of this genetic issue. The film is available at: http://www.inagemp.bio.br/videos/quatro-herancas-genetica-medica-populacional/; See also "Doenças hereditárias, aconselhamento genético e redes familiares e sociais: da ética intergeracional ao papel dos mais

Gene Editing

The academic literature on the ethics of gene editing is only starting to emerge in Brazil. However, the recent international discussion, and press coverage, on the use of CRISPR on human embryos has sparked some academic debate on this topic in Brazil.[124]

Methodology

The search for academic articles was conducted with Google Scholar Brazil at: https://scholar.google.com.br/

An alternative data bank for academic research used for the preparation of the present report was the Brazilian Scielo Plataform at:

 http://www.scielo.br/

The search for media academic articles and journalistic articles was conducted with Google. Seven major Brazilian newspapers and magazines were the main focus of the Google searches, namely, *Veja*, *Época, IstoÉ, O Globo (G1), Folha de São Paulo, Estado de São Paulo,* and *Valor Econômico.* Many search results obtained during this research related to press coverage of recent topics such as gene editing, genetic human enhancement and genetic screening, which have also been addressed in the international press. For the purpose of the present report, though, only search results that involved direct reference to Brazil were considered.

The relevant keywords were:

Brasil + Ética + Genética

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velhos" ("Hereditary illnesses, genetic counselling and family and social networks: from intergenerational ethics to the role of the elderly" by Mendes. (2012).

[124] See for instance "Editing the genome of human beings: CRISPR-Cas9 and the ethics of genetic enhancement", Araujo (2017), and the academic media articles published by the Brazilian ethicist Darlei Dall'Agnol *"Edição do genoma humano: Algumas reflexões éticas" (Editing the human genome: An ethical approach) (2016);* "Edição de genes e problemas morais na interface entre bioética e neuroética'" *(Gene editing and moral problems in the bioethics and neuroethics interface) (2016);* "The ethics of embryo editing" (*The ethics of embryo editing)* (2015); In 2018, ethicist Darlei Dall'Agnol along with other Brazilian philosophers organized a symposium in order to discuss bioethical issues that matter for public policies in Brazil. The symposium also included the participation of the Oxford philosopher Roger Crisp. Some of the topics addressed during the symposium related to ELSI issues such as genetic enhancement, genetic testing and genetic screening. The contributions to the symposium have been turned into a collection of essays called *"Ética aplicada e políticas públicas" (Applied ethics and public policies).* (Ed.) Crisp, Roger; Dall'Agnol, Darlei; Savulescu, Julian; and Tonetto, Milene. Florianópolis: Editora UFSC (ISBN: 9788532808271). Available at: https://livraria.ufsc.br/produto/888/etica-aplicada-e-politicas-publicas.

Brasil + Ética + Genômica
Brasil + Discussão + Genética
Brasil + Discussão + Genômica
Brasil + legislação + Ética + Genética
Brasil + legislação + Ética + Genômica
Brasil + Edição Genômica
Brasil + Edição Genética
Brasil + CRISPR
Brasil + CRISPR-Cas9
Brasil + TESTE GENÉTICO
Brasil + Aconselhamento Genético
Brasil + Banco + Genético

Translation:
Ética: ethics (noun), ethical (adj. fem.)
Genética: genetics (noun), genetic (adj. fem.)
Legislação: law, legislation (noun)
Edição genética: gene editing
Edição genômica: gene editing
Aconselhamento Genético: genetic counselling

4.2.2 China

Based on the searches performed, the ethics in the field of human germline gene editing (both research and clinical) were found to be the most studied and focussed, while the research on other fields was found to be relatively rare and scattered (e.g. genetic testing, genetic screening, prenatal screening, new-born screening, etc.).

In China, it is required that government authorities and scientists jointly create development plans and measures for regulating **genetic editing** and developing ethical guidelines and legal norms for disruptive technology applications such as genetic editing, as well as clarifying the scope of permission and prohibition of genetic editing technology. This also involves the support for research directions and clinical trials on a safe and orderly basis (such as somatic and adult stem cell gene editing) that some have claimed have less significant ethical controversy and have significant value for medical applications. According to the consensus view of the academic community, there are a number of important areas of agreement. Firstly, it is considered that work on social issues of gene editing is important and should lead to (such as changing human embryonic and germ cell genome sequences, etc.) set strict research boundaries and temporarily prohibit clinical trials and applications. The government needs to attach great importance to the original innovation and patent protection of genetic editing technology, strengthen data privacy protection, and respect the basic values of human autonomy, rights, dignity, fairness and informed consent, etc. Further promote the dialogue and communication between humanities, scientists and the public, strengthen cooperation

and dialogue with international counterparts, truly respect human life in the frontier exploration and clinical practice of science and technology. Only let people clarify the principles and norms of the above aspects, let genetic technology play a full role in research and clinical, while avoiding biosafety risks, avoiding bioethical risks, avoiding social disputes, and making technology benefit the society.

Judging from the available literature, to our knowledge, the Chinese government and academia pay attention to the legal and ethical challenges brought by the widespread application of genetic technology. China's response to the development of genetics and genomics is effective, the problem of relatively lagging genetic technology legislation in many countries exists in China to a certain extent, but this issue has already attracted the attention of relevant Chinese departments. Relevant ethical norms have been slowly established for medical research and clinical practice using genetic technology, and China has formulated a series of laws to regulate various challenges caused by genetic technology. Given the continuous development of this technology, the corresponding adjustments and improvements are made to ensure that technical research and application practices do not exceed the parameters laid out by ethics and law.

China attaches great importance to drawing on international experience, and based on its national conditions, has promulgated a series of legal documents to regulate the research and clinical practice of genetic technology. And it has also carried out in-depth reflection and discussion on the related ethical issues arising from genetic technology. The Chinese government adopts a prudent attitude toward the legislation of genetic technology, and puts direct administrative management first in order to solve specific problems. After the technology develops to a certain extent and undergoes sufficient ethical considerations, it will then enact legislation, combine legislative work with specific practices.

Methods

The literature collection of this report is mainly from the database - China Knowledge Network index (http://www.cnki.net/), the search keyword format mainly as: (ethic or law or legal) + country + (genomic or genetic), the search format for specific questions is a little different. For all kinds of documents in the report, one needs to register the account of China Knowledge Network Index Database to download.

The language used in the report is mainly English, supplemented by Chinese. It should be noted that there is no official uniform format for the translation of relevant government documents. Due to the limitation of the number of documents and the specific stage of the development of genetic technology in China, the analysis and summary in the report are not divided into multiple time periods for detailed discussion.

Faced with a large number of documents, due to the multiple limitations of time and energy, it is inevitable that there will be some omissions in the representativeness of the documents listed in the report, which will be further improved by future research.

4.2.3 Germany

The search for academic publications in the field of human genetics and genomics in Germany showed a significant list of ethical, legal and social issues (ELSI) which are probably the most debated (see below). Although it is difficult to say if the listed ELSI are German specific or if some ELSI are more (or less) discussed in Germany compared to other countries. Like most academics, German academics want to be international and therefore the German debate is in general very much oriented to the international debate on Genetics and Genomics. Exceptions are, for instance, debates triggered by national legal developments. For example, in 2011, Germany passed a new law on **preimplantation genetic diagnosis (PGD) techniques** and, as might be expected, in the years before and after PGD becomes legal under certain circumstances, the academic debate mostly revolved around this. A good example for ELSI discussed in Germany likely in the same way as in other countries is with regard to **gene editing.** This is a prominent topic for German academics, but, as not specifically German, the discussion on ELSI in Germany might not differ from the debate in other countries.

The main research questions discussed in the academic articles and book publications found are:
- What is **genetic discrimination** and how to deal with it?
- What are the attitudes towards **psychiatric genetic research** and predictive testing?
- What are risks and benefits of genetic testing/screening?
- Which model of informed consent should be implemented in research biobanks?
- How can research institutions foster the responsible handling of genetic information in bio-bank-based research throughout the institution?
- How to deal with genetic incidental findings in an ethical way?
- What is a responsible way to store personal data?
- What are chances and risks of gene editing?

The most often discussed ELSI are:
- **Genetic discrimination**
- **Long-term effects/risks of gene editing**
- Risks for the society
- Transparency issues
- Protection of data
- Human dignity violation
- Self-determination
- Violation of privacy
- Physician-patient relation
- Misuse of results
- Rights and duties of patients and researchers

- Commercialization
- Availability and fair access
- The right not to know but also the right to know
- Protection of minors

Discrimination is a keyword that appears regularly in the academic literature. It is said that interventions in the human genome will lead to discrimination of people with 'bad' genes (although it is not clear, what 'bad' genes are). This discrimination based on genetic information can have an influence on everyday life as well as on the decisions of insurance companies or job applicants. Any development in that direction could force people to use gene therapies and could finally lead to disparities in society.

In terms of methodology, the Google Scholar database was used for the research. The search language was set to German to just display the German debate. Then the search was run several times with the following keywords, always combined with 'Germany' and 'human genomic or human genetic': ethical legal; social; ethic; legal; law; debate. Each time, the first 100 results were scanned, to find proper articles (after the first search runs it became clear that the results were almost the same for the most keywords). Because many of the articles were not recently published, the search was complemented with the keywords 'Präimplantationsdiagnostik' and 'gene editing'. In doing so, only articles published after 2013 were included. From the list of all articles and books, the most relevant ones (from the ones we had access to) were chosen for further analysis.

The most media articles we found gave attention to **genetic or genomic testing**. The ELSI raised here are mainly questions of self-determination and the 'right to know' and the 'right not to know'. The unborn child cannot decide if s/he wants to be tested or not, and it is always a difficult decision if the parents want to know about a possible disability of their future child or not.

These tests on embryos again raise some ethical questions. Is it okay to actively 'choose' a certain embryo and therefore a child? And which diseases are bad enough to allow these practices and to 'decline' a certain possible child? The articles cannot give answers to these questions, but it is important that they are raised and publicly discussed. And they must be raised and discussed to provoke politician's attention and make them work on these topics. The fear is, that there will be discrimination through these new techniques and tests. Organisations that work with disabled persons are particularly afraid of this. If one can see a disability at a very early stage of the pregnancy or even before the pregnancy via embryo testing, there is a question of how many (if any) disabled persons will be born in the future. An additional question could be on whether this would discriminate against the ones alive, thereby also putting a lot of pressure on parents to want and choose a healthy child. These are relevant questions that need to be discussed and it is also important to say that these tests are just currently allowed when there is the danger of a risky pregnancy. But nevertheless, these tests are quite expensive which makes it possible that just some

people can afford them. This would lead to a deeper distinction between 'rich' and 'poor' and would connect these attributions with 'healthy' and 'unhealthy'.

Another topic raised in the articles is **genome modification/ gene editing,** mainly focused on the CRISPR technique. This technique is said to be potentially very important and useful in the future, but, in the present context, scepticism is predominant. To use it properly there is not enough information nor is the technique safe enough yet. For example, we do not know what impacts the use of CRISPR may have on future generations. The articles raise fears of new diseases that can emerge and seek international laws to regulate the use of this technique. That also applies to the debate about where therapy ends and enhancement begins.

Aspects that are hardly mentioned in the articles are questions about patents (it is just mentioned that there should not be patents on genetic tests), databases or pharmacogenomics. But there are some aspects that might be particular to the German debate. Repeatedly, the articles mention the strict and, in parts, unclear laws in Germany. In this context, it is difficult to conduct research and scientists as well as patients often go to foreign countries for research or treatment. This raises the fear of Germany falling behind other countries and losing potential economic advantages. The scepticism about the topic 'human genomics' might also link back to the **euthanasia** programme in the Nazi-era. That's why German politicians may want strict and clear rules, at best on an international level, to prevent misuse of these new and powerful techniques.

In terms of methodology here, the database BELIT was used for the research. BELIT is an integrated bibliographic database developed by the German Reference Centre for Ethics in the Life Sciences (DRZE, Bonn) and operated in co-operation with the Information and Documentation Centre on Ethics in Medicine (IDEM, Göttingen), the International Centre for Ethics in the Sciences and Humanities (IZEW, Tübingen), the Bioethics Research Library at Georgetown University (Kennedy Institute of Ethics (KIE), Washington, DC) and the *Centre de documentation en éthique* (CDE, *Comité consultatif national d'éthique*, Paris) (DRZE 2018). The search included all media articles in the German language with the keywords 'genetics or genomics', 'Präimplantationsdiagnostik' (preimplantation diagnostics), 'Crispr' and 'gene editing'. The search was limited to the years 2011-2019 to illustrate the current debate. For the keywords 'genetics or genomics' the first 100 results were scanned, and for 'Präimplantationsdiagnostik' the first 50 results were scanned. In so doing, the results were sorted by date as well as by relevance. For the keywords 'Crispr' and 'gene editing' all article results were considered. Unfortunately, some of the articles could not be read for free and so they are not included in this summary. Also, not all articles to widespread discussed topics (like the PID law in Germany 2011 or the Chinese twins in 2018) are listed in table 5, because they contained the same information. For both topics, one or two articles were chosen as exemplars.

4.2.4 France

For reasons of expertise, the focus here is mainly on the ethical, academic debates, rather than on media studies. Most of the articles of newspapers were descriptive of the technology and had a significant value for informing a vast public about highly technical developments. However, they were often very generic and of minor interest in scientific terms. Academic articles were, on the contrary, highly relevant to understand the issues at stake with genomics and the related discussion in France. By searching on Google Scholar, on the main journals discussing bioethical issues, and via suggestions by colleagues, the most recent articles, discussing genomics and the ethics issues connected to it, were examined. This temporal choice was motivated by the fact that the developments of research and the consequent potential issues change very rapidly. Offering an up-to-date perspective can then help to avoid overlooking the most current highlights in the area. This section focuses only on French authors, publishing in French and, to a certain extent, offering a "French perspective".

In France, the debate strongly revolves around the legal regulations and its response to the development of research in genomics. France appears to be democratic in the ways it tries to implement this dialogue between scientists and society (Pierron et al. 2018). For instance, the *Comité consultatif national d'éthique pour les sciences de la vie et de la santé* (CCNE) is in charge of discussing the ethical issues around genomics and suggest, when needed, changes to the laws that are then evaluated by policy-makers. Accordingly, it is common to find several articles discussing the legal aspects around genomics and the necessity to keep the discussion open to the new developments of the technology.

However, discussions about the more philosophical principles at stake are also to be found.

According to Dechaux (2017), the debate in France is not intense because of the rigid legal framework as well as due to a lack of French investment in genomics. This is partially in contrast to the agreement between France and the UK (Genome 2025) to make genomics a central and economically relevant aspect of research (sequencing the whole genome of French population)[125]. The tendency towards genomics is confirmed by Noiville (2019) in a contribution discussing the ethical and judicial challenges connected to this plan. However, it might also be recognized that Dechaux is right when he highlights that the judicial restrictions are a strong barrier to genome modifications together with a broader discussion on its ethical challenges.

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[125]https://www.aviesan.fr/aviesan/accueil/toute-l-actualite/plan-france-medecine-genomique-2025#xd_co_f=NDNmZTY0YzgtNTczYi00YjQyLWJkMWItNjZlYTM0MWJiMmM5~
https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/france-genomique

According to Pierron & Valadier (2018), this is a peculiarity of the French debate, which makes it unique in the world. They believe that France is the only case in the world to think in terms of bioethical laws, under a subtle alliance between the ethical and the judicial, as well as to anticipate revisable laws (2011); to propose a socio-political experience of participatory democracy; to refuse a simple expert approach and to resist to the domination of one ethical tradition over the others, preserving their pluralism. According to the two authors, this scenario can be traced back to the spirit underlying the Enlightenment sceptical of all 'traditions'.

Although it is difficult to prove this historical peculiarity, it is reasonable to agree that in France certain topics, and the perspectives through which they are discussed, are perhaps more clearly identifiable than in other European countries. One of these is the criticism against mass discipline and surveillance that one finds in Foucault's studies and this is an influential factor. The general debate about medicalization of society and its negative consequences are summarised for instance by Julian Larregue[126].

This often intertwines with the possible neo-liberal influences in the development of technologies. For instance, the issue concerning "le bébé à la carte" is often addressed through an anti-capitalist framework. The objective is to alert society to two main related aspects. The first is the necessity to prevent genomics from being a refined tool exacerbating social inequalities. The second is mass surveillance and the consequent control that would derive from it. In this sense, it can be read into the points raised in several contributions about incidental findings and the autonomy of individuals with respect to prediction (right not to know).

One set of serious and 'alternative' questions are those addressing the risks connected to biodiversity that genomics could generate. If empowerment of social and cultural groups can be seen as a promising objective, we find several contributions highlighting the necessity to adopt a broader perspective when assessing the consequences of genome modifications, as summarized, for instance, by the concept of 'soft-heredity'. Irreversibility of results is also a risk on which authors agree to warn society about.

In order to broaden the assessment of potential outcomes but also of the overall trajectory that genomics should undertake, a stronger integration of societal aspects is consistently endorsed. It is not surprising then to find texts discussing the huge investments made by some private actors like Google or Pfizer and the necessity to regulate genetic testing through public frameworks. Under this perspective, the inclusion of different stakeholders and a better balance of public/private partnerships is also seen as an urgent measure to be taken. Such a societal relevance could then hopefully protect genomics from the risks connected to privacy that all big data collections imply.

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[126] Larregue, "La Nouvelle Orange Mécanique: La Contribution Des Bio-Criminologues à La Médicalisation Du Contrôle Social".

However, considering the growth in data collection, the secondary use of data and the opening to a global ground of exchanges, Noiville wonders what kind of consent in data processing we could realistically think of for the future (2019).

4.2.5 Greece

On academic articles:

The search of academic articles with ethical analyses focused on the Greek context highlighted that most documents that fit the criteria relate to personal genomics/pharmacogenomics/ and DTC genetic testing. Also noted were texts on the ethics of prenatal screening/testing, insurance and DNA databases used in court, views on cloning and artificial insemination, experts' views on clinical sequencing and the ethics of CRISPR-Cas9. Documents focusing on genomics, nutrigenomics and personal genomics show that Greece has a rather liberal policy on these issues. However, texts on DTC genetic tests criticize the lack of regulation on how these DTC genetic tests are offered and they criticize, for example, the lack of a doctor counsellor in these cases (where for example kits are sent via internet at home and people take these tests alone). Pharmacists' and lay people's views as stated in these documents support this conclusion. Cloning seems to be acceptable by the public in Greece when used towards a cure of disease; a conclusion in opposition to the law which prohibits cloning. The crimes related to cloning and genome modification are reported by experts as unduly harsh in the Greek law. The CRISPR-Cas9 method is known in Greece and the documents are more supportive than not, although they do mention possible ethical conflicts.

On media articles:

The Greek media have shown a strong interest in the ELSI of genetics/genomics. To illustrate this, 135 media articles and contributions from a much larger set of relevant articles have been selected aiming at a fair representation. The Greek media have followed practically all announcements in the international press on important developments and new technologies related to genetic and genomics which shows a great interest in these matters by the general public, the readers and users of internet newspapers and informative journals. The news on the genome modification and the possibility to have a "child by three parents" (mitochondrial donation etc) was widely reported and quite positively so. The same is true for the CRISPR-Cas9 method. Cloning is also widely reported, with the reference to the ethical dilemmas posed, but it is also seen positively under certain conditions. There is a range of articles on nutrigenomics and the ethics of pharmacogenomics. Genetic engineering and eugenics are also analysed in the media articles, with many references to important ethical slippery slope arguments against such practices. Gene therapy is viewed positively throughout many texts while the opposite is true for genetic doping. In general, a wide collection of these ELSI issues can be seen in the media in Greece which suggests that people are interested on these topics and that they are likely to be generally well informed on the new technologies (both pros and cons) of genetic engineering, DNA tests, DTC genetic tests, gene therapy, cloning, CRISPR-Cas9 method, etc. A positive trend towards acceptance of the genetic/genomic developments in bioethics can be seen, in line with the well-known liberal attitude of the Greek people on all these issues.

Methodology:

After doing a search on Google Scholar to check the first 100 results obtained, the search was continued on three legal databases: NOMOS, dsa.gr and sakkoulas.gr. For the media articles, various newspaper websites were also searched, like kathimerini.gr and tovima.gr (vima science). Many search terms for each search were examined and, each time, the first 100 results obtained were observed. In the search for academic articles on the ethical debates focused on the Greek context, the search terms used were a combination of ethic(s) + genomic/genetic/gene + Greece, ethics + nutrigenomics + Greece, ethics+ DNA databases+ Greece etc. For the media analysis, the search terms were: media + genetic/genomic/gene + Greece, ethics + nutrigenomics + Greece, ethics + DNA databases + Greece etc. After these searches, references of the most relevant and recent collected documents were checked in order to find documents possibly missed through the search on the databases.

4.2.6 The Netherlands

Findings:

Although the findings were listed chronologically, no interesting shift in focus or topics can be identified: there are too little results for such a conclusion. Concerns about bio-banking, databanks and information control seem to be raised most often. The most prominent topic of concern is to the assessment of ''consent'' and especially ''informed consent'' in combination with ''privacy''. The regulation of genetic testing has an important role as well, with special attention for the legislation of direct-to-consumer testing.

Somewhat puzzling is that there are not many articles addressing specific concerns about embryos or young children in the Netherlands. Another search with more specific search tags did not result in this either. However, children (minors) are mentioned alongside adults.[127]

Media coverage:

The academic media studies search was difficult and yielded no satisfying results. There is a report on the publications of The Health Council of the Netherlands about genetic screening and testing. This work discusses the publications of 1977, 1979, 1980, 1988, 1990, 1994. So, it might give the insight (on how Dutch concerns change over time) that was aimed for by putting the result in chronological order.

In addition, prominent newspapers in the Netherlands were researched. While archival research was initiated, it proved too time costly to continue. Among the overall results are two Master theses which focus on media coverage on a relevant topic).

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[127] If an article did not come up in the results using the ''general search terms'' but did occur when a more specific term was added, this key search term is added in the table.

Search:

It was found, when searching on this topic, that while a lot is written about human genomics and genetics, there are not many sources/articles that are specifically addressing Dutch ELSI or ELSI based on the situation in the Netherlands.[128] Some of the articles included consider a selection of countries of which the Netherlands is one, or to which the Dutch situation is compared. In those cases, it will be specified as to which sections are recommended to focus upon. There are, however, many articles to be found about the ELSI in the European situation (that indirectly applies on the Dutch situation). As they are not specific enough, these articles are not included in the tables. Also, there are a lot of articles about ELSI of nonhuman-genetics in the Netherlands to be found.

4.2.7 Poland

This section is based on the analysis of results of a search conducted with Google scholar with the aim of providing an overview of the academic discourse on ethical, legal, and social issues of human genetics and genomics in Poland. The research is exploratory in nature. The report does not contain an exhaustive analysis of the existing Polish scholarship on ELSI in genomics. It rather presents a sample of academic literature, which allows us to discern certain trends. These trends are outlined below.

As far as the number of search results is concerned, the search with: genetyka + etyka, returned 6,730 results. "Genetyk + etyka + Polska" returned 5,410 results. The search with: genomika+etyka+Polska returned 153 results. The search with: genetyka + ELSI returned 27 results. Adding "Polska" to the search decreased the number to 18. The search was not limited in terms of years. In the end 18 articles were considered relevant and included in Table 1, out of which 12 articles were analysed in greater detail.

In many of the articles, the different sub-areas of genetics (e.g. testing and editing) have been addressed together. The majority of texts referred to the use of genetic technologies in the clinic. The theme of genetic research tends to appear in relation to bio-banking.

There were few studies with original empirical data while most of the analysed texts were conceptual or policy oriented. Many of the analysed texts did not contain an explicit research question.

As far as the main ELSI considerations are concerned, considerable attention has been paid to issues related to prenatal genetic diagnosis, including the status of the embryo. The question of abortion is a subject of an ongoing public debate in Poland, as Poland remains to be among the countries with strict anti-abortion laws. The ethical issues related to the possibility that genetic tests may lead to a termination of pregnancy has drawn attention of Polish scholars. This may be seen as specific to

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[128] Both 'the Netherlands and 'Dutch' were used to specify the search

Poland. It may be noteworthy that the Catholic Church, who has presented a very strong anti-abortion stance, plays a considerable role in social life in Poland.

Bio-banking is another area where more publications on ELSI have appeared. This can be linked with the recent creation of the Consortium of Polish Biobanks. Here the issues related to data protection and informed consent draw particular attention. None of the academic articles related specifically to ELSI of genetic modification. There seem to be no clear line between genetic or genomic testing and screening.

As far as academic media studies are concerned, three relevant sources have been identified: two articles and one book. All of them were based on an analysis of traditional paper media: daily and weeklies. M. Jewdokimow looked at the context in which clinical genetics and genetics texts are addressed and how they are presented. He concluded that the presentation of genetics contributes to validation of tests as tools of disease prevention. The work of J. Domaradzki explores the concept and consequences of "geneticization". In his book, he argues, among other things, that genetics are not only a scientific fact but also a cultural fact. He analyzes genetics as a culturally created reality.

4.2.8 South Africa

Academic literature around genetics, genomics and biobanking
South African academic literature on genetics, genomics and biobanking primarily focuses on *research* and not on clinical practice in genomics/genetics. The literature largely focuses on macro and micro-level ethical issues. At the macro level, the concerns evolve **around exploitation, justice and fairness**. At the micro-level the focus is on issues around **informed consent, community engagement** and other practices aiming at making research and clinical practice more ethical.

Many of the papers commenting on the micro-level issues employ qualitative research methods (primarily focus group discussions and in-depth interviews). Authors like Schalkwyk et al. (2012), Moodley et al. (2014), Moodley and Singh (2016), Masiye et al. (2016) and Denny et al. (2015) use such qualitative empirical evidence to explore what stakeholders think about **data and sample sharing**, (broad) **consen**t for sharing and re-use and community engagement. They mostly interview participants in ongoing genomics or biobanking research as well as researchers involved in such research. Overall, this literature suggests that genomic and biobanking research in South Africa takes place in the context of **trust**, most often between researchers and their institutions, and participants. Procedures and practices that promote trust and trustworthy behaviour seem preferred over practices that do not. This is given as a reason for emphasising **community engagement as an essential component of genomics and biobanking research.** Although the importance of community engagement for research is also premised on the predominance of communitarian or Ubuntu-inspired philosophical orientations (which prevail in many African contexts over more individualist worldviews). The literature also suggests that people have divergent attitudes to the acceptability of **broad consent** which allows for the broad re-use of samples and data. Some participants prefer specific consent whilst others are more open to the use of broad consent. What seems to lie at the basis of a preference for specific consent is also **trust** – whether the participants can indeed trust other researchers to do good and not to harm them or their communities. Nevertheless, participants in the empirical studies reported overall support for genomics and biobanking research and emphasized the importance of altruism in motivating participation which would be in line with a

communitarian worldview. Important issues also covered in this literature are to do with benefit sharing (and ensuring that research leads to actual benefits for those involved in it). Associated with this theme is a concern about ownership of samples.

Important to note is that a communitarian worldview also emphasizes *reciprocity* as a key value that balances out the exchange and keeps it fair. Although this concept is only touched on lightly in some of these sources, the importance of 'giving back' or of expecting something in return for the donation of samples to a research study pervades the data provided.

There are also quite a number of authors that analyse the regulatory landscape for genomics in the country. Papers by for instance Nienaber (2011), Mahesh (2015), and Pepper (2017) fall into this category.

With regard to macro-level issues, the strongest concern emanating from the review of South African literature published on ethics of genomics and biobanking research relates to **exploitation**: i.e. genomics research and biobanking could lead to the exploitation of South African researchers, communities and participants. This concern is strongly located in the fact that most genomics and biobanking research in the country takes place in collaborations with researchers and institutions from wealthier parts of the world, and often involves the export of samples and data. Because of inequalities in scientific capacity and infrastructure, the experience is that such research often leads to significant benefits to the researchers and institutions in high-income countries (in the form of publications, subsequent grant applications, health or therapeutic innovations and patents) and less or no benefits to South Africans. The various works by Pepper (e.g. 2017a and b), De Vries and Pepper (2012) and Staunton and Moodley (2016) highlight and investigate these concerns.

A second, and more implicit, concern is how genomics research can be used to promote the interests of the poor and vulnerable in South African society – in other words, how genomics research can be used to promote **social justice**. South Africa has one of the highest GINI inequality coefficients in the world and there is a real concern how novel scientific technologies could be used to promote the interests of the poor and not the wealthy. This translates, on the one hand, in more protective attitudes towards the poor and a fear that more permissive or liberal science policies (including those concerning data sharing and broad consent) would be to their detriment. It also leads to an emphasis being placed on, for instance, benefit sharing as a requirement in research.

South Africa – Newspaper analysis

With regard to the newspaper analysis, we found that whilst there is a fair number of newspaper articles published on genomics broadly (although fewer on 'human genomics') the majority of these are drawn from Reuters and AFP or from the main UK newspapers (Guardian UK and The Independent) and as such the text is not specific to South Africa. We found only three publications published in popular media in South Africa in the past five years that are specific to concerns in the South African context (notably, sources 9, 17 and 18 in Table 6). Sources 9 and 18 touch on macro-level issues of justice whilst source 17 highlights the importance of informed consent for biobanking.

4.2.9 Spain

In this section, an abundant academic literature on ethical implications of human genetics / genomics that puts the focus of attention in Spain was not found. On the other hand, there were many academic articles that focused on the technical information of the subject but dispensed with a more social approach to the topic. More interest seems paid to the new techniques used and their practical applications, than to the possible human / ethical / social consequences that these may imply. In the cases in which these issues are addressed, the conservative perspective from which they are addressed is very notable. Given the emphasis on possible dangers that this perspective gives, , from the point of view of human rights, the notion of irresponsible development of the latest genetic techniques is very evident.

Thus, the main relevant ELSI highlighted in the Spanish context is related to the supposed moral dangers of carrying out genetic modifications in embryos or human individuals. However, the way in which the subject is approached and conclusions are drawn is far removed from a true analysis of practical ethics, where ideology and prejudice seems to substitute for the true analysis. This conservative perspective becomes especially evident when the topic of analysis focuses on gene editing. However, another important line of research found is related to biobanks. The main ELSI in this case is not as ideological as in the previous area but, on the contrary, reveals a more formed approach.

Another area highlighted in this review of academic articles regards the role of informed consent in relation to areas of research that are especially sensitive from the point of view of the ethical values addressed (transparency, autonomy, responsibility, etc.). It is striking the special interest that the issue of public perception of new biotechnologies arouses in Spain, especially with respect to those in which the use of sensitive human material and genetic editing are involved. The public dissemination of scientific information, it is admitted, is directly related to the *way* in which it is transmitted. The media have an important role here, as reflected in the relevant selection of articles. The way in which possible conflicts of interest in this sense have to be addressed seem to be particularly important, according to the literature reviewed. There is agreement in that experts, directly affected individuals and social actors must have a leading role, for which an adequate treatment of information is the first step.

4.2.10 Sweden

An overview of ELSI raised in academic literature in Sweden in the context of human genetics and genomics

The academic report is based on five academic articles. In total, twenty-three articles were found, but they did not all specifically address the situation within Sweden.

The following search keywords were used: *genetik och genomik* in Google scholar. *Human genetics and genomics* + Sweden were used in Google Scholar and in PubMed. The search was run with no time period restrictions. The article from Santa Slokenberga was found after a media search in google.se.

The articles found were mostly peer reviewed research articles, but also some B.Sc and Ph.D theses.

The main ELSI that were addressed in Sweden were governance of science, ethical consent and human dignity. In his PhD thesis, Kirik Ufuk explored the potential of personalized medicine using proteomics in curing cancer. Conventional chemotherapy puts a significant burden both on both the patient and on the Swedish health-care systems. Functional characterization of protein expression regulation in cancer remains an open question. Using genomics and proteomics may help to understand, in detail, how tumours arise and develop, but the data analysis methods are still not fully established. Ekløv (2013) also argues for the potential benefits from personalized medicine in the future treatment of diabetes.

Adam Ameur (2017) from Uppsala University constructed the SweGen, the first map of genetic variation in Sweden a population-based cross-sectional cohort that reflects the genetic structure of the Swedish population. The map is based on whole genome DNA sequencing of one thousand individuals, selected from a twin register to cover the variation in the whole country. As a result, Sweden now has a national resource, which will facilitate research and diagnostics of genetic diseases. The data can be used in clinical diagnostics to determine whether a genetic variation in a patient is a cause of disease, or if it is also present among healthy individuals in the population. This is possible since no information about single individuals are given out, only how frequently occurring a certain gene variant is within the group. Although, a genetic stratification within a population may introduce a bias, particularly for rare variants. The does not however, reflect the genetic background of the most recent migrants to Sweden.

When it comes to Human genome and commercialisation, Bengtson (2008). recommended not to capitalize on genetic material: "Commercialization of human genetic material is ethically sensitive, to such an extent that it cannot be justified and that the current legal frameworks need to be changed to accommodate this.

Sweden's regulatory environment pertaining to human germline modification is affected by the international and European regional legal orders and organizations of which Sweden is a member. Santa Slokenberga (2019) analysed the national regulatory responses in Sweden with a particular focus on the Genetic Integrity Act and the right to science. The Genetic Integrity Act was drafted in 2006 and defines the limits of genetic interventions in Sweden. Disregarding the limited effect of the Biomedicine Convention in Sweden, Sweden is bound to the European Convention on Human Rights (ECHR). Sweden cannot legislate nationally differently than EU law mandates. Slokenberga concludes that "*challenges stemming from the Genetic Integrity Act, if not tackled nationally through other mechanisms, could be seen as a systemic deficiency in the Swedish national law*".

In terms of the remainder of the literature, many articles contribute to the future potential of human genetics and genomics but were not specific to the Swedish national context.

Overall, the picture that emerges from this analysis, is that politics and ethical concerns that guarantee a standard level of safety and security lags behind when it comes to human genetics and genomics.

An overview of ELSI raised in popular media in Sweden in the context of human genetics and genomics.

The media report is based on six media articles. One was a from a popular scientific magazine. Two where short notes and three were radio interviews/debates. The following search keywords were used: *genetik och genomik* and *Human genetics and genomics* +Sweden. The search was ran in google.se with no time period restrictions. Only two of the radio interviews were used since they covered most of the ELSIs discussed.

While the first search did not find many articles, a list of the most important newspapers in Sweden was then searched using the same search words. As this was constrained by the fact that most articles were hidden behind paywalls, three radio interviews have been included from Sveriges Radio, the Swedish national radio station, using only *genetik* as a search word.

The main ELSI that were addressed specific to Sweden were *governance of science*, *the right to know/not to know about genetic findings*, and *data security*.

It seems that politics and the much-needed ethical debate tends to lag behind science when it comes to genetic engineering in Sweden. In an ethical debate on Sveriges radio from 2015, led by Annika Östman, the discussion evolved around CRISPR-Cas9 and human germline testing. A key question is how to look at a technique that has great societal benefit, but where the outcome still represents many unknowns. Emmanuelle Charpentier from Umeå University, (best known for her role in deciphering the molecular mechanisms of the bacterial CRISPR-Cas9 immune system) said it that the usage had to be limited because CRISPR-Cas9 is a tool that can change the human genetic code. She added that ethical committees will make sure that there will be restrictions in the use. Conversely, Jessica Nihlen Fahlquist, a researcher in biomedical ethics at Uppsala University does not agree and thinks the responsibility should not only lie in the hands of the bioethical committees, but also on the researchers in the field of genetics. There is a general agreement that the ethical debate has to come at an earlier stage, and that money has to be allocated not only to the scientific development of the technique, but also to ethical research and to keep politicians updated. One of the questions that came up in the debate was: "What happens if Sweden alone restricts research and clinical usage [while] China and the United States do not impose the same restrictions?"

Fahlquist said that we can only control the discussion in Sweden, but she did not find that the ethical discussion was very vibrant in Sweden when compared to other countries (e.g. compared with the Netherlands). The difference, she thinks, lies in cultural and historical differences. In the Netherlands, scientists and ethicists are much involved in the debate together.

In another radio debate from 2016 led by Ylva Carlquist Warnborg, the discussion revolved around data security and consent. Questions arose regarding what we want to know about our hereditary diseases and our genetic risk. One former breast cancer patient said that she would not like to know about her genetic risks for other diseases as she prefers not to worry about a disease that may never arrive.

Another key question arises over what happens if incidental or secondary findings are found during a genetic test. Richard Rosenquist Brandell, a researcher and medical doctor from Uppsala university explained that in Sweden, a medical doctor does not have the right to tell his patient about hereditary diseases from incidental findings, unless the patient asks for it. If a hereditary disease where a cure exists is found, then the risk level for each situation has to be evaluated. Brandell has

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also experienced cases where hereditary information was not passed on as his patient chose not to inform his relatives. Then, as a medical doctor, there is no right to inform the same relative about what the doctor already knows.

In the United States, scientific knowledge is favoured compared to personal integrity. Leroy Hood from the Hugo project in Seattle explains: "*In Europe ethics can get in the way of doing science. Sometimes ethics can get in the way from science and it is sometimes a misguided ethics.*"

A key issue noted is how to balance data protection and genetic research. Jane Reichel, a professor in bioethical law from Uppsala University, confirmed that there is a higher restriction in Sweden and Europe as opposed to the United States when it comes to mapping human DNA. Commercial genetic tests are becoming very popular in Sweden, but can, as Jane Reichel's student Santa Slokenberg experienced, easily give false information. She notes that: *"[w]e do not know about the value about these tests, and they are often compared with genetic horoscopes".* Another aspect is that it is not clear what happens to our genetic information afterwards, since the tests are sent abroad. Protection of integrity is highly valued in Europe and Sweden. The issue here is on how can we best manage that the view on genetic information varies so much from country to country and whether it is possible to agree on global ethical legislation. Reichel thinks that would be impossible and states that it is important to have a debate about what collecting so much individual information implies. For instance, one could reflect about what would have happened if this kind of information were available under the Second World War. This would also highlight questions over possible rights to accept or refuse genetic information.

Overall there seems to be more questions than answers. The take home message seems to be that there is a clear need for a vibrant ethical debate, and that all groups involved should be included. In the future, if we have a certainty that our personal genetic data will not be misused in any ways, maybe our view of personal integrity will change.

4.2.11 UK

Findings:

With regards to the search for academic articles with ethical analyses focused on the UK context, most documents that fit the selection criteria related to **biobanks and databases**. However, it cannot be concluded from this that this is the sole focus of the ethical debate on human genomics/genetics in the UK. Considering that biobanks and databases are national infrastructures, these naturally seem to be prevalent in the discussions our research found. The nature of the ethical analysis hardly fits within strict national boundaries. This was made clear by a search that did not reveal many analyses exclusively focussed on the UK context, in particular. This methodological difficulty was further exacerbated by the fact that the search conducted for the UK was carried out in English which is the dominant language for international academic writing. Documents discussing databases and biobanks primarily focused on questions of public engagement, tensions between right of the individual and public good, and governance.

The search on academic ethical analyses reveals that a number of documents focus on issues related to the **healthcare professionals' training** on genetics and genomics. This may be a particular concern in the UK. However, here again, this result has to be contextualised within the methodology used for

this research. Indeed, issues related to training of professionals clearly have a national scope; hence, it is not surprising that such issues come up when exploring ethical debate on genetics/genomics in a particular national context.

Regarding the media analysis search, only a few of the documents that fitted the selection criteria were from the 2010s (four articles), the majority being from the **2000s** (twelve). This might reflect the fact that the way the UK media represent human genomics and genetics is no longer as much a concern as it was in the 2000s. Many identified articles were concerned with **quality of the reporting on human genetics**, and **overstatements** in relation to the potential benefits and risks of genomics/genetics research. As a number of the collected media analyses show, media in general tend to overstate the potential benefits or risks of the technology at stake.[129] Related to this point, the concern was identified regarding whether the media coverage of genomics and genetics actually contributes to growing **public understanding** on this topic or, on the contrary, contributes to the science fiction imagery and illusions that surround this technology.[130] Finally, a number of media analyses highlighted the **fictional and metaphorical way with which human genomics and genetics are represented** in the UK media.[131]

Methodology:
 A search on Google Scholar was first conducted to skim through the first hundred results obtained and to identify potentially relevant articles. However, considering that the search required accessing the full-text of the articles to determine whether the article was specifically focused on the UK context or not, two academic library catalogues were used, providing full access to them: the

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[129] Almomani, Basima, Ahmed F. Hawwa, Nicola A Goodfellow, Jefferey S Millership, and James C. McElnay, "Pharmacogenetics and the print media: what is the public told?", *BMC Med Genet.*, Vol. 16, Issue 32, 2015; Bubela, Tania M. and Timothy A. Caulfield, "Do the print media "hype" genetic research? A comparison of newspaper stories and peer-reviewed research papers", *Canadian Medical Association Journal*, Vol. 170, Issue 9, 2004, pp. 1399-1407; Jensen, Eric, "The Dao of human cloning: utopian/dystopian hype in the British press and popular films", *Public Understanding of Science*, Vol. 12, Issue 2, 2008, pp. 123-143; Smart, Andrew, "Reporting the dawn of the post-genomic era: who wants to live forever?", *Sociology of Health and Illness*, Vol. 25, Issue 1, 2003, pp. 24-49.

[130] Brigite Nerlich, and David D Clarke, "Anatomy of a media event: How arguments clashed in the 2001 human cloning debate", *New Genetics and Society*, Vol. 22, Issue 1, 2003, pp. 43-59; Eric Jensen, "Celebrity life politics in US and UK journalistic coverage of therapeutic cloning research", *New Genetics and Society*, Vol. 29, Issue 2, 2010, pp. 119-132; Sandra P. González Santos, Neil Stephens, and Rebecca Dimond, (2018). "Narrating the First 'Three-Parent Baby': The Initial Press Reactions From the United Kingdom, the United States, and Mexico", *Science Communication*, Vol. 40, Issue 4, 2018, pp. 419–441.

[131] Petersen, Alan, Alison Anderson, and Stuart Allan, "Science fiction/science fact: medical genetics in news stories", *New Genetics and Society*, Vol. 24, Issue 3, 2005, pp. 337-353; Hellsten, Lina, "From sequencing to annotating: extending the metaphor of the book of life from genetics to genomics", *New Genetics and Society*, Vol. 24, Issue 3, 2005, pp. 283-297.

Sciences Po catalogue and the Fondation Maison des Sciences de l'Homme (FMSH) catalogue.[132] Various search terms were used for each search conducted and looked each time at the first hundred results. For the search for academic articles on the ethics debate in the UK, the search terms used were a combination of: ethic(s) + genomic/genetic/gene + UK/British. For the media analysis, the search terms were: media + genetic/genomic/gene + UK/British. After these searches, the list of references of the most relevant and recent documents was reviewed to identify any documents that might have been missed through the catalogues search.

4.3 Preliminary analysis, discussion, limitations and relevance to other SIENNA tasks

This exploratory study on discussions and debates on ELSI of human genetics and genomics in partner countries reveals a variety of ELSI perspectives which are discussed in the partners' countries, some of which are common to a few countries, others seem specific to a given country (see section below).

Different numbers of articles were found in the searches. Spanish and Dutch partners, for example, reported that there was not much academic literature on ELSI of genomics. In Greece, media coverage on ELSI of genomics seems to be rather extensive. In South Africa, meanwhile, only few newspapers relating specifically to the country context were found. There were also differences as to whether most articles addressed clinical context (Poland) or whether they were focused on research (South Africa).

4.3.1 Common themes and country-specific issues

The partners were asked to summarise *the main* ELSI issues that appeared in the searches as specific to their countries; the summaries from each partner are presented above. Below we recapitulate the content of these summaries focusing on the themes that 1) appeared to be common to a few partners and 2) topics or aspects that were highlighted by the partners as specific to their countries. We stress that this is a preliminary and non-systematic analysis (please see the section 4.3.3 for details of limitations of this study).

Based on the partners' summaries, we may observe that there are topics which have been present in the discourse (academic and/or in media) in many of the countries studied. These include:

- biobanks (Germany, Poland, the Netherlands, Spain, South Africa, the UK)

- gene editing (China, Germany, Spain, Sweden, Greece)

- informed consent (the Netherlands, Spain, South Africa, Sweden)

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[132] These library catalogues are based in France but provide access to most journals on Social Sciences and Humanities internationally.

- genetic, genomic testing (Brazil, Germany, Greece, the Netherlands)

The perspective on these issues, however, may vary from country to country.

Furthermore, the partners identified issues which seemed specific to their countries. Our Chinese partner reported that there is discussion on gene editing in the specific Chinese context, which focuses, among others things, on the need for an adequate framework within which this technology could be used.

In France, the debate revolved around the legislation and its adequacy. Furthermore, our French partner indicated the initiatives to facilitate dialogue between scientists and society.

Meanwhile, in Germany, the country-specific discussions were related to, among others things, preimplantation diagnosis, which was triggered by the changes in legislation on this issue. Furthermore, the word discrimination appeared often in the relevant literature.

Our Greek partner found articles, which indicated problems related to direct-to-consumer genetic testing and lack of adequate regulation in this matter in Greece.

Our Polish partner indicated that discussions related to prenatal diagnosis and status of embryo were seemingly specific to Poland. Furthermore, the Polish partner pointed out that only a few studies with original empirical data were found; the majority of publications were conceptual or policy oriented.

The Spanish partner emphasised the presence of a conservative perspective on gene editing, which underlines potential problems related to this technology.

In South Africa, the themes of trust, community engagement, and possibility of exploitation were found in the academic literature.

ELSI issues seemingly specific to Sweden include governance of science, the right to know/not to know about genetic findings, and data security.

In the UK, questions related to healthcare professionals' training in genomics were addressed by academic literature. The UK partner found also articles discussing problems related to media reporting on ELSI issues in genetics and genomics, including overstating benefits, questions relating to the influence of media on public understanding of a given topic and metaphors which are used in media.

The results of the country studies are relevant to the next tasks of SIENNA project, in particular to the task 2.7, in which ethical framework for genomics will be elaborated. The preliminary analysis of country studies indicates topics which are relevant in many countries; these issues may be particularly important to focus on in 2.7 task. At the same time, it is clear that each country has its particular perspective/main issue; such information may be potentially useful to consider whether or to what extent our framework can be relevant for all countries.

4.3.2 Do guidelines found in 2.3 task address the main ELSI issues identified in 2.4 "country studies" task?

As outlined in the method section, after the first drafts of the country reports were provided and reviewed, additional instruction to fill in a summary table was sent to each partner; the summary tables provide additional context to the summaries presented above by linking the results of this study to the findings of task 2.3 and underlining things that may need attention when developing the ethical framework (task 2.7).

We received summary tables from eight countries, which we merged below into one table (Table 6). Each partner reported different ELSI issues, which appeared *most frequently* in their search results; this suggests that the debate in their countries, academic and/or in media is concentrated on those different issues. Consequently, each country may have different needs when it comes to the aspects that should be addressed in an ethical framework. Importantly, most of the issues indicated by the partners as prominent are addressed in the guidelines (either professional ethics codes or documents from national advisory/ethics groups) that were found in the 2.3 task. However, the issues of **geneticization** in Poland; **quality of media reporting** of human genetics issues in the UK; **social justice/equity**, **consent**, and **community engagement** in South Africa were reported by the partners as not addressed (comprehensively) by the guidelines found in the task 2.3. Additionally, some partners reported issues that they considered as underrepresented in the results of their searches, yet, according to the partners they were important in their countries. These include: **rare genetic diseases** in Brazil, and **data sharing** and **gene editing** in South Africa. These topics may need attention when developing ethical framework for human genomics.

4.3.3 Methodological limitations

To conclude, we would like to emphasise that this study was exploratory in nature and indicates topics which could be explored further. We allowed for flexibility of the terms used in the search, that is, if a given search terms did not return relevant results, the partners were allowed to modify the terms based on their knowledge of specific context of a given country. Furthermore, the partners were allowed to conduct the search in English, in the country's native language or both. These factors should be considered when discussing the results; this study indicates trends rather than providing methodologically sound comparison. Furthermore, partners were asked to outline issues which seemed specific to their country; we should be aware that answers to these requests are based on authors experience/interpretations and should not be taken as objective.

Moreover, it should be noted that search engines use algorithms that are not "neutral" and Google Scholar reflects some academic norms, situated in specific sociohistorical contexts. To identify and

consider biases[133] related to the choice of the search engine in the interpretation of the results, additional time would have to be allocated to this study. Additionally, country partners who led country studies were not necessarily trained in the type of analysis that was requested in this study. The analysis thus did not take into account various aspects of the texts analysed, especially media coverage: their audience, credibility of the source, the context of the message, to be "*able to capture the context within which a media text becomes meaningful*"[134].

The partners reported methodological difficulties, for example the search performed by the UK partner resulted in many articles, which did not address given issue specifically to the UK context. Similarly, the German partner indicated that it was difficult to distinguish whether given ELSI considerations are country specific or not, given that German debate focuses also on international issues.

This preliminary analysis reveals the complexity of ELSI topics relating to specific context of each country. Each of these issues in a given country could be studied separately. This underlines the challenge of SIENNA approach in addressing the ELSI of human genomics – due to time constraints, we were not able to address all the issues in all specific contexts herein. Notwithstanding, these country studies provide indications about what can be addressed in the further work on task 2.7, that is what are the needs/peculiarities which may be considered in development of the ethical framework.

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[133] Noble, *Algorithms of Oppression: How Search Engines Reinforce Racism*.
[134] Newbold, Boyd-Barrett, and Van den Bulck, *The Media Book*.

Country	Please outline 3 ELSI issues that appeared most often in all your searches Please answer in the summary why you think they occurred most often	Are these issues addressed in the guidelines that you found in the task 2.3 (either professional ethics codes or guidelines on documents from national advisory/ethics groups)? Please say yes/no by the number referring to the issues found. In brackets please note if the documents from 2.3 addressed a given issue as their main topic (write: specific docs) or whether these issues are mentioned in guidelines who have other topic as main (non-specific docs)	In which search strategy did you obtain most of the findings? In which strategy did you obtain smallest number of findings?	Are there any genomics ELSI issues that according to you are not represented or are underrepresented in your findings but are important currently in your country? Please list them Please write in the summary why you think it is the case.
Brazil	1. Genomics in general 2. Genetic Testing and Genetic Screening 3. Gene Editing	We do have relevant findings to report as far as this topic is concerned.	Most findings: Search strategy in Google using the *keywords Brasil + Ética + genética*	Some of rare genetic diseases that are reported to be prevalent in some regions of Brazil. This occurs, mainly, due to interbreeding within small, poorer communities. Because these diseases occur in small communities media coverage is scarce, leading to a smaller number of findings in our search. Otherwise

			findings. Few findings: Search strategy in Google using the keywords *Brasil + banco + genético* (Translated: Brazil + genetic + biobank) resulted in the smallest number of findings.	
China	1. genetic editing of human embryos 2. human germline gene editing (research and clinical) 3. Genetic editing	An explanation is needed here. In fact, as far as China's specific situation is concerned, the documents of gene-related laws and guidelines issued by the Chinese government are comprehensive. Each document refers to many related issues of gene ELSI at the same time, and has inherent coherence and complementarity in the	Most findings: (ethic or law or legal) + country + (genomic or genetic) Few findings: (ethic or law or legal) + country +(genetic testing, genetic screening, prenatal screening, newborn screening, etc.)	No.

		expression of the context.		
Germany	1. genetic discrimination 2. long-term risks 3. Justice/Fairness	1. yes 2. yes 3. yes	Most findings: Few findings:	1. 2. 3.
Poland	1. status of the embryo 2. data protection 3. geneticization (genetic essentialism)	1. yes, non-specific docs 2. yes, non-specific docs 3. no	Most findings: Few findings:	n/a
South Africa	1. Social justice and equity. Considering SA's history and its status as the most unequal country in the world, it is hardly surprising that this issue is top on the ethics agenda. 2. Consent: there is an ongoing discussion between people favouring a broad consent model, and others objecting that this would be exploitative for African populations. The Protection of Personal Information Act 2013,	Not really – mostly because I found very few guidelines supporting genomics research and clinical practice. The guidelines I did find seemed to be either very short or not specific to genomics. E.g. the National Health Research Ethics Guidelines do speak about the permissibility of broad consent, but that discussion is generic to all medical research and not just genomics. Similarly, the Code of Conduct for Genetic Counsellors is	Most findings: Search for academic papers and newspaper articles Few findings: Search for guidelines and regulations	1. One of the issues that is starting to receive a lot more attention relates to data sharing. This issue wasn't really identified in the 2.3 and 2.4 analysis but the science community in the country has just realized that a new law may really change the playing field for research that involves the sharing of data. We have just published a paper in the South African Medical Journal on this (http://www.samj.org.za/index.php/samj/article/view/12657) and there have been several workshops and events discussing this. 2. There is also increasing interest in issues around gene editing and gene therapy research and this didn't come up very strongly in our analysis. I haven't seen many papers come out on gene editing yet, but I know that there will be a gene editing & ethics national conference happening later in the year.

	which is likely to become effective in 2020, has inflamed this debate because it favours specific consent. There is no real resolution to this debate and it is ongoing. 3. Community engagement: there is quite a lot of focus on how to ensure that communities are involved in decisions about genomics, how the technologies are best explained to people with low research and health literacy etc.	very generic about the practice of Genetic Counsellors. It makes a generic recommendation that "*Genetic Counsellors should uphold informed consent*" but it doesn't really inform on the kinds of consent that could be sought. Similarly, the Human Genetics Policy for the country is broadly premised on ideas of social justice – in that everyone should have equal access to healthcare – but it is not specific to this.		
Spain	1. BIOBANKS 2. HUMAN GENETIC PUBLIC PERCEPTION 3. EMBRYO MORAL/LEGAL STATUS	1. Yes STEMBIO (specific) INFCON (specific) 2. Yes PUOP (specific) RESOCON (specific)	Most findings: Database of Spanish academic articles *DIALNET*: "ética genética humana"	I consider little depth in the treatment of ethical issues from a normative point of view. I find that argumentative weakness occurs in a double sense. On the one hand, that the articles offer overly general ethical recommendations. In addition, the approach is too conservative, which implies ignoring the true ethical dimension of the current challenges in genetics / genomics. On the other hand, that the scientific issues involved

		HEALPRO (specific) 3. Yes BIODIAG (specific) EMBRY (specific)	Few findings: Google scholar: "ética España genómica humana"	are treated superficially. The lack of precision in this regard is detrimental in order to be able to implement the ethical guidelines in practice.
Sweden	1. -Human dignity/Human integrity 2. -Ethical Consent (inclusion criteria; research clinic) 3. -governance of science	1. yes (non-specific documents e.g. on CRISPR-Cas9) 2. yes (non-specific documents) 3. yes (both specific and non specific documentss)	Most findings: Few findings:	1. 2. 3.
UK	1.Tension between autonomy of the individual and responsibility for others/public good 2. Public engagement and awareness 3. Quality of media reporting of human genetic issues	1.Yes (non-specific docs) 2.Yes (non-specific docs) 3. No (because the documents covered in task 2.3 did not deal with the media specifically)	The ethical and media analyses gave approximately the same number of results.	It is difficult to answer this question conclusively and solely based on the limited search permitted by this study.

Table 6: Summary table for country studies.

5. Empirical investigations in SIENNA: Public views of Human Genetics and Genomics

5.1 Evolution of public engagement in ethical analysis of genetics and genomics

From a historical perspective, the public has been assigned a passive role in the governance of science and technologies[135]. In the "classical" public understanding of science (PUS) approach developed in the mid 1980's, the public was conceptualized as having knowledge deficits on technoscientific issues, which would prevent them from seeing the benefits of medical progress and other innovations foresighted by experts[136]. Expertise in this model was on the side of science and the public was in need of "education".

Over recent years, this approach has lost its dominance in conceptualizing and performing science–society activities. The rhetoric of "deficit" and "education" has been replaced by discourses of "public engagement with science", "public participation" and dialogue[137]. The public is conceptualized as carrying its own legitimate values and opinions towards science and, in some areas such as patient movements in biomedicine, even being able to contribute its own "lay expertise"[138] (Epstein, 1996). In this "culture of public consultation", "citizens", "laypeople" or the "public(s)" are actors to be more actively involved in the policy process, even though it largely remains unclear who concretely is to speak in the name of the society.

However, recent contributions have criticized many of these experiments for being situated too far "downstream" in the innovation process[139]. This implies that by focusing on assessing the risks linked to imminent application or implementation, public engagement is involved at a point at which many institutional commitments concerning a technoscientific development are already decided. Thus, instead of opening up fundamental questions such as "Do we need such an innovation?" or "What kind of society is implied in the visions supported by this innovation?", the issue may be narrowed down to questions of risks and benefits and may serve merely as a superficial "check" to show that there were some form of interaction with lay publics.

It is not only on the policy level that the relation between scientific or ethical expertise and public engagement, or more precisely representation of the public produced by social science expertise, is debated. The significance of empirical social sciences for ethical reasoning has been vividly discussed

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[135] Bauer, "The Evolution of Public Understanding of Science - Discourse and Comparative Evidence".

[136] Bodmer, *The Public Understanding of Science*.

[137] Woolley et al., "Citizen Science or Scientific Citizenship? Disentangling the Uses of Public Engagement Rhetoric in National Research Initiatives"; Irwin, "The Politics of Talk: Coming to Terms with the 'New' Scientific Governance"; Irwin, "Constructing the Scientific Citizen : Science and Democracy in the Biosciences".

[138] Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge*.

[139] Wilsdon and Willis, *See-through Science: Why Public Engagement Needs to Move Upstream*; Wilsdon, Wynne, and Stilgoe, *The Public Value of Science. Or How to Ensure That Science Really Matters.*

in bioethics journals under the label of "empirical ethics" over recent years[140]. For those arguing for a stronger inclusion of empirical approaches in bioethics, the principalist approach of expert ethics is the main point of critique[141]. According to these authors, this approach would not be able to embrace the complexity of the issues at stake in shaping socio-technical futures. In particular, applied ethics approaches in policy advice would tend to rely on narrow definitions of the issues at stake. As Burgess states: *"[t]he institutionalization of ethics as a source of policy analysis encourages narrow definitions of issues and terms of reference in response to short time frames"*[142]. According to the same author, integrating ethical reflection and public consultation would benefit both sides of the ethics-social science divide since social scientific research would contribute to a more fine-grained understanding of the societal complexities at stake, while ethical analysis would play a key role in analyzing the values involved in different scenarios and political decision-making options. It should be noted however, that Burgess' version of public consultation is a form of deliberative process that is rarely performed in bioethics; one that happens over many days (and not just hours) and that is often centred around a specific policy question.

There are however arguments against empirical bioethics and, more precisely, public engagement in bioethics. One of the most common arguments is that while ethics is concerned with values and what society "ought" to do, the social sciences do research on the "is," or on the "facts" of social reality and it would be a logical fallacy to deduct a moral imperative from a social fact[143]. Another common argument against public involvement in this context is that the "moral" convictions of laypeople do not necessarily have any significance to (experts') ethical reflection. In this line of argumentation, validity and quality of an ethical argument do not stem from its support by public opinion but from the sophistication and coherence of the argument itself[144]. Similar to classical PUS approaches, expert rationality associated with ethics is here assumed to be a priori more "rational" than "moral sentiments" of laypeople. A third argument, based on a Foucauldian perspective, recognizes that the reflexive representation of society in the production of (ethical) knowledge is in itself an epistemological claim but also plays a role in producing social order [145]. Empirical methods as well as public engagement designs would thus not only represent but also perform social realities and ethical norms [146]. This last argument stresses the importance of the design of the study.

Although these critiques need to be taken into account, they do not provide substantial reason why

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[140] Haimes, "What Can the Social Sciences Contribute to the Study of Ethics? Theoretical, Empirical and Substantive Considerations."

[141] Hedgecoe, "Critical Bioethics: Beyond the Social Science Critique of Applied Ethics."; Lopez, "How Sociology Can Save Bioethics... Maybe".

[142] Burgess, "Public Consultation in Ethics an Experiment in Representative Ethics", p. 10.

[143] Levitt, "Public Consultation in Bioethics. What's the Point of Asking the Public When They Have Neither Scientific nor Ethical Expertise?"

[144] Crosthwaite, "Moral Expertise: A Problem in the Professional Ethics of Professional Ethicists".

[145] Ashcroft, "Constructing Empirical Bioethics: Foucauldian Reflections on the Empirical Turn in Bioethics Research".

[146] Law, *After Method: Mess in Social Science Research*; Rose, *Powers of Freedom: Reframing Political Thought*.

"social" and "political" questions should be subject to public engagement and "ethical" restricted to expert committees. Furthermore, PUS research has shown that public views may bring rich insights into understanding of science due to their differentiated positioning towards technoscience[147] and the questions associated with it on the basis of their experiences and situated perspectives. Similarly integrating public views in the ethical inquiry may broaden the scope of questions considered and enrich the analysis[148].

Various methods have been used to involve publics with ethical analysis and policymaking regarding human genetics and genomics:

- polls conducted in United States[149], Europe[150] and elsewhere[151]
- focus-groups with lay-people[152], patients[153] and research participants[154]
- citizen panels[155]

5.2 Including public views in the SIENNA project ethical analysis: goals and limitations of the empirical work

The SWAFs[156] call requested input from civil society on all three areas of technology. In the SIENNA handbook, the "public" is conceived as one of the stakeholders of technology development whose contributions are required for the "legitimacy of ethical analysis". While the issue of legitimacy is certainly debatable (and is debated within the SIENNA partners), the SIENNA project used two approaches, one quantitative and one qualitative, to include public views in the overall project. We outline the approaches below and direct the reader to the full reports 2.5 and 2.6 for additional

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[147] Law and Mol, "Situating Technoscience: An Inquiry into Spatialities".

[148] Soulier, Leonard, and Cambon-Thomsen, "From the Arcane to the Mundane".

[149] Almeling and Gadarian, "Public Opinion on Policy Issues in Genetics and Genomics".

[150] Gaskell et al., "Public Views on Gene Editing and Its Uses"; Gaskell et al., "The 2010 Eurobarometer on the Life Sciences".

[151] Etchegary et al., "Public Attitudes about Genetic Testing in the Newborn Period"; Etchegary et al., "Interest in Newborn Genetic Testing: A Survey of Prospective Parents and the General Public"; Ishiyama et al., "Relationship between Public Attitudes toward Genomic Studies Related to Medicine and Their Level of Genomic Literacy in Japan".

[152] Kerr, Cunningham-Burley, and Amos, "Drawing the Line: An Analysis of Lay People's Discussions about the New Genetics".

[153] Stuckey et al., "Enhancing Genomic Laboratory Reports from the Patients' View: A Qualitative Analysis"; Townsend et al., "'I Want to Know What's in Pandora's Box': Comparing Stakeholder Perspectives on Incidental Findings in Clinical Whole Genomic Sequencing"; Schneider et al., "'Is It Worth Knowing?' Focus Group Participants' Perceived Utility of Genomic Preconception Carrier Screening".

[154] McGuire et al., "DNA Data Sharing: Research Participants' Perspectives"; Biesecker et al., "How Do Research Participants Perceive 'Uncertainty' in Genome Sequencing?"

[155] Bombard et al., "Citizens' Perspectives on Personalized Medicine: A Qualitative Public Deliberation Study".

[156] Science with and for Society, https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/swafs-18-2016

details. In this section, we provide an overview of the approaches and the main aim is to state the pros and cons of the approaches, especially as they will be used in the ethical analysis.

1. **Quantitative Survey:** an exploratory phone-survey of publics' views and opinions was conducted in 11 countries, including seven EU countries and four countries outside Europe.

    a. The 11 countries were surveys were conducted are: France, Germany, Greece, the Netherlands, Poland, Spain, Sweden, Brazil, South Africa, South Korea and the USA.

    b. The phone survey lasted approximately 15 minutes and in that time questions were posed on artificial intelligence/robotics, human enhancement and human genetics/genomics as well as demographic questions. Hence each technology area had a bit less than 5 minutes for questions.

    c. The section on human genetics and genomics included in 10 closed ended multiple-choice questions, which were posed and answered in approximately 5 minutes. It covered specific situations relating to the following: self-reported awareness of genetics or DNA; basic knowledge questions about genetics; perceptions about analysing all genes/DNA at birth; perceptions about the consequences of increased prenatal testing on persons with disabilities and on prospective parents; self-reported awareness of gene editing; perception regarding research with embryos; responsibility to make decisions about genetics; if publics think that lay audiences should know more about genetics; and what publics believe experts understand about gene editing.

    d. Kantar Public, a for-profit market intelligence company, as a hired subcontractor of SIENNA, was given the task to prepare, conduct and report on the surveys. A detailed description of this work can be found in deliverable 2.5.

2. **Qualitative focus groups:** Full day focus groups were held in 5 countries: France, Germany, Poland, Greece, and Spain to discuss with members of the lay publics regarding the three areas of technology (Artificial intelligence/robotics, human enhancement and human genetics/genomics) and ethical and social issues.

    a. Each focus-group consisted of 50-53 participants (total n= 253) and each was made up, on average, of 40 general public participants and a minimum of 10 participants from pre-specified vulnerable groups.

    b. Each day included three 2-hour sessions for each of the three technology areas, human genomics, human enhancement and artificial intelligence. Each 2-hour session included information sessions on the subjects and then discussion amongst the citizens.

    c. The specific objectives for the genomics sessions were to explore citizen awareness, understanding, views and concerns about genomic sequencing and modification, specifically: prenatal genome screening, storage and use of whole genome sequence, somatic genome editing, and germline genome editing.

d. Kantar Public, a for-profit market intelligence company, as a hired subcontractor of SIENNA was given the task to prepare, conduct and report on the focus-groups. A detailed description of this work can be found in deliverable 2.6

Conceptualization of the "public" and recruitment of the participants:
- In SIENNA, the "public" is conceived as one of the stakeholders of technology development whose contributions are required for the "legitimacy of ethical analysis"[157].
- In both investigations, members of the public have been recruited from a cross-section of demographics (age, gender, ethnicity, family status, working status, educational attainment and/or income), including, among others, vulnerable people with mental or physical disabilities. In focus-groups, participants with these vulnerabilities were integrated alongside non-vulnerable participants, with adjustments made to enable their participation (such as, wheelchair access, interpreter, provision for carer etc.)

Challenges faced by both empirical approaches within the SIENNA project
- ensuring that the research objectives are met within the various constraints of a large project (especially within the context of a SWAFs call, which was seemingly created by non-experts in the three areas of technology; and specifically within SIENNA, which was originally conceived and continues to be coordinated and controlled by an academic coordinator without experience in empirical research)
- prioritizing some areas of inquiry since all of the areas of interest in relation to genomics could be covered within the budget allotted (approximately 1 million Euro to Kantar Public) to these tasks.
- keeping the length of questions and discussion on human genetics and genomics very brief (less than 5 minutes in the survey; and less than two hours in the focus-group) yet trying to gather meaningful data that will be informative to the bioethics context and potentially also indirectly to policy-making
- developing content on complex topics in a way that is understandable to lay publics
- adapting to varying perspectives in different countries (e.g., various cultural contexts)
- having the empirical work conceived, and carried out by a for-profit market intelligence company who have no expertise in human genetics/genomics or in ethical, legal and social issues of human human genetics/genomics.
  - The constant two-way discussions for the surveys and the focus-groups were incredibly time-consuming and this had not been taken into account in the planning of the tasks
  - There was a lot of time needed to fully resolve misunderstanding concerning the need for detailed accounting of the methodology and the quality criteria needed for the work (i.e the details needed in the methodology, the need to be transparent about limitations etc). Indeed, and not surprisingly, academic researchers have

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[157] SIENNA Handbook, p. 29.

different quality criteria than market research companies.

- o The company was not able (within the allotted budget of approx. 1 million euro) to conduct a thorough review of the literature before the surveys or the focus-groups. This was left to the expertise of the SIENNA work package leaders; while UU has expertise both in genetics/genomics and the ELSI of genetics/genomics, there was no time allotted to UU for this time-consuming task and Kantar Public either did not have the time or expertise to conduct such a search and synthesis. Hence both reports as written by Kantar Public are lacking the contextualization of the results within current literature; this is an important limitation.

Limitations of the timing of the empirical work:

Both the survey and the focus-groups were prepared and took place between August 2018 and May 2019. Furthermore, the surveys and the focus-groups were run almost in parallel, which prevented the results of one to feed into the preparation of the next. For projects with a mixed-method approach (i.e. a mixture of quantitative and qualitative methods), a larger window would be required between the stages to allow the findings from one method to feed-into the design of the other method. This allows for more relevant and in-depth research into specific themes. This was not possible however, within the overall SIENNA timetable as priority was given by the coordinator to ensuring that all tasks from X.1-X.6 be completed before the end of year two. Quantitative and qualitative investigations were therefore conducted separately.

5.2.1 Pros and Cons of the public survey in SIENNA

In addition to the challenges mentioned above for both approaches, the survey in particular had the following pros and cons. Two sessions of a SIENNA workshop (june 2019, Goteborg) addressed the empirical approaches in SIENNA. Participants expert in ELSI of genetics and genomics, including empirical research were asked to comment on the approaches. The remarks taken directly from these workshops are followed by "WSP"[158]. This section, therefore, includes expert input beyond the SIENNA consortium.

i. PROS

- Telephone method used is supposedly more representative than an online method. The dual frame design proposed covers more than 90% of the population in all 11 countries. Bias in the sample is minimized by randomly selecting an adult at random to participate in fixed line households and making repeat calls to numbers to maximise the chance of an interview.

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[158] A workshop was held on June 14-15th 2019 in Goteborg (Sweden) where we assembled a total of 20 experts (15 external to SIENNA, and 5 from SIENNA) in the ELSI of genetics and genomics, as well as some experts in the science of genetics and genomics. During the workshop, two sessions were used to discuss the empirical work conducted by Kantar Public within the context of the SIENNA project.

- The telephone method used is supposedly more cost-effective than face-to-face interviewing to complete the survey. For a face-to-face approach the number of countries and/or respondents per country would have had to be reduced.
- The survey was conducted in 11 different countries.
- The sample size of 1000, while completely an arbitrary number and based on the total budget rather than a needed sample size to show any effect size (i.e. this is an exploratory survey and not one that tests a hypothesis) is useful in case we would like to study differences between subgroups (based on the demographic facts like age or gender)

ii.   CONS

- Inconsistency in style and skills of telephone interviewers in all 11 countries may lead to inconsistent findings, especially considering the importance of their role in keeping respondents engaged in the survey, given the complexity of some of the topics covered.
- We have no way of knowing what respondents really understood about the questions (WSP).
- Conducting an over the phone survey, meant that an interviewer had to read out all the questions and the proposed answers in a short time frame. This forced respondents to answer on the spot. An online survey would have had the benefit of letting respondents take their time.
- Interviewers did not read out all answers for all questions. The "I don't know" and "I prefer to not answer" were not read out which may have forced some respondents to choose blindly. This also reduces the information about respondent knowledge about certain questions
- While a lot of time was placed on wording the questions carefully, the lack of expertise in human genomics and ELSI of human genomics by the company doing the field work and running the survey meant that questions were still not as refined as they could have been. Bias (either positive or negative) still remain (WSP). (e.g. the survey company were reluctant to pose any questions that they deemed too "controversial")
- Posing questions about hypothetical situations to publics who already likely do not understand or know about this technology make the meaning of the answers questionable (WPS).
- Questions about impact on society may have been too vague or conceptually difficult. Perhaps questions about impact on individuals would have been preferable. (WSP)
- The SWAFs call included many topics for human genetics/genomics to cover (i.e. genetic testing, screening, patents, biobanks, pharmacogenomics) and while WP2 already refined these topics within high-throughput sequencing/genome sequencing and genome editing, we concede that 10 questions on these two large topics may have been too much, especially in the time allotted.

Workshop participants were also clear about the fact that we cannot base policy on publics' opinions.

5.2.2 Pros and Cons of the focus-groups with lay-people in SIENNA

i. PROS

- Informing ethical analysis: The themes emerging during the discussions, the style of reasoning of participants and the values associated with their arguments can inform ethical analysis on different levels.
- Exploration: Laypeople's perspectives can provide new perspectives on ethical issues that can then be elaborated further during ethical analysis
- Cost and time expense: the set-up of the focus-groups is less demanding (in terms of time and money) than citizen panels which usually require to be representative of the country's demographics and typically involve multiple activities.

ii. CONS:

- Qualitative research is not representative or generalisable
- Complexity of the topics and restricted time may lead to uninformed discussions
- Inconsistency in moderation styles and skills
- Absence of transcription
- Great Amounts of data to be analysed in different languages
- Complexity in defining the role of these results in ethical analysis and recommendations
- Unintentional short-cuts in interpretation of results, when not considering all limitations of the study.
- opaque reporting when it comes to methodology for the content analysis and the weaknesses of the work

In conclusion, while we acknowledge the potential utility of incorporating empirical studies in Bioethics, (including in the SIENNA project), and the importance of being aware and understanding publics' views regarding new technologies, we must caution readers regarding the complexity of doing so in a meaningful manner. While a lot of data may be generated through empirical approaches and this may be impressive, one must always contextualise and interpret data with the methodology used, and the existing academic literature. Moreover, it is not always the case that bioethics teams will have the necessary expertise to properly conduct empirical studies. The approach taken by SIENNA to hire a social and policy research company to perform all the fieldwork would seemingly address this issue, but it also has its challenges since the company will usually not have expertise in the content, only in the methodology. Hiring a commercial company to do the work did allow for a lot of work to be done consistently across many countries, and in a relatively short period of time. However, this approach was also relatively expensive (1 million euros, approx. 25% of the total budget for all SIENNA work over 42 months) and created some problematic situations around the transparency and quality of reporting (and in some cases analysis) as well as a conflict of interest when it came to having to decide how much of the weaknesses and problems with the approach to report in Deliverables 2.5 and 2.6

6. Foresight approach: Ethical issues raised by foresight human genomics

Under the umbrella of ELSI investigations, the ethics of human genomics has largely consisted in advance assessment of the "implications" of (certain) scientific, technological and especially medical developments before or in the process of being implemented. As noted earlier, these accounts rely on a simplified linear model of innovation pathways and outcomes and can encourage a narrowed scope of enquiry. These dynamics have been encapsulated under the notion of "compressed foresight" (p.51), which is based on the assumption that ethically informed and conducted research will have ethically desirable outcomes. According to this simplified view of the value-artefact or value-science relationship, social implications are built-into science or into technologies in their early development, conceived as some kind of reflection of design practices and values, then simply reproduced when those technologies are subsequently applied.

Anticipatory research, being foresight in general or ELSI as a form of "compressed foresight" (p.51), raises important theoretical and practical issues that are well addressed in the so-called Collingridge dilemma[159]. Although it is most effective to shape innovative technologies in a societally desirable direction at an early stage of development, it is difficult during this early stage to assess what the societal effects of the technology will be. In more advanced phases, societal effects will become clearer, but there is less room for change. In other words, although impacts cannot be easily predicted until the technology is extensively developed and widely used, steering becomes more difficult when the technology has already become entrenched.

Being aware of these pitfalls, experts' input about foresight human genomics in SIENNA has been collected through two different methods: a survey and a workshop. They were composed according to the research objectives and the experts targeted, and the methods of the workshop were designed to reflexively engage with the complexities raised by foresight.

- The objective of the survey was to collect up-to-date insights from scientists, clinicians and genetic counsellors on currently developed genomic technologies or emerging technological developments.
- The objective of the workshop was to reflect with ELSI researchers and members of patient organizations on the role of foresight in ethics and to broaden the scope of ethical enquiry.

6.1 Experts' survey on foresight of genomic technologies

6.1.1 Methods

In January 2019, a qualitative online survey has been distributed to experts in the fields of genetics and genomics via email and Twitter with the objective to collect up-to-date insights on genomic technologies which are currently being developed or are expected to be developed in the next five to ten years. The objective was to complete the state-of-the-art review presented in the deliverable 2.1,

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[159] Collingridge, *The Social Control of Technology*.

which was based on a review of the literature and interviews with experts and ensure that it is up-to-date.

Thirteen complete responses have been collected from various fields of expertise, including genomic research, genetic counselling and clinical genetics.

The survey included the following open questions:

> • What are the important upcoming technological developments?
> • Why?
> • At what stage of development the technology is?
> • Any other technologies?
> • In which field do you have expertise?
> • In which country?

6.1.2   Preliminary results

Results of the survey are summarized in Annex 4, p.197. Experts who replied to the survey mentioned several technologies that were already described (and for which ethical issues were addressed) in previous ethical report: D.2.1, Review of the state-of-art of human genomic technologies. However, some technological developments reported in the survey were not mentioned or not fully addressed in D.2.1 – namely:

- Development of Artificial Intelligence in genomic research and healthcare
- Development of nanotechnology in genomic research and healthcare
- Development of polygenic risk score for embryos

We therefore chose to focus on these specific developments in the ethical analysis of this report, since those were, among the results of the survey, the technology developments that had not been substantially addressed in the previous deliverable (See p.97).

6.2 Presentation of the workshop on foresight of genomic technologies

6.2.1   Methods and activities

The Human Genetics and Genomics Foresight Workshop took place the 18th of January 2019, in London. Consortium partners and 14 experts in genomics have attended it, among which: ELSI researchers, clinical geneticist, genetic counsellor, and representative of a patient organization. It covered three activities along the day: scenario development; science fiction reading; critical brainstorming on pros and cons of the foresight approach in bioethics.

These activities were designed to project participants in a future distant enough to enhance creative thinking and help broaden ethical discussion but not too distant, to become unproductive. Plenary sessions were also organized so as to reflect on foresight activities and discuss their role in ethical analysis. Feedback on the workshop was finally asked collectively at the end of the day and also individually. See Annex 1 for the detailed agenda of the workshop.

In order to build on the insights developed during the workshop, group discussions and plenary sessions have been audio-recorded; in each group, one expert was asked to take notes of the discussions and to give back the notes to the organizers; four consortium partners took notes of the day; other notes taken by the participants during the workshop (individual or group lists of ELSI) had also been collected in the end of the day.

The summary of activities included:

→ **Activity 1: Scenario Construction and ELSI identification**

Each group was assigned a different preliminary scenario about an application of genomic technology: Prenatal genome sequencing; DIY sequencing, Germ line editing.

Scenario 1: Genome sequencing

In the near to medium term future, technological advances have continuously changed genome sequencing from an expensive and burdensome undertaking to a rapid and less costly option for many purposes. The validity of genomic testing has been found to establish the molecular diagnosis for hundreds of genetic disorders, to assess pharmacogenomic variants, including identifying treatable targets of malignant tumours. With the aim that the availability of genomic information will provide clinical benefit to individuals and provide anticipatory insights for their future health care, whole genome screening of foetuses is proposed to all new pregnant women from week 10.

Scenario 2: DIY sequencing

In the near to medium term future, mini DNA sequencers are available at affordable prices – these are small devices which can sequence DNA, including entire exomes or genomes. They can be connected to a computer and a "user-friendly" software can analyse the sequence and give information about the type of organism sequenced. If the DNA is human, the software can give information about disease predisposition, physical traits e.g. eye colour, as well as ancestry. The software can also allow users to connect to different existing DNA databases, and potentially allow for the identification of the individual whose DNA was sequenced.

Scenario 3: Germ line gene editing

In the near to medium term future, technical aspects of germ line gene modification have been further studied and in some countries, the safety-benefit ratio has been deemed acceptable to allow for clinical trials to take place; some countries are already at the stage of rolling out germ line gene editing as a pilot treatment programme both from the "traditional" public health care system as well as from private providers. In such countries, parents with a chance of passing on a severe disorder to their child could be eligible for the treatment. The criteria for being offered such a treatment are still heterogeneous between countries and are still being worked out.

The scenarios were general and short. The experts were then invited to complete each scenario with specific details about the context of the use of the technology so as to highlight specific ELSI considerations arising and to advance ethical discussion around them.

Each group then presented their scenario(s), justifying their orientation and connected their scenarios elaborations with ethical issues.

→ **Activity 2: Science fiction commenting and ELSI identification**

This activity was based around the literary text called "*The Oracle*", by Matthew Warren. This short story is part of a collection of science fiction literary essays *Writing the future*, published by Kaleidoscope Health&Care and which is available online at:https://indd.adobe.com/view/e23bd9de-1d2f-4d27-9b0d-c2589724873d.

Each expert read the text and identified ELSI considerations. Experts then shared a specific ELSI issue in a tour de table. After this first round, participants further discussed the narrative from various perspectives, questioning the role of health professionals, medical ethics and parenting when Big Data and AI is more involved in our future healthcare.

Experts went back to their groups and connected this foresight narrative to specific ELSI, that they presented in plenary sessions.

→ **Activity 3: Discussion on foresight in Bioethics**
Experts paired-up to brainstorm on the following questions:
1. Do you think that today's activities are useful/not useful for ELSI analysis?
2. How is it similar and different from what you have done before?
3. Did you know anything about foresight methods before today?
4. Do you think that today's activities correspond to a foresight approach?

Experts were then invited to present the result of their discussions. Plenary sharing ended on the question whether foresight could be of use in bioethics and for what purpose, as compared to already established methods.

6.2.2 Preliminary results

In the overall methodology of SIENNA, foresight analysis occupies a significant place in the framework (cf. SIENNA Handbook). As previously mentioned, ELSI already includes "compressed foresight" views and faces theoretical and practical critiques for this specific reason (cf. p.51). Accordingly, one of our most pressing goals in this workshop was to explore how experts in ELSI perceived foresight analysis, what they would do with different forms of foresight exercises and if they (i) would estimate these explicitly foresight-oriented activities to bring an added value to their practice of ELSI, (ii.) would perceive it as redundant or (iii) would consider them as damaging to ethical analysis.

i. During activity 1, the three groups handled the exercise quite differently.

- Scenario 1: Prenatal genome
On the theme of prenatal genome sequencing, the group did not opt for specific country and time but created two scenarios: Dystopia and Utopia – and discussed them.

- In Dystopia, the test is not proposed to pregnant ladies but it is mandatory: there is no right to choose, no right not to know. It raises unsolvable ethical issues that are not debated societally. The system decides and it is coercive. The data gathered through the tests are used both for healthcare purposes but for other purposes (known and unknown). Regarding health, the test is used primarily for preventive measures (and in fine-tuned social control) but not for effective care and leads eventually to psychosocial harm, since it creates a lot data insufficient in terms of validity and interpretation. Regarding other uses, the test is used for social control, biological weapons and forensics – leading to generalized effects of stigmatisation. There is an unregulated commercial use of the information, particularly highlighted in its aggressive marketing.
- In Utopia: there is sufficient funding for screening, counselling and related healthcare. The law ensures freedom for participants by allowing ample room for personal choices and through ethical guidelines such as the right to be forgotten and to leave at any time. There would be continuing and engaging societal debate. Individuals would have access to their sensitive information in a secure way. Professionals would also be appropriately educated. Genomics would be conceived as one (among others) form of knowledge that affects your health and the risk of genetic determinism would be kept in check.

- There were several issues that could not fit within either one of these categories, such as points raised on the validity of genomic information; on legal issues such as what the data is to be used for (e.g. healthcare system or beyond), public-private healthcare relationships, and so on.

Experts who developed this scenario identified a series of shortcomings related to this "foresight activity":

- They feared that they focussed more on disadvantages than advantages and that they were ultimately not able to balance ethical reflections between Dystopia and Utopia alternatives;
- They discussed many aspects of prenatal testing that were already happening, covering issues that had already been anticipated and discussed since the 1980's, so that it didn't feel very futuristic in significant respects.
- The absence of context was also considered a shortfall in ethical analysis since the development of a technology is largely shaped by its environment and the idea of considering issues disconnected from the wider social reality and from a specific context impeded detailed ethical analysis.

- Scenario 2: DIY sequencing.

The scenario here takes place in ten years' time in the US. This location was selected because DIY sequencing was conceived here as a development of current consumer trends, which are particularly well implemented in the US where the principle of liberty is strongly valued both in conservative and libertarian thinking.

The idea of using DIY technology in one's household raises issues as to how people would manage that type of technology by themselves, how its use should be regulated, and more generally how to empower people while minimising (illegitimate) dual use or misuse. Another clear concern would be related with the technological divide between those who have access to these technologies and those who have not. Finally, one can ask how data would be shared with other parties, whether health data or other types of data.

The group thus tried to identify risks and benefits of having such a sequencer in every household.

- Benefit: Quick, cheap and personal access to genetic information; extension of individual freedoms; benefits for research with a massive generation of data that could possibly be easily accessed to. Such devices could also increase individual interest in genomics and healthcare.
- Risks: Misinterpretation of genetic information; problems in sharing genetic information and unintended data sharing (accessed by third parties, and hacking); potential for social and health inequalities, depending on who uses this information. The generalization of genomic data might also increase discriminatory actions and enhance the role of genomics in framing discussions about identity and reproduction. Financial issues are also relevant (financial gains in reselling the info) – risk of exploitation when someone is asked to share info for money. Finally, mini sequencers may be used to generate genomic data on people who did not consent, thus raising important questions in terms of autonomy and privacy.

Experts who developed this scenario created their own context for discussion, thus exploring rather ELSI in a rather explorative way.

- Scenario 3: Germ line gene editing.

Experts engaged in this discussion developed an approach in terms of safety/benefit ratio. They did not develop a single scenario per se but discussed the possibility of clinical trials for germ-line gene editing aimed at targeting therapeutics uses. If, in a given country such clinical trials were authorised, the national government could set up an expert committee that would supervise the evolution of the field so as to give the green light to use of the technology. However, the composition and functioning of this committee would have to be open to public scrutiny and oversight . The clinical trial would be through IVF and couples affected by a genetic disorder would be offered the trial. This possibility for clinical trials would raise many ethical issues concerning left over embryos carrying the mutation; what this would mean for people affected by the diseases that would be candidate for genome editing; who would be entitled to make a decision and take the risk; how to inform parents properly on a process that would be highly experimental.

Experts in this group were rather disappointed by the exercise because the particular group dynamics did not allow them for the construction of a scenario. The scenario was too basic and there were too many tensions among the members of the group about the basics of genome editing so they could not consider the implications of genome editing and were stuck at the very beginning of their foresight discussion.

According to the different groups, activity 1 became either a source of exploration or frustration. One important message conveyed by this activity is the importance of contextualizing foresight analysis. The group where experts advanced the discussion most successfully was the group who elaborated on the time frame, location, and political context of technology development. Although these were suggested as tasks to develop by the experts, the different groups did not follow them to the same extent and these efforts on contextualizing proved to be essential for accuracy and innovation of ethical analysis.

Another important aspect of this activity as with any collective endeavour is to ensure a proper group dynamic. Although it is difficult to know in advance how participants will behave in a group discussion, some measures could have been proposed in advance to ensure the best possible process: revising the rules for the discussion and having a moderator exterior to the discussion who can make sure that every member can contribute, who can re-launch the discussion when it is stuck and more generally make sure that there is an open, fair and free-flowing discussion.

ii.   During activity 2, each expert read the literary text entitled *The Oracle*, identified ELSI and shared these in a tour de table (presenting a specific ELSI). Experts then discussed the narrative from various perspectives: Artificial Intelligence, Health Care and Parenting. In the plenary on the short story discussion, reporters summarised the main topics that were discussed within the groups.

As expected from a literary text, each group had its own interpretation of the ethical issues addressed in it. Here are examples of the types of discussions proposed:

- Group 1, for instance, discussed what would be the job (if there were still any) for health professionals in a world where every decision is calculated by a machine.
- Group 2 discussed among other issues how this text did question the sheer definition of "health" in terms of quality or length of life.
- Group 3 questioned in particular the social norms embedded in AI that in the end would rule over all aspects of a person's life while leading to more social isolation, as is the case for the parents in the story.

During the general discussion, one important issue that was discussed was if technologies that automate healthcare delivery could be designed in a way that could liberate more time for professional-patients relationship rather than replace it. Experts thus questioned who would benefit from this kind of scenario where people would obey the machines – benefits here being, health, quality of life, financial cost etc.

This activity was more successful than the previous one in the sense that all experts appreciated the literary text and elaborated on it in a manner that connected the text with explorative ELSI. The explorative mission of foresight in this activity led to exchanges that have enriched our discussion of ethical issues at the interface of genomics and Artificial Intelligence in the final section of this report (p.117).

  iii.   During activity 3, we asked experts their feedback about their perception of foresight framework in ethical analysis.

About the proposed activities: they were perceived as "interesting" and "exciting" since they were open and rather complementary. The methods were however not new and rather close to the methods in the focus groups. Experts however feared that such activities would be complicated to "use" in terms of content, except for flagging up issues. Some perceived it as too short and would have wanted more sessions. The literary text was unanimously acclaimed but some experts proposed role-play so that every character could defend its own position in the story, thus developing thorough argumentation. However, this would require more time and commitment from participants. In order to avoid too general and abstract discussions, clinical cases of the future would have been appreciated instead of scenarios.

About foresight *per se*: experts emphasized the tension in foresight between the breadth of issues to be explored in an open imaginative way and the need for focus on specific methods and devices to lead ethical analysis – the question being: how precise can we be in the future?

7. Review of present and future ethical issues raised in human genomics subfields

7.1 Brief summary of the overall approach of ethical analysis in SIENNA:

As previously mentioned the SIENNA approach (p.17) comprises six steps. Steps 4 and 5 are the identification and analysis of issues respectively. The ethical analysis involves several perspectives:
-   The framework relies on foresight perspectives: it is directed toward developing technologies and prospective views regarding genomic development (p.91).
-   The analysis is to be informed by empirical work in which stakeholders are engaged: hence the methods are aimed at gathering experts' perspectives on the future of genomics (p.94), collecting laypeople's opinions on emerging and future developments of genomics (p.85) and exploring the different and/or similar media coverage of ethical issues surrounding genomic development (p.53).

More specifically, the ethical analysis (step 5) includes three sub-steps:
  i.   describing the social and ethical impacts of technological developments (D.2.1)

ii. identifying issues and values that may be affected or challenged by a given technology, partly based on its applications; identifying roles, rights and interests of stakeholders; identifying reasons or arguments for and against certain moral judgments, and identifying the pros and cons of particular ways of resolving conflicting values while remaining as neutral as possible (D.2.4).

iii. evaluating the conflicts of values identified, i.e. making and defending moral judgments regarding the goodness or rightness of particular actions, persons, things and events, and the rightness or wrongness of possible courses of action in relation to the ethical issues (to be further addressed in task 2.7).

Furthermore, the ethical analysis includes specific attention towards "vulnerable people" and involves an analysis of risks and benefits regarding disadvantaged groups, such as the elderly, disabled, etc.

The SIENNA framework for ethical analysis can thus be defined as:
- foresight-orientated,
- empirically-informed, requiring stakeholder engagement/input,
- multi-staged with a strong emphasis on the identification and evaluation of values,
- with an attention to vulnerable persons.

The notions of *value* and *vulnerability* are not strictly defined in SIENNA. Based on their use in SIENNA's handbook, they will be used in the following sense in this report:
- Value: any principle or quality that reflects a sense of right and wrong and what ought to be.
- Vulnerability: a state of lesser ability to withstand adverse impacts from technological developments to which they are exposed.

7.2 Summary of the approach for ethical analyses in this report

The work herein reports on the second sub-step (ii above) of the SIENNA ethical analysis (step 5) and aims at identifying issues and values that may be affected or challenged by genomic technology. It relies on the description of innovative technologies in genomics and identification of related social and ethical impacts provided in D2.1, which was based on a review of the literature and consultations with experts.

Following SIENNA's framework, the ethical analysis at this stage relies on an identification of ethical issues corresponding to genomic developments in different subfields (as identified *a priori,* or, in a deductive manner by the coordinating team of SIENNA):
1. Research
2. Clinical applications
3. Security and Democracy
4. Infrastructures
5. Companionship

In this section of the report, and according to areas of highest interest and impact identified in 2.1, we divide genomic technologies into two main fields: whole genome sequencing and gene editing.

We then proceed to identify ethical issues related to genomic development in the different subfields (a-d above) already outlined by SIENNA.

Since the completion of D.2.1 however, the contributions of experts based on a survey (cf. p.94) and on two workshops (cf. London workshop p.92 and Goteborg workshop p. 18) have allowed us to extend the scope of the genomic technologies (and related applications) likely to have a large impact on society and to raise significant ethical issues.

Accordingly, in this section, we identify ethical issues related to:
- Areas of technological development already mentioned in D.2.1
- Areas of technological development not mentioned nor substantially analysed in D.2.1 that have been brought to our attention by experts consulted in SIENNA since the completion of D.2.1. We chose to highlight these technological developments by providing a specific *focus* on these areas.

Finally, developments that took place in the field of genomics in 2018 have forced us to reflect on the rapidly evolving ethical discourse about gene editing. The birth of two infant girls with edited genomes has further highlighted the importance of anticipating a range of scenarios, some of which may have already happened (p. 144).

In the following report, ethical issues concerning the following vulnerable groups are in particular analysed where relevant: elderly people; children; women; people with disabilities; people with mental and physical illness; poor people and people in lower income countries; migrants and minorities.

7.3 Genome Sequencing

Next-generation sequencing (NGS) technologies, which have been developed in the last decade, make it possible to obtain a whole genome sequence (albeit without a complete interpretation) within a few weeks at a cost under 1,000 U.S. dollars, with plans, by some companies, to further reduce this amount to just 100 U.S. dollars[160]. NGS technologies are increasingly used in the clinic, in research setting sand in direct-to-consumer setting (i.e. where tests are advertised and/or sold directly to consumers, and not to healthcare professionals).

As explained in D.2.1 and recapitulated in the table below, three types of NGS can be distinguished according to the amount of the genome sequenced and the volume of data generated (- a large amount in the cases of whole genome and exome sequencing:

NGS type	Definition

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[160] "Illumina. Press Release."

Targeted sequencing	Sequencing of selected genes or fragments of the genome related to set of disorders, for example, cardiomyopathies, immune deficiencies, neurological disorders, among others[161].
Whole exome sequencing	Involves the sequencing of DNA that codes for proteins. This includes 1-2% of all the DNA in human organisms, and contains around 85% of known disease-causing variants[162]. While all genes may be sequenced, it is then usually that case, that only a targeted few are analysed (targeted analysis).
Whole genome sequencing	Obtaining sequence of nearly all DNA of a given organism. Whole genome sequencing has some advantages over whole exome sequencing, such as overall higher ability to detect more variants[163]. Again, targeted analysis is usually performed on the sequence data.

Table 7: Definitions of three types of NGS (based on D.2.1)

These various types of NGS can be used for a number of purposes and in various settings (table 8). In a clinical setting, however whole genome and exome sequencing are currently performed with a focus on diagnosis or guidance for therapy.

Test type	Purpose description	Current example(s)
Diagnostic testing	To precisely identify a disease and assist in clinical decision-making	Creatine kinase (CK) level testing for Duchenne muscular dystrophy
Predictive testing	To predict the likelihood of developing a disease	*HTT* gene test for Huntington disease; *BRCA* gene testing for breast cancer
Carrier testing	To understand the likelihood of passing a genetic disease to a child	*CFTR* gene testing for cystic fibrosis
Prenatal testing	To identify disease in a foetus	Expanded alpha-fetoprotein (AFP) for risk of neural tube defects, such as spina bifida and Down syndrome
Newborn screening	To determine if a newborn has a disease known to cause problems in health and development	All states must screen for at least 21 disorders by law, and some states test for 30 or more. Metabolic (e.g. classic galactosemia (GALT)), endocrine (e.g. congenital hypothyroidism) and other disorders tested
Pharmacogenomics (PGx) testing	To determine the optimal drug therapy and dose	The vitamin K epoxide reductase complex subunit 1 (*VKORC1*) test for likely response to

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[161] Yohe and Thyagarajan, "Review of Clinical Next-Generation Sequencing".
[162] Rehm et al., "ACMG Clinical Laboratory Standards for Next-Generation Sequencing."
[163] Levy and Myers, "Advancements in Next-Generation Sequencing".

	given a person's metabolic response	the anticoagulant warfarin. *TPMT* gene testing for likely response to thiopurine immunosuppressive therapies
Research testing	To contribute to our understanding of underlying cause of disease	Genome-wide association studies (GWAS) to determine the association of a variant with a trait

Table 8: Summary of types and goals of genetic testing. Published in Susan K. Delaney and others, 'Toward Clinical Genomics in Everyday Medicine: Perspectives and Recommendations', Expert Review of Molecular Diagnostics, 16/5 (2016), 521–32 licensed Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/). (This table has been shown in D.2.1)

7.3.1   Research

7.3.1.1 General definitions

Since it was shown in D.2.1 that characterizing the context of applications of NGS is necessary to determine their ethical impact, we summarise the key distinctions between the settings related to genomic research applications:

Setting	Definition
Genomic research	The process to derive meaningful generalizable knowledge from the wider focus on all the DNA in the cell (as opposed to the narrower focus previously taken by genetics looking at one gene at a time)
Clinical genetics	A medical specialisation that proposes genetic testing (diagnosis) and genetic counselling (support for diagnosis) to individuals and families with, or at risk of, genetic disorders.
Technology transfer or translational research or step	In context, it consists in the flow of know-how and technical knowledge that accompany the implementation of high throughput technologies of genome sequencing from research to clinic, i.e. from the organisational and institutional setting where these technologies were developed to generate genomic knowledge to another organisational and institutional setting where they will serve clinical applications.

Table 9: Definitions of settings for genomic research applications (Based on D.2.1)

The main differences between clinical genetic testing and research testing are the purpose of the test and who receives the results, the legal framework, and responsibility of stakeholders. Researchers intend to find unknown genes or more information on the workings of known genes, to learn how genes work and interact within the genome and with the environment, and to develop new tests; whereas clinicians intend to find out about an inherited disorder in order to make decisions about treatment and management (care and therapies) and/or reproductive issues. Research participants usually do not get individual results, while patients usually do. Physicians have a duty of care towards their patients, while (genomic) researchers generally do not have this duty in the same sense. One could argue, however, that both have a duty to rescue.

Concerning technology transfer, as was shown in D.2.1, "*the implementation of new genetic tests into the clinic ideally depends on the evaluation by different experts of each specific test's (including the specification of disease, variant, population and methodology) analytic validity, clinical validity, clinical utility, associated ethical, legal and social implications[164] as well as their cost-effectiveness[165] – all aspects then being compared with current tests (for the same specifications). In practice, for a number of practical, logistical, and financial reasons, this does not necessarily always happen, even for "simple" single gene tests.*" Since NGS is not meant to search for a single variant for a specific disease, its evaluation for single gene tests is greatly challenged[166], as well as its clinical utility [167] and associated ELSI[168].

7.3.1.2 Ethical issues with regard to general applications of genomic sequencing in research

i.   *Genetic patents*

Since the first proposals for patents on human gene sequences, there have been controversies about the definition of invention in relation with living entities[169]; patent litigation on gene patents for therapeutic protein (e.g. insulin, growth hormone, and erythropoietin[170]) and a discussion about the risk that gene patents may prevent certain research endeavours and even obstruct clinical access, thus leading to unjustified deaths[171]. While most of these issues are more legal than ethical (see deliverable D.2.2 for legal analysis of patents in genomics), one of the ethical issues at the heart of patents are a form of injustice between the vulnerable patients and the researchers and companies that then develop testing and/or treatments. The fact that patients would donate their time and samples to researchers to make discoveries (publish the results, advance their career, perhaps make money off of the research) and then have to pay exorbitant amounts to have access to the testing or treatments that would never exist without their generosity in the first place, is not only unjust, it is also usually disrespectful in that these terms are never transparently presented to the research subjects initially.

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[164] Sanderson et al., "How Can the Evaluation of Genetic Tests Be Enhanced? Lessons Learned from the ACCE Framework and Evaluating Genetic Tests in the United Kingdom".

[165] Payne et al., "Cost-Effectiveness Analyses of Genetic and Genomic Diagnostic Tests".

[166] Howard and Iwarsson, "Mapping Uncertainty in Genomics".

[167] Grosse and Khoury, "What Is the Clinical Utility of Genetic Testing?"; McPherson, "Genetic Diagnosis and Testing in Clinical Practice."; Hastings et al., "The Changing Landscape of Genetic Testing and Its Impact on Clinical and Laboratory Services and Research in Europe".

[168] Burke, Pinsky, and Press, "Categorizing Genetic Tests to Identify Their Ethical, Legal, and Social Implications".

[169] Eisenberg, "A Technology Policy Perspective on the NIH Gene Patenting Controversy"; Cassier, "Brevet et Ethique: Les Controverses Sur La Brevetabilité Des Gènes Humains".

[170] Cook-Deegan and Heaney, "Patents in Genomics and Human Genetics".

[171] Critchton, "Patenting Life".

ii. Potential harm for participants

As already mentioned in the section devoted to the history of human genetic research ethics (p.23), main ethical issues related to genomic research pertain to privacy[172], confidentiality[173], informed consent[174], possibility to withdraw from research[175] and issues regarding the return of research results[176] (including the right not to know). These "usual suspects" have however been subject to a renewed interest in genetic research since the increasing use of NGS for two main reasons:

- Managing uncertainty: uncertainty can be defined as "the personal perception of ignorance, in contrast to the state of being ignorant"[177] and it has to be addressed for both research participants and researchers. Although uncertainty can be considered inherent to the research process, "its scope in genomics may be unprecedented"[178] because of the amount of "incidental findings" generated along large volumes of data (-"*even when just examining the exome, which constitutes only about 1.2% of the genome, 20,000 variants in every tested person will be generated*"[179]) and because of "the changing categorisation of variants with upgrading from uncertain to pathogenic and downgrading to benign as more evidence is accumulated and incorporated in the interpretation"[180]. This uncertainty makes returning research results to participants especially difficult.

- Increasingly data-intensive (research) environments: again, because of the large volumes of data being generated, large genetic databases are being constructed as well as infrastructures developed to connect databases with larger research communities[181]. Not only do these entities expose participants to risks of a public data release [182], research participants could also be re-identified due to the triangulation of these databases that respect strict rules of anonymization with the proliferation of genetic data outside of research settings[183].

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[172] Lin, Owen, and Altman, "Genomic Research and Human Subject Privacy".

[173] Lowrance and Collins, "Ethics. Identifiability in Genomic Research."

[174] Master et al., "Biobanks, Consent and Claims of Consensus"; Gibson and Copenhaver, "Consent and Internet-Enabled Human Genomics"; Ducournau, "The Viewpoint of DNA Donors on the Consent Procedure".

[175] Karimi-Busheri, *Biobanking in the 21st Century*.

[176] Appelbaum et al., "Models of Consent to Return of Incidental Findings in Genomic Research."

[177] Han, Klein, and Arora, "Varieties of Uncertainty in Health Care: A Conceptual Taxonomy".

[178] Biesecker et al., "How Do Research Participants Perceive 'Uncertainty' in Genome Sequencing?"

[179] Stewart, "The Certainty of Uncertainty in Genomic Medicine: Managing the Challenge".

[180] Ibid.

[181] Jirotka, Lee, and Olson, "Supporting Scientific Collaboration: Methods, Tools and Concepts"; Larsson, "The Need for Research Infrastructures: A Narrative Review of Large-Scale Research Infrastructures in Biobanking".

[182] Bull, Roberts, and Parker, "Views of Ethical Best Practices in Sharing Individual-Level Data From Medical and Public Health Research: A Systematic Scoping Review".

[183] Homer et al., "Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays"; Gitschier, "Inferential Genotyping of Y Chromosomes in Latter-Day Saints Founders and Comparison to Utah Samples in the HapMap Project".

iii.   *Genetic discrimination*

Over the past two decades numerous studies in social science and ethics have predicted the emergence of a new "genetic underclass", ie. people who either because of their genetic results or because they cannot afford genetic testing involved in more and more social activities would be excluded from many aspects of social life – for instance: insurance,, investment, employment[184]. This threat of genetic discrimination has already generated policy responses. In D2.1, we showed that "*in Europe, in the US and in Australia, a plethora of laws, guidelines and policies had been adopted, both at the regional (Council of Europe, European Union) and national level*[185]". The most well known is the Genetic Information Nondiscrimination Act (GINA), which was published in 2008 and addresses health insurance and job discrimination [186].

iv.   *Health disparities*

Genomic research could play a role either to ameliorate solidarity among members of a community by helping to better situate research needs and allocate funds[187] but also exacerbate health disparities between ethnic groups by focusing research (funds) on biological causes of disease instead of more compelling social and environmental risk factors[188]. As was shown in D.2.1, "*another concern comes from the fact that allele frequencies in genes associated with various diseases are known to differ by racial and ethnic groups, when the populations enrolled in studies of disease risk often lack diversity on this dimension [189]. In these conditions, genomic research may lead to further health disparities.*"

7.3.1.3 Focus: Ethical issues with regard to nanotechnology in genomic and proteomic research

Nanotechnology was one of the technologies mentioned by experts, in our foresight survey (p.94), expected to have an important impact in the field of genomics. Since we did not describe this technology in D.2.1, we describe it herein. We then report on the main ethical issues raised by such

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[184] Lemmens, "Selective Justice, Genetic Discrimination, and Insurance: Should We Single out Genes in Our Laws"; Martin, Greenwood, and Nisker, "Public Perceptions of Ethical Issues Regarding Adult Predictive Genetic Testing".

[185] Otlowski, Taylor, and Bombard, "Genetic Discrimination: International Perspectives"; Joly, Braker, and Le Huynh, "Genetic Discrimination in Private Insurance: Global Perspectives".

[186] Feldman, "The Genetic Information Nondiscrimination Act (GINA): Public Policy and Medical Practice in the Age of Personalized Medicine".

[187] Knoppers and Chadwick, "Human Genetic Research: Emerging Trends in Ethics"; Prainsack, "The 'We' in the 'Me' Solidarity and Health Care in the Era of Personalized Medicine"; Prainsack and Buyx, "Solidarity in Contemporary Bioethics--towards a New Approach."

[188] Sankar et al., "Genetic Research and Health Disparities".

[189] Bustamante, Burchard, and De la Vega, "Genomics for the World".

developments.

Nanotechnology (NT) is an innovative and rapidly expanding field, "*focused on the creation of functional materials, devices, and systems through the control of matter on the nanometre scale, and the exploitation of novel phenomena and properties at that length scale*"[190]. It is expected to contribute to several fields, among which biomedical science because of the possibility it opens to manipulate entities at the molecular level. Recent breakthroughs in nanotechnology and nanofabrication techniques have been used to develop new techniques and innovative biomedical devices for genomics and proteomics, the large-scale study of proteins, with the following goals:

- to miniaturize biomedical devices
- to perform different processes with greater precision
- to automate processes

The ultimate goal is thus to replace conventional genome and proteome analysis devices which are expensive and labour intensive with fast and low-cost analysis techniques. Compared with conventional methods, NT procedures may have several advantages such as smaller dimensions, lower sample consumption, high-throughput ability, and ease of automation[191]. For instance, contrary to current microarray/biochip methods, which require samples to be labelled with a fluorescent tag — a procedure that is time-consuming and expensive, NT can provide label-free detection[192]. Acting at the nanoscale also allows a high separation performance and fast analysis of double- and single- stranded DNA, thus enhancing the capabilities of genomic, diagnostic, pharmacogenetic, and forensic tests[193].

NT has also been applied to proteomics, which contributes to several disciplines in biology "*including injury, cancer, aging, and different neurological conditions, as well as psychiatric conditions including drug/substance abuse, schizophrenia, and depression*"[194]. *Proteins are central components in biological processes with diverse functions "including cytoskeletal building blocks, enzymes catalysing biochemical reactions, antibodies contributing to immunity, or transcription factors affecting gene expression*"[195]. Proteomics provides an analysis of proteins in terms of abundance and dynamics in response to physiological and pathological changes, as well as environmental influences. The time, effort, and money required to identify a protein, sequence and characterize its structure impose important constraints on researchers[196]. NT has been used mainly to enhance biomarker discovery capabilities, thus functioning as protein amplification techniques similar to PCR[197].

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[190] Mnyusiwalla, Daar, and Singer, "' Mind the Gap ': Science and Ethics in Nanotechnology".

[191] Mohamadi et al., "Nanotechnology for Genomics & Proteomics".

[192] Elingarami, Li, and He, "Applications of Nanotechnology , Next Generation Sequencing and Microarrays in Biomedical Research".

[193] Mohamadi et al., "Nanotechnology for Genomics & Proteomics".

[194] Gulbakan et al., "Post-Genomics Nanotechnology Is Gaining Momentum : Nanoproteomics and Applications in Life Sciences".

[195] Ibid.

[196] Ibid.

[197] Ibid.

In healthcare, concerning either genomics or proteomics, NT extends the limits of molecular diagnostics to the nanoscale. Applications of this technology can have impact in the following cases:

- Many of the current serology techniques to diagnose autoimmune diseases (such as rheumatoid arthritis, celiac disease, Wegener's granulomatosis) do not demonstrate optimal sensitivity to the limited ability of these techniques to detect low levels of autoantibodies in the sera of suspected patients. Here, the application of nanoproteomics techniques could be promising[198].
- Since several plasma protein biomarkers have been associated with different types of cancer and considering the lack of sensitivity of current screening techniques, NT may provide means to advance cancer screening[199].
- NT could be used for biomarker discovery and drug delivery[200], making it particularly important for precision medicine[201].

NT allows researchers to overcome several technical limitations in genomic and proteomic analysis, including biological complexities, sensitivity, and dynamic range. These ultrasensitive and high-throughput technologies can facilitate identification and characterisation of biomarkers for human diseases and contribute to clinical applications, providing the possibility for early and accurate diagnosis, tailored drug selection, and monitoring of disease progression and therapy.

Application of NT is genomics poses however a number of ethical challenges in terms of:

- **Equity**. Who will benefit from advances in NT? If there is already a genomic divide[202] globally widening the gulf between those who can benefit from genomics and those who cannot, we may fear that this very 'high-tech' and costly research will be irrelevant in developing countries and may even widen international inequalities.

- **Privacy and security**. If NT is capable of miniaturising sequencing devices, surveillance applications of genome sequencing may become more ubiquitous.

- **Environmental risks**: since smaller particles are more reactive, they may thus be more toxic in certain contexts. Indeed, a major challenge associated with the growing field of NT is increased human exposure to particulate matter and associated respiratory and

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[198] Gharagozloo, Majewski, and Foldvari, "Therapeutic Applications of Nanomedicine in Autoimmune Diseases: From Immunosuppression to Tolerance Induction".

[199] Ji et al., "Carbon Nanotubes in Cancer Diagnosis and Therapy".

[200] Suri, Fenniri, and Singh, "Nanotechnology-Based Drug Delivery Systems".

[201] Streeter Jr., Beron, and Iyer, "Precision Medicine: Genomic Profiles to Individualize Therapy".

[202] Singer and Daar, "Harnessing Genomics and Biotechnology to Improve Global Health Equity".

cardiovascular toxicity[203]. The use of these particles *in vivo* is strictly regulated[204], but the associated environmental pollution with these particles may increase potential risks upon inhalation, especially among industrial workers. "*Therefore, despite the promises that nanotechnology holds for both basic science and clinical research, the escalating trend in using nanoparticles should be cautious and should take into concern environmental and toxicological side effects*" [205].

- **Public distrust**: a lack of public discussion on the subject of NT research may create misunderstandings between professionals and the public and cause potential social contestation like the one with GM crops[206].

7.3.2   Clinical and public health applications

Clinical use of genome sequencing provides a way to identify the cause of rare and/or persistent diseases of unknown aetiology through the screening of thousands of loci for pathogenic mutations. Clinical sequencing is also used to sequence biological specimens for the genomic signatures of novel infectious agents. It is expected "*to improve diagnosis and management of some disorders with a strong heritable component, as well as improve personalized diagnosis and personalized drug therapy and treatment*"[207]. In some clinical contexts, high throughput sequencing technologies are replacing array and sanger sequencing technologies thanks to the formers decreasing costs, and increased throughput and automated processes.

Certain features of genome sequencing, which set it apart from more 'traditional' clinical genetics, are critical to understand the ELSI:

- Genome sequencing gives rise to significant volumes of data. This data when interpreted can provide a lot of health information for patients and their families. The information may go beyond the initial reason(s) why sequencing was prescribed in the first place.
- Not all of the data is yet understood with respect to interpretation of whether variants are "normal" or pathogenic, hence the meaning or interpretation of sequencing data will almost certainly change with time;
- Genome sequencing will not always lead to certainty (e.g. one clear answer to the molecular diagnosis or cause of a disease), and may introduce new uncertainties.

These critical features create specific issues depending on "how and when" genome sequencing is implemented in the course of clinical care. Genomics, for instance, challenges presumptions, such as

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[203] Singh and Nalwa, "Nanotechnology and Health Safety–Toxicity and Risk Assessments of Nanostructured Materials on Human Health".

[204] Ferrari, "Cancer Nanotechnology: Opportunities and Challenges".

[205] Gulbakan et al., "Post-Genomics Nanotechnology Is Gaining Momentum : Nanoproteomics and Applications in Life Sciences".

[206] Mnyusiwalla, Daar, and Singer, "' Mind the Gap ': Science and Ethics in Nanotechnology".

[207] Howard et al., "Whole-Genome Sequencing in Newborn Screening? A Statement on the Continued Importance of Targeted Approaches in Newborn Screening Programmes".

whether the mere possibility of applications of a technology should lead to a wide implementation of it (i.e. the technological imperative). This stands in sharp contrast to the vision according to which clinical questions or needs should rather guide the use of new technologies. Yet, when the individual being tested is a foetus or a child, these considerations become even more significant in order to assure responsible use of new technologies.

7.3.2.1   Ethical issues with regard to clinical applications of genomics

History of the ethics of clinical genetics, as presented earlier in this report (p.21), has strongly influenced the perception of ethical issues raised by the clinical applications of genomics. As is the case for the transition from genetic research ethics to the ethics of research involving NGS technologies, "usual suspects", such as "privacy", "confidentiality", "informed consent", "return of uncertain results and incidental findings" are still burning issues but they need to be analysed in the light of NGS specific features: generation of massive amounts of data; unprecedented scope uncertainty and data-intensive environments (p.102). An important difference between genomic research ethics and clinical genetics ethics however lies in the specific duty of physicians towards their patients (p.101).

Based on the description of genome sequencing applications in D.2.1, we provide a summary of ethical issues with regard to clinical applications of genomics at different times in the human life cycle and for different purposes.

i.   ***Genome sequencing in adults***

Clinical genetic testing in adults is at present typically proposed to a relatively small number of patients who, as a result of family history or clinical indications, are considered at risk of carrying genetic variations that are linked to a particular disease or disease predisposition. NGS greatly expands the breadth of testing from genes associated with a particular disease to large parts of the genome and, potentially, all the information that the genome contains about diseases (including common complex diseases such as some cancers, diabetes or cardiac diseases) or traits.

As was shown in D.2.1, genomic sequencing in the clinic faces similar ELSI challenges as those involved in research (p.102), including: privacy and confidentiality; informed consent for both the clinical and research aspects; return of results, including incidental and secondary findings as well as long term challenges in recontacting participants when/if new knowledge is generated; public data release and commercialisation to third parties; communication with family members of results; evolving roles and responsibilities of different health care professionals towards patients, their family and society as genomics enters health care.

ii.   ***Paediatric genome sequencing***

Genome sequencing is gradually being implemented in paediatric genetics in order to improve diagnosis yield for children and families and optimise treatments. There are however several concerns related to the use of genomic testing for children – especially regarding, utility, consent and

privacy. All the other ELSI raised previously for adults also apply here, as well as in the contexts below, but one could consider that with each context including (more) vulnerable stages of life, these ELSI are amplified.

Until recently, predictive genetic testing was seen as justified only when clear clinical indications called for genetic information; when clear treatment or prevention could start in childhood to help alleviate or treat the condition[208]. Because parents consent for genetic testing on the behalf of their child (who is not able to provide consent, but from whom assent should be obtained), this practice raises the issue of the child's right not to know (about genetic information). In the research context, which, as mentioned above, is increasingly attached to the clinical context, there are proposals to re-contact children once they reach the age of majority in order to give them the opportunity to consent for themselves whether or not they want their samples and data to be kept for research[209].

iii.   ***Newborn Screening Programs (NBS)***

Public health programmes aim at "*the early identification in asymptomatic newborns of conditions for which early and timely interventions can lead to the elimination or reduction of associated mortality, morbidity and disabilities*"[210]. Genomic sequencing could be used to increase the predictive value of NBS results[211] and to expand such programs by testing for (many) other disease-associated variants[212]. Babies would be screened at birth, '*to produce a comprehensive map of their key genetic markers, or even their entire genome*': '*the baby's genetic information could then be securely stored on their electronic patient record for future use. It could then be used throughout their lifetime to tailor prevention and treatment regimens to their needs as further knowledge becomes available about how our genes affect our risk of disease and our response to medicines*'[213].

In additions to problems of cost-effectiveness, this perspective raises several issues[214]:

- this electronic patient record produced once and stored for a lifetime[215] would be a source of security if hacked or altered;
- unanticipated information delivered by genomic testing (e.g., incidental findings including mutations associated with high risk for hereditary cancer syndromes) for infants who may have otherwise normal NBS results could result in the labelling of a group of individuals, called "patients-in-waiting", who are diagnosed with a disorder but are "waiting" for

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[208] Borry et al., "Predictive Genetic Testing in Minors for Adult-Onset Genetic Diseases".

[209] Gurwitz et al., "Children and Population Biobanks"

[210] Howard et al., "Whole-Genome Sequencing in Newborn Screening? A Statement on the Continued Importance of Targeted Approaches in Newborn Screening Programmes", p. 1593.

[211] McCandless et al., "Sequencing from Dried Blood Spots in Infants with 'False Positive' Newborn Screen for MCAD Deficiency".

[212] Roberts, Dolinoy, and Tarini, "Emerging Issues in Public Health Genomics".

[213] Health, *Our Inheritance, Our Future. Realising the Potential of Genetics in the NHS*.

[214] Roberts, Dolinoy, and Tarini, "Emerging Issues in Public Health Genomics".

[215] Goldenberg and Sharp, "The Ethical Hazards and Programmatic Challenges of Genomic Newborn Screening".

symptoms of their disorder to develop[216].. The problem is that "*[s]ome of that information, like carrier results, may not be immediately actionable for the child. Moreover, some of the information may be predictive, not diagnostic, and related to the onset of adult conditions*"[217]. These situations would be all the more complicated to manage when parents may not have consented to receive such information in routine NBS, where screening of infants is considered to be a public good and does not necessarily require parental informed consent in the same way as for non-public health testing.

Although NBS programs have been (repeatedly) suggested as being occupying a privileged place to implement whole genome sequencing, they have also been, rightly criticised[218] since there are many logistical, financial and ethical problems with implementing genomic sequencing in NGS.

iv. *Foetal genome sequencing*

As was shown in D.2.1, "*two trends have dominated recent technological advances in prenatal diagnosis: the exploration of the foetal genome in increasingly higher resolutions and the development of non-invasive methods of foetal testing using cell-free DNA in maternal plasma[219] (i.e. non-invasive prenatal testing or NIPT)".* These developments aim towards the facilitation of increasing personal reproductive choices[220].

In the future, a pregnant woman will thus possibly be offered, more or less systematically, a first-trimester blood test that will inform her as to "*whether her foetus has a chromosome abnormality and/or dozens of single gene mutations, and/or thousands of polymorphisms*"[221], either in the clinic or through DTC[222], ie. without a process ensuring their clinical value, without any or adequate counselling and having clinical professionals to monitor the performance of such tests and potentially used for non-medical reasons (e.g. sex selection or other traits[223]). In both scenarios, one can fear that any premature implementation of NIPT covering genomic aberrations for which knowledge remains incomplete would generate patient anxiety at a time when they are particularly vulnerable[224].

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[216] Timmermans and Buchbinder, "Patients-in-Waiting: Living between Sickness and Health in the Genomics Era".

[217] Roberts, Dolinoy, and Tarini, "Emerging Issues in Public Health Genomics".

[218] Howard et al., "Whole-Genome Sequencing in Newborn Screening? A Statement on the Continued Importance of Targeted Approaches in Newborn Screening Programmes".

[219] de Jong, Maya, and van Lith, "Prenatal Screening: Current Practice, New Developments, Ethical Challenges".

[220] Dondorp et al., "Non-Invasive Prenatal Testing for Aneuploidy and beyond: Challenges of Responsible Innovation in Prenatal Screening".

[221] Hui and Bianchi, "Recent Advances in the Prenatal Interrogation of the Human Fetal Genome".

[222] Lo, "Non-Invasive Prenatal Testing Using Massively Parallel Sequencing of Maternal Plasma DNA: From Molecular Karyotyping to Fetal Whole-Genome Sequencing".

[223] Minear et al., "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues".

[224] McGillivray et al., "Genetic Counselling and Ethical Issues with Chromosome Microarray Analysis in Prenatal Testing".

Because of the relative ease of performing NIPT compared with conventional invasive testing, more women are likely to undergo prenatal testing for screening purposes than would otherwise be the case, thus reinforcing the expanding perception that 'natural' biological parenthood is "*in need of being managed, assisted, monitored*"[225]. There is a risk that the routinisation of such tests could contribute to the selection and termination of pregnancies based on gender preference and genetic stigma and to a greater desire to have "perfect babies"[226] or at least to have babies conform to the parents' desires[227].

v. ***Risk of misinterpretation of genetic/genomic information leading to psychological and social harms***

As was shown in D.2.1, "*educating the public about public health genomic information is difficult especially since researchers are still determining its meaning across various contexts themselves[228]. The complexity of most medical disorders makes it also difficult to understand and to explain how genetics interacts with several other factors that influence disease expression, such as health behaviours, environmental exposures, co-morbid conditions, and social determinants of health. Communicating genetic information requires an ability to translate complicated findings to individuals who may lack the advanced skills in health literacy, numeracy, and genetic literacy that would be required to fully appreciate the meaning and implications of results from genetic testing and research*". The model of genetic counselling[229] may not be practical from a public health perspective, especially as a greater numbers of people require genetic services.

The development of genomic technologies in public health cannot happen without well-developed plans to educate and engage the public as well as all professions that would have specific interactions with, and duties to, patients or research subjects or persons with results – from local GP, to social workers, to dietician etc. However the tendencies in public opinion toward genetic exceptionalism[230] and essentialism may impede this educational[231].

vi. ***Discrimination from insurers and employers***

As was shown in D.2.1, the regulation of access to genomic information is a prominent policy challenge in public health genomics because of its risk for discrimination in various aspects of social life. Insurers might indeed wish to use a genetic test result in the same way as they would use other medical or family history data and employers might wish to ensure that an individual does not have a genetic risk which might affect his ability to work or which might lead to problems of safety (e.g.

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[225] Franklin, "Conception through a Looking Glass: The Paradox of IVF".

[226] Garver and Garver, "The Human Genome Project and Eugenic Concerns."; Duster, *Backdoor to Eugenics*.

[227] Häyry, "There Is a Difference between Selecting a Deaf Embryo and Deafening a Hearing Child".

[228] Roberts, Dolinoy, and Tarini, "Emerging Issues in Public Health Genomics".

[229] Ibid.

[230] Ilkilic, "Coming to Grips with Genetic Exceptionalism: Roots and Reach of an Explanatory Model".

[231] Ruiz-Canela, Valle-Mansilla, and Sulmasy, "What Research Participants Want to Know About Genetic Research Results: The Impact of 'Genetic Exceptionalism'".

airline pilots, bus drivers). However, such practices leading to people being denied employment or insurance (or charged higher premiums on the basis of genetic traits), are considered inequalities of treatments leading to discrimination of individuals or groups. As is stated in the UNESCO Universal Declaration on the Human Genome and Human Rights (1997): '*no one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity*'.

Measures developed to prevent from genetic discrimination led to two legal frameworks in Europe and in the US:

- The 1997 Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Applications of Biology and Medicine specifies in Article 11: 'Any form of discrimination against a person on grounds of his or her genetic heritage is prohibited'. At the national level, the approaches used vary greatly[232]. *"In respect to insurance, three solutions are usually proposed: (1) prohibition of any use of genetic information by insurers outright; (2) legislation prohibiting this below a certain amount of coverage; and (3) moratoria; the adoption of moratoria on the use of genetic information has been a widespread response of the insurance industry throughout Europe. Among the countries where there is no regulation, bills have been presented or states that have ratified the 1997 Council of Europe's Convention are bound by it [233]."* [234]

- In the U.S., the federal Genetic Information Nondiscrimination Act (GINA) was passed in 2008, prohibiting health insurers and employers from using genetic information (including family history) to inform decisions about coverage, premiums, or hiring [235]. However, GINA does not cover life, disability, or long-term care insurance, which is important to note given the availability of genetic susceptibility testing for disorders like Alzheimer's disease [236].

Although we focussed on misuses of genetic information from insurers and employers, genetic discrimination can happen in different spheres of our life – eventually inasmuch as genetics penetrates various aspects of our social life, either intimate or public. Specific attention should thus be given to vulnerable groups, in particular migrants or refugees, who could be subjected to genetic surveillance (p.130) and for whom genetic testing could be used to disallow their refugee claims[237].

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[232] Godard et al., "Genetic Information and Testing in Insurance and Employment: Technical, Social and Ethical Issues."

[233] I and Horstman, "European Practices of Genetic Information and Insurance: Lessons for the Genetic Information Nondiscrimination Act".

[234] Godard et al., "Genetic Information and Testing in Insurance and Employment: Technical, Social and Ethical Issues."

[235] Feldman, "The Genetic Information Nondiscrimination Act (GINA): Public Policy and Medical Practice in the Age of Personalized Medicine".

[236] Taylor et al., "Genetic Testing For Alzheimer's And Long-Term Care Insurance".

[237] Milanich, "'Rapid DNA' Promises to Identify Fake Families at the Border. It Won't".

7.3.2.2 Focus: ethical issues with regard to testing embryos for non-Mendelian traits

Polygenic risk scores used in embryos is one of the application areas of genomic technology mentioned by experts, in our foresight survey (p.94), expected to have an important impact in the future. Since we did not describe technologies used for embryo selection, nor addressed polygenic risk scores in D.2.1, we describe them herein before reporting on the main ethical issues raised by such developments.

Since the 1990s, couples undergoing IVF (in vitro fertilization) have been able to screen their embryos for mutations in single genes that are implicated in serious diseases such as cystic fibrosis, as well as conditions like Down's syndrome, caused by chromosome abnormalities. The process of pre-implantation genetic diagnosis (PGD) relies on the procedure of genetic profiling of embryos prior to implantation (and sometimes even oocytes prior to fertilization)[238].

> "*Since the clinical implementation of PGD, the European Society of Human Reproduction (ESHRE) PGD Consortium has recorded the number of PGD cycles performed in Europe and elsewhere over the past 10 years. In 2010, the most recent year for which numbers are available, 2,753 PGD cycles were performed, of which 1,071 were for chromosomal abnormalities, 108 were for X-linked disorders and 1,574 were for Mendelian disorders*".[239]

For couples who are known carriers of mutant alleles and are at risk of transmitting serious diseases to their offspring, PGD enables the detection of genetic disorders in embryos that have been fertilized in vitro. Several embryos are generally developed and tested, where it is then common practice to rank embryos and select the embryo with the highest chance of resulting in a healthy individual[240].

This raises many questions for gene variants used in a predictive context since these are not diagnostic tests confirming the nature of a disease when symptoms are already present (and where treatment may be required). This is exacerbated by diseases where there is variable expressivity; that is to say where the expression of the disease may differ greatly form one patient to another, such as being very mild with few symptoms or being very severe with many complications. For instance, as Rothman explains, "*to predict Down syndrome is not to predict the experience of Down syndrome. One foetus so diagnosed is not strong enough to survive the pregnancy; another is born with grave physical and mental handicaps and dies very young; and another grows up well and strong and stars in a television show*"[241]. In the context where potential parents are looking for a specific disease

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[238] Vermeesch, Voet, and Devriendt, "Prenatal and Pre-Implantation Genetic Diagnosis".
[239] Ibid.p. 649.
[240] Hens, Dondorp, and de Wert, "A Leap of Faith? An Interview Study with Professionals on the Use of Mitochondrial Replacement to Avoid Transfer of Mitochondrial Diseases".
[241] Rothman, *Genetic Maps and Human Imaginations: The Limits of Science in Understanding Who We Are*.

however, the question of how to select the foetuses without that disease is rather straightforward, since these would be the ones whose tests are negative for that causal variant.

In the current context, the questions raised by PGD are evolving rapidly. Tests targeted at a particular mutation are time-consuming, leading to long waiting lists for couples that undergo this procedure. Novel genome-wide screening approaches, such as microarrays and genome sequencing, have begun to overcome these limitations for a cost that keeps decreasing[242], even though they remain affordable only in some countries and for some people in these countries[243]. Genome-wide analysis allows for much more information to be collected about foetuses, information that is not only about genetic conditions but also about many traits, including height, physical appearance or disease susceptibility.

Such common and/or complex traits are indeed known to be partly inheritable but their genetic component thought to be influenced by hundreds or even thousands (or more) DNA regions, making it previously impossible to be screened. In the past decade though, with the development of vast genetic databases, it has become possible to calculate "polygenic risk scores", which give a person's likelihood of getting a particular disease or having a certain trait[244].

Tests that result in polygenic risk scores (could) make it possible for potential parents to rank embryos on the basis of test results concerning traits that are not monogenic diseases or not even considered diseases. This possibility raises both scientific and ethical questions. From a scientific point of view, these tests raise several questions:

- Predicting the traits of a person for which thousands of genes are implicated and where the environment is also susceptible to play a decisive role is even more a complicate task than for monogenic disorders.

- Results are based on populations studies but a rare gene variant may only account for a tiny percentage of variation in a trait across a population, while making a big difference to the phenotype of those who have it.

- Risk scores are very hard to interpret and hard to transfer between different countries and different ethnic groups. Due to the lack of diversity in ethnic representation in genetic databases[245], studies underlying these tests may be biased and thus test results may be less accurate for minorities.

- There are significant uncertainties about what polygenic scores may be measuring for complex traits such as intelligence. Indeed, the scientific claim that intelligence could be predicted by genetic tests is highly contentious.

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[242] Payne et al., "Cost-Effectiveness Analyses of Genetic and Genomic Diagnostic Tests".
[243] Ebomoyi and Ebomoyi, "Global Genomics Disparities in the Wake of Personalised Medical Services".
[244] Dudbridge, "Power and Predictive Accuracy of Polygenic Risk Scores",p.298
[245] Rotimi, "Health Disparities in the Genomic Era : The Case for Diversifying Ethnic Representation".

The complexity of the developmental process and our inability to comprehend the genome-environment interactions (yet) render embryo implementation based on polygenic risk scores highly problematic. There may be unintended consequences, since, for instance, there is some evidence linking higher polygenic scores for academic ability to higher likelihood of autism[246].

Beside these scientific and medical issues, this practice raises important ethical questions since such practice can been seen as the slippery slope towards the "designer child"[247]:

- The first question is whether parents should have the right to decide which embryo is the "best": this questions the sheer notion of the dignity of human life, which is recognized in the right to be valued for one's own sake[248].

- In abortion history, legal abortions for medical reasons were restricted to the very rare cases for which medical doctors found compelling reasons. Although PGD is not abortion, the polygenic risk score may allow for selection of human embryos for non-medical reasons in a medical setting.

- Freedom of choice: although the debate about these issues is framed in terms of freedom and choice, it is important to be aware of the pressure than can be exerted on parents in a social context where pressures for presymptomatic testing are growing and insurance coverage diminishes[249]

- Deepening existing social inequalities: due to its lack of affordability, access limited to upper classes in technology-advanced countries could widen the gulf between a "genetically privileged" and the "genetic underclass", i.e. people who can afford to select their offspring based on traits that are desirable in a society and the others[250].

- Eugenics: This practice can be argued to be a version of new eugenics, or liberal eugenics, where individuals can make private choices on the basis of genetic screening results – in contrast with the old state-mandatory eugenics, where state breeding imposed selections on people.[251] However, the cumulative effect of these individual private decisions could alter demographic patterns based on cultural hierarchies and prejudice. In a scenario where enough potential parents would make the choice to select children according to society most desirable traits, one can expect the norms to ratchet up, thus reinforcing the pressure for

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[246] Grove et al., "Identification of Common Genetic Risk Variants for Autism Spectrum Disorder".

[247] Sterckx et al., "'I Prefer a Child with …': Designer Babies, Another Controversial Patent in the Arena of Direct-to-Consumer Genomics."

[248] Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*.

[249] Wexler, *Mapping Fate: A Memoir of Family, Risk and Genetic Research*.

[250] Mehlman and Jeffrey R., *Access to the Genome: The Challenge to Equality*.

[251] Duster, *Backdoor to Eugenics*.

potential parents to create "superior" human beings and reinforcing inequalities with those who would not have access to such technologies.

- Discrimination of people with disabilities: an impact of such selective practices would possibly entail "*making many genetically disable people (particularly those with visible or severe disabilities) feel like [they] must defend [their] very existence*"[252]. Although disability rights activists may either defend pro-choice or pro-life arguments[253], there is a call for genetic professionals to be aware of the societal context where genetic technologies emerge from and further influence, namely severe societal discriminations against people with disabilities in employment, education, access to community resources and political power, that risks being reinforced with geneticisation. This is the term "*coined to capture the ever-growing tendency to distinguish people one from another on the basis of genetics; to define most disorders, behaviors, and physiological variations as wholly or in part genetics in origin*"[254]. Rather than focussing on reducing the hardships and inconveniences of being different in society and addressing the suffering caused by the prejudice against people with disabilities, we risk turning exclusively to a medical model to help eliminate disabilities.

- Genetic versus sociopolitical framing of reproductive issues: framing reproductive issues entirely within a medical and scientific domain drains public attention away from the social and political forces that also affect the health of babies, children and families.

- Genetic versus environmental determinism: in these discussions, there are plethora of arguments to denounce embryo selection as a procedure of instrumentalisation of embryo/child that may close their open future[255] and treat the child as a designed artefact[256]. Such arguments are however counter-argued by approaches that highlight the fundamental influence that the environment – specifically the social and parental environment – play in the determination of a human being. Allen Buchanan dismisses objections that argue that genetic enhancements causing changes 'in us' are fundamentally different from 'external' or 'environmental' enhancements[257], since these external or environmental enhancements are not avoidable, nor are they less profound than our genetic influences[258]. In the 2018 Report from the Nuffield Council on genome editing, this "normative genetic determinism" is

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[252] Saxton, "Disability Rights and Selective Abortion", p.391
[253] Heyer, "Prenatal Testing and Disability Rights: Challenging 'Genetic Genocide'".
[254] Lippman, "Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities".
[255] Habermas, "An Argument against Human Cloning. Three Replies"; Häyry, "Protecting Humanity: Habermas and His Critics on the Ethics of Emerging Biotechnologies".
[256] Sparrow, "Yesterday's Child: How Gene Editing for Enhancement Will Produce Obsolescence—and Why It Matters".
[257] Buchanan, *Beyond Humanity?: The Ethics of Biomedical Enhancement*.
[258] Bearman, "Exploring Genetics and Social Structure".

recognised because the report questions why genomic interventions are considered exceptional when compared to other parental interventions such as education and inculcating the moral conscience, highlighting the belief of changes 'indelibly inscribed into a future person's biology' even where the actual effects are of lesser magnitude[259].

Indeed, most (if not all) of these ELSI are only exacerbated if we consider polygenic risk scores being used to supposedly predict IQ (which is already a contentious and debatable "genetic" trait) and add to this an offer direct-to-consumer and the concerns only amplify. For example, "Genomic Prediction" is "*the first company to take embryo screening into this grey area of risk forecasting, offering to alert couples if an embryo has an "outlier" score for risk of cancers, diabetes, heart disease, dwarfism, inflammatory bowel disease or low IQ*"[260]. The firm is already offering these tests in fertility clinics in the US; it has started the procedure to get approval from the Human Fertilisation and Embryology Authority (HFEA) to provide those tests in the UK and is expecting to develop in the Asian market[261]. It is important to underlie that even if it is forbidden in a country, one can expect parents to undergo the test in another country where such procedure is legal (or where the relevant laws do not exist). At the moment, "Genomic Prediction" offers the option of screening for "mental disability", "giving prospective parents the option of avoiding embryos with a high chance of an IQ 25 points below average"[262], but the same approach could be developed to identify embryos with genes that make them more likely to have a high IQ.

7.3.2.3 Focus: Artificial Intelligence and Genomic application in the clinics

Artificial intelligence is one of the technology areas mentioned by experts, in our foresight survey (p.94), expected to have an important impact in human genomics. Since we did not describe this area of technology in D.2.1, we describe herein how artificial intelligence may be used in genomics and what role it could play in the clinic (for the purpose of optimizing healthcare delivery, automating clinical processes and personalising medicine). We then report on the main ethical issues raised by such developments.

Considering the interface between artificial Intelligence and genomics is all the more important in SIENNA since these refer to two main areas of concern in the project, which are expected to overlap in the future and lead to impactful applications.

This section is based on literature and discussions with genomic experts during London workshop (p. 96) and Goteborg workshop (p. 18).

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[259] Yeung, *Genome Editing and Human Reproduction*.

We will use the two following definitions throughout this section:

> - Artificial Intelligence (AI): it is a field of computer science concerned with the intelligence demonstrated by machines, in contrast to the natural intelligence displayed by humans. Given the ambiguity of the term "intelligence", AI may refer to different types of functions associated with human mind, such as "learning" and problem solving" but also with human behaviour[263].
>
> - Machine Learning (ML): it is a branch of computational algorithms, designed to emulate human intelligence by learning from the environment[264]. Based on sample data, also known as training data, ML algorithms build mathematical models that make predictions or take decisions. Techniques based on machine learning have been applied in diverse fields ranging from pattern recognition, computer vision, spacecraft engineering, finance, entertainment, and computational biology to biomedical and medical applications.

Since the development of high throughput sequencing in genomic research and its progressing translation into the clinic, both sectors are undergoing an explosion of growth, especially in terms of data[265]. According to experts in AI, such developments provide an opportunity to develop ''machine learning that matters''[266]. More crucially some state that machine learning would also be the only way to deal with the deluge of genomic data and to make enough progress in our understanding of the genome to truly engage in genomic medicine. Leung et al. hold that:

> *"[i]t is our view that to make genomic medicine a reality, we must develop computer systems that can accurately interpret the text of the genome just as the machinery inside the cell does. While this is a difficult challenge, it will enable the effects of genetic variation and potential therapies to be explored quickly, cheaply, and more accurately than can be achieved using laboratory experiments and model organisms."[267]*

According to this goal, it could be possible to mimic our cellular ability to decode the genome through AI, in the same way that ML has already achieved human-level performance in domains such as image recognition, speech recognition, and natural language processing. However, from a machine learning perspective, genome biology differs from these other biological domains in a very important way. Seeing images, hearing speech or grabbing an object are cognitive tasks that involve human perception and human action. However, cell functioning involves a rather different set of

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[263] Russel and Norvig, "Artificial Intelligence: A Modern Approach Third Edition".
[264] El Naqa and Murphy, "What Is Machine Learning?"
[265] Bell, Hey, and Szalay, "Beyond the Data Deluge."
[266] Wagstaff, "Machine Learning That Matters".
[267] Leung et al., "Machine Learning in Genomic Medicine : A Review of Computational Problems and Data Sets".

tasks. We do not naturally perceive and interpret genomic sequences nor do we understand all the mechanisms, pathways, and interactions that animate a living cell. Moreover, cells do not function in the same way as human brains, or not as far as we know currently. Consequently, AI developed with the aim of advancing our knowledge of genomics (and/or cell functioning), cannot be used in the same way that AI developed to reproduce human intelligence[268].

When applied to genomics, AI models are required to receive the latest biological knowledge and to be trained through large and diverse datasets. However experts acknowledge that "*it is possible that the association of the genome to some diseases might simply be too complex to be modelled from a practical number of ''inputs'' and that computational methods should not be expected to be able to entirely replace laboratory and clinical diagnosis, but they should greatly shorten the time required for these methods of analysis by reducing the search space of hypotheses that need to be validated*"[269].

This knowledge ought to determine how variations in the DNA of individuals can affect the risk of different diseases, and to find causal explanations so that targeted therapies can be designed. AI algorithms are finally developed to support diagnosis and clinical decisions

i. *The use of Machine Learning in genomics: from bench to bedside and back*

One of the massive questions pursued by researchers in genomics is to explore the genotype-phenotype relationship. Their goal is to understand how genotypes (the inherited material transmitted by gametes) map onto phenotypes (the observable attributes of an individual), which, in a medical perspective can be formulated as how genetic variants map with disease risks. As of today, the predominant thinking in biology for complex traits (i.e. traits that are not Mendelian, and ultimately most traits) is that multiple genes interact with multiple environmental variables to produce the phenotype[270]. There are two main strategies to explore this relationship; we briefly explain these below primarily to then state how AI can also be used as a tool to help in these approaches and beyond in genomics:

- Comparative genomics allows studying evolutionary conservation. Comparative genomics is based on a view of evolution as driven by two forces: the accumulation of random mutations for adaptation purposes, and selective pressures against deleterious mutations, i.e. mutations that damage reproductive fitness within a population[271]. Assuming that the genomes of different species have diverged from a common ancestor long ago, random mutations have had plenty of time to occur, but when comparing these different genomes,

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[268] Ibid.

[269] Ibid.

[270] Orgogozo, Morizot, and Martin, "The Differential View of Genotype–Phenotype Relationships".

[271] Ureta-Vidal, Ettwiller, and Birney, "Comparative Genomics: Genome-Wide Analysis in Metazoan Eukaryotes".

many long distinct sequences are found that are nearly identical, or ''conserved,'' across species, "*it is strong evidence that evolution is exerting selective pressure on the positions within those sequences*"[272]. Comparative genomics thus indicates zones of the genome where function is conserved throughout time and provides information about deleterious mutations.

- Genome-Wide Association Studies (GWASs): their goal is to detect how traits within a population can be related to variants in particular genomic locations, or loci[273]. Early GWAS experiments used microarrays that were designed by the most easily determined variants in the human population: single-nucleotide polymorphisms (SNPs), which are variations that are relatively frequent across humans (frequency greater than 1%). The main problem in GWAS and any association-based technique [e.g., expression quantitative trait loci (eQTLs)] is that they indicate correlation, not causation.

In summary, the two main existing strategies that researchers rely on to explore the genotype-phenotype relationship have methodological limitations besides being data-intensive and raising ethical issues[274].

AI is conceived as an additional tool for genomic researchers in the quest of understanding the genotype-phenotype relationship, i.e. to predict phenotypes, and in particular disease risks, from the genome sequence. In terms of ML[275], modelling the genetic basis of disease risks seems to be a "supervised ML problem" [276] where the inputs would be a stretch of DNA sequence (genotype) relevant to the underlying biology, and the outputs would be the phenotypes (disease risks)[277].
But this broad approach is complicated for, at least, two reasons:

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[272] Leung et al., "Machine Learning in Genomic Medicine : A Review of Computational Problems and Data Sets".

[273] Luo et al., "Big Data Application in Biomedical Research and Health Care: A Literature Review".

[274] Kaye et al., "Ethical Implications of the Use of Whole Genome Methods in Medical Research."; Gibson and Copenhaver, "Consent and Internet-Enabled Human Genomics"; Fullerton et al., "Return of Individual Research Results from Genome-Wide Association Studies: Experience of the Electronic Medical Records and Genomics (EMERGE) Network".

[275] There are 3 main types of ML processes:
- Supervised learning algorithms build a mathematical model of a set of data that contains both the inputs and the desired outputs.
- Unsupervised learning algorithms take a set of data that contains only inputs, and elaborate structure in the data, like grouping or clustering of data points. The algorithms therefore learn from test data that has not been labelled, classified or categorized.
- Reinforcement learning is an area of machine learning concerned with how software agents ought to take actions in an environment so as to maximize their reward, thus simulating living agents acting in their own interest.

[276] Russell and Norvig, *Artificial Intelligence: A Modern Approach*.

[277] Leung et al., "Machine Learning in Genomic Medicine : A Review of Computational Problems and Data Sets".

- The genotype-phenotype relationship is not straightforward and, even within a single cell, the genome directs the cell's state through many layers of biophysical processes and control mechanisms.
- Even if models predictive of disease risks could be inferred, they would most likely not correspond to biological mechanisms that can be acted upon and thus would not useful for therapeutic purpose.

A preferred approach consists in training the computational model to predict measurable cell variables[278] – and then these variables can be linked to phenotype. This approach is preferred because it addresses the two problems previously mentioned:

- Since these cell variables are more easily determined from genomic sequences than are phenotypes, models that map from DNA to cell variables can be more straightforward.
- Since the cell variables correspond to biochemically active quantities, they may be good targets for therapies. If a disease risk is associated with a change in a cell variable compared to a healthy individual, restoring that cell variable to its normal state could prove an effective therapy.

The approach of ML now developed in genomics thus involves this intermediary step, where researchers use a model to ask "*whether a cell variable will increase or decrease if a particular nucleotide is changed, or, whether changing a pair of nucleotides leads to a change in the cell variable*"[279]. This approach provides a quantitative, data-driven interpretation of the genotype-phenotype relationship.

From a practical perspective, cell variables are more difficult to measure than phenotypic observations (such as whether a patient is sick). However, the research strategy that relies on cell variables rather than phenotype characterisations is now possible because of the recent development of high-throughput assay technologies that generate massive amounts of data, profiling these cell variables under diverse conditions, including disease conditions. Whereas, until the 1990's, biological assays typically required several manual steps and generated small amounts of data, massive data sets are thus available or can be obtained through single low-cost experiment to train ML models. So-called next generation sequencing technologies can be used to identify protein-binding sites[280]; to profile the genomes of individuals in medical studies for the purpose of discovering variations, either in regions of interest or across the entire genome[281], to measure

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[278] . Examples of cell variables include the locations where a protein binds to a strand of DNA containing a gene, the number of copies of a gene (transcripts) in a cell, the distribution of proteins along the transcript, and concentration of proteins. Ibid.

[279] Leung et al., "Machine Learning in Genomic Medicine : A Review of Computational Problems and Data Sets".

[280] Metzker, "Sequencing Technologies—the next Generation".

[281] Shendure and Ji, "Next-Generation DNA Sequencing".

different transcripts[282] etc. This approach is based on taking hundreds of thousands of cell variable measurements per patient for a smaller group of people rather than measuring few variables per patient for a large number of individuals[283].

An important aspect of ML development is its need for accurate input and for validation. Data are not only gathered in the lab but scientists, who create models of data that are used for analysis of genetic diseases also need to rely on clinical data and population data.

-   Fundamental research and the clinic: in order to predict disease risks, a model can be developed from the publicly available reference genome and data profiling transcripts in healthy tissues, but then it needs to be applied to the genome of a diseased cell so as to understand how the distribution of transcripts changes in the diseased cell. Validation here refers to a necessary step of exposing a model to data for cell states that are different from those used during training.

-   Fundamental research and genomic epidemiology: Such models are used for diseases that are caused by mutations that change cell variables[284]. They can however lead to false positives when a mutation causes a large change in cell variables that have no impact on disease or to false negatives when the mutations that act through cell variables are not being modelled. Population data are important here to filter sets of candidate mutations that are most likely to have a causal effect on a cell variable.

ML in genomic research is connected with public health and the clinics. But there is also an ambition for ML researchers to assist genomic medicine. ML approach now developed in genomic research provides *in silico* predictions of disease risks according to genetic variants, based on a pattern and thus may provide insight to disease mechanisms or point to effective therapies without securing an explanation. Its proponents nonetheless argue that throughout history, many medical advances were made by noticing a pattern without understanding the precise causal mechanisms involved[285].

ML may help thus increase the quality of personal care by supporting medical advances, advancing diagnosis and developing therapies. Technologies such as AI and ML have the potential to transform healthcare from personalising or automating treatments and predicting outcomes for prevention, through to empowering patients by self-monitoring. This could result in longer-term patient benefit through supporting the development and evaluation of new interventions, diagnostics (especially early diagnosis), medical devices and digital health tools. AI may also be used in clinics to assist decision–making for a specific course of action.

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[282] Lister, Gregory, and Ecker, "Next Is Now: New Technologies for Sequencing of Genomes, Transcriptomes, and Beyond".
[283] Leung et al., "Machine Learning in Genomic Medicine : A Review of Computational Problems and Data Sets".
[284] Xiong et al., "The Human Splicing Code Reveals New Insights into the Genetic Determinants of Disease".
[285] Leung et al., "Machine Learning in Genomic Medicine : A Review of Computational Problems and Data Sets".

ii.   Machine Learning and genomics: Opportunities and limitations

ML methods have been applied to a huge variety of problems in genomics and genetics, especially to identify a wide variety of genomic sequence elements[286]. ML can thus learn to recognize any given elements in DNA sequences:

> *"(i)n general, if you can compile a list of sequence elements of a given type, then you can probably train a machine learning method to recognize those elements. Furthermore, models that each recognize an individual type of genomic elements can be combined, along with (learned) logic about their relative locations, to build machine learning systems capable of annotating genes, including their full UTR/intron/exon structure (...)"[287].*

In addition, ML can be used to assign functional annotations to genes (under the form of Gene Ontology terms[288]); to learn to distinguish between different disease phenotypes and to identify potentially valuable disease biomarkers[289].

Main challenges:
- As already stated, experts in AI do not expect ML to completely determine the phenotype of an individual based on their genotype, due to the sheer complexity of the genotype-phenotype relationship but also to the inherent stochasticity of cellular processes and environmental factors that differ from person to person (even for identical twins)[290].
- The success of ML depends on the prior biological, clinical and epidemiological knowledge encoded in the models developed. Although AI is data-intensive it thus also heavily relies on the art of different kinds of research and the cooperation being developed among researchers outside of computer science.
- ML models applied to genomics are also challenging in the sense that they require handling heterogeneous data, either biological or of another nature, which challenge exiting computational models.
- In ML, researcher must decide which data to provide as input to the algorithm. The selection of proper biological features to study is thus highly determinant for the success of a model. It highly depends of the ability to produce experimental data and the availability of population data. Key for the development of ML in genomics is thus the growth and increasing variety of

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[286] Ohler et al., "Computational Analysis of Core Promoters in the Drosophila Genome"; Degroeve et al., "Feature Subset Selection for Splice Site Prediction"; Bucher, "Weight Matrix Descriptions of Four Eukaryotic RNA Polymerase II Promoter Elements Derived from 502 Unrelated Promoter Sequences".

[287] Libbrecht and Noble, "Machine Learning in Genetics and Genomics".

[288] Ashburner et al., "Gene Ontology: Tool for the Unification of Biology".

[289] Libbrecht and Noble, "Machine Learning in Genetics and Genomics".

[290] Burga and Lehner, "Beyond Genotype to Phenotype: Why the Phenotype of an Individual Cannot Always Be Predicted from Their Genome Sequence and the Environment That They Experience".

''omic'' data (including genomic, transcriptomic, epigenomic, and proteomic information) to be made publicly available through large international effort. Genomic databases however have their own challenges in terms of privacy, confidentiality and respect of consent for participants.

In research, the growth of "omic" data poses storage, privacy, and computing challenges that are particularly difficult to handle for research groups. It is also worth noticing that, in the context of genomic medicine, for a computational model to be useful in making predictions, inputs should be easily obtainable. For these computational models to be used in the clinic, patients' genomes have to be available which requires an affordable cost for whole genome sequencing[291], the creation of data environments robust and secure enough to accompany such data-intensive medical developments[292] and progress in dealing with ethical and legal issues related to whole genome sequencing[293].

> iii. *Expected benefits, risks and ethical issues related to the application of artificial intelligence to genomics*

The use of AI in genomic research and in healthcare is expected to provide benefits but it is also accompanied by a set of risks and challenges. Some relate to the opacity of the systems, to the use of participants and/or patient data or to the security and reliability of the technology itself.

- **Supporting medical research and innovation:** Through innovative research strategies, AI ought to develop new health interventions that may improve patient outcomes. This could include increasing personalisation of treatments so that care can be better targeted to the patient.

- **Increasing the quality of individual care**: Medical advances achieved through AI ought to improve patient safety and outcomes by allowing to predict, diagnose, treat or manage illnesses at the point of care through novel analyses which can support faster, more efficient care pathways. This may involve earlier diagnosis, as well as enabling more effective use of healthcare professionals' time.

- **Supporting public health:** Information derived from new, linked data sources can also support population health management, as well as the planning and commissioning of health and social care services[294].

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[291] Ashley et al., "Clinical Assessment Incorporating a Personal Genome".
[292] Stark et al., "Integrating Genomics into Healthcare: A Global Responsibility".
[293] Ormond et al., "Challenges in the Clinical Application of Whole-Genome Sequencing".
[294] Hamet and Tremblay, "Artificial Intelligence in Medicine".

- **Increasing equity:** AI could be used to allocate resources so as to enable equitable access for all patients and healthcare professionals[295].

- **Accountability and liability**: With AI, an important question is to determine who is accountable in case of error made by the system – which, in case of medical error, may have dramatic medical and legal consequences[296].

- **Bias and Data fairness**: Poorly representative training data sets can introduce biases into ML algorithms. Bias refers to two situations: cases in which the data sources themselves do not reflect true epidemiology within a given demographic and cases in which an algorithm is trained on a data set that does not contain enough members of a given demographic—for instance, an algorithm trained mostly on data from older white men. Such an algorithm would make poor predictions, for example, among younger black women. If algorithms trained on data sets with these characteristics are adopted in healthcare, they have the potential to exacerbate health disparities[297]. To avoid this pitfall and to avoid unfair conclusions in research and unfair access to treatments, scientific societies and regulatory agencies must develop best practices for recognising and minimising the downstream effects of biased training data sets, while bodies such as institutional review boards, ethics review committees, and health technology assessment organizations should check for compliance with such standards[298].

- **Lack of Disclosure**[299]: this refers to the lack of awareness of subjects (research participants and/or patients) that automated decision-making and profiling activities are being carried out. This kind of opacity prevents data subjects from exercising some specific data-related rights and may have tangible consequences in the context of medical applications. It is also worth noticing that an increasing variety of data generated and collected outside the clinical setting, and not initially intended for medical use are now starting to be employed in diagnosis, health-risk predictive models and to guide medical decisions. These include, for instance, lifestyle data, data about dietary habits, socio-economic data, but also data such as keystroke dynamics, and in general data collected through smartphones or wearable devices.
  Disclosure should be delivered about:

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[295] Academy of Medical Sciences, *Our Data-Driven Future in Healthcare*.
[296] Pesapane et al., "Artificial Intelligence as a Medical Device in Radiology: Ethical and Regulatory Issues in Europe and the United States".
[297] Braveman, "Health Disparities and Health Equity: Concepts and Measurement".
[298] Vayena, Blasimme, and Cohen, "Machine Learning in Medicine : Addressing Ethical Challenges".
[299] Lack of disclosure may be a way to avoid objections to data collection, but it can also be due to the need to protect intellectual property, copyright and trade secrets, since the value of algorithms and data, once disclosed, dramatically reduces unless protected through patents. Private corporations may be particularly inclined to use trade secrets to protect against competitors.

a) When and where data are being collected and data-driven technologies are being used, including in clinical and non-clinical settings, and the level of patient awareness and control over this.

b) What data the technologies are collecting and whether these are in a personally identifiable or depersonalised form.

c) Who will curate, have access to, or use the data.

d) Why data-driven technologies are being used and the value of doing so.

e) How data are collected and how they are used for decision-making, and when this is with the knowledge of the patient and when it is not.

- **Opacity**: ML relies on non-interpretable, so-called black- box algorithms, the inner logic of which is usually hidden (even to their developers). This lack of transparency can be interpreted in a few ways[300] (see below) and is problematic particularly for informed consent in medicine, including genomics in the clinic:

  o **Epistemic Opacity**: this relates to the question of *how* an AI system provides a specific outcome. This type of opacity can have two sources: a) procedural darkness or b) procedural ignorance.

    a) **Procedural Darkness**: Information and rules in a ML system are usually encoded in an abstract form and not readily accessible in a semantically readable form. While the general working principles of a system might be explained, programmers and users may thus not be able to understand how a specific output has been reached.

    b) **Procedural Ignorance**: Even assuming that the rules of an AI system are accessible in a semantic form, acquiring a meaningful understanding of their role in data processing activities may require a considerable amount of background knowledge, both in computer science and biology or medicine when AI is applied in genomic medicine.

  Epistemic opacity limits the possibility of providing thorough explanations of either the inner workings of AI systems. However, these limitations do not entail the impossibility of explaining the foreseeable consequences of such processing.

  o **Explanatory Opacity**: this relates to the question of *why* an AI system provides a specific outcome. ML systems are used in medicine to discover patterns between huge numbers of variables in a training dataset, and to leverage these patterns to make clinical classifications, predictions and decisions regarding new input data. These patterns do not show biological mechanisms between a property and an

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[300] Vayena, Blasimme, and Cohen, "Machine Learning in Medicine : Addressing Ethical Challenges".

observed phenotype and thus provide scientific explanation[301].

-   **Transparency:** In the European Data Protection Regulation[302], the principle of transparency is defined as requiring "*that any information and communication relating to the processing of ... personal data be easily accessible and easy to understand, and that clear and plain language be used*"[303]. Some scholars argue that transparency is incompatible with the opacity of AI systems[304], while others argue for a presumed 'right to explanation', in order to counterbalance the opacity of automated systems. Among them, the level and scope of "explanation" to be deemed sufficient are however discussed[305]. Some argue in favour of explaining its 'logic, significance, envisaged consequences, and general functionality'[306], while others demand an explanation of the *specific decisions* taken through or by an artificial intelligence system, i.e. 'the rationale, reasons, and individual circumstances of a specific automated decision, e.g. the weighting of features, [or] machine-defined case-specific decision rules'[307].

    According to the European Data Protection Regulation (GDPR), "data subjects" are entitled to receive information, explanation and protection regarding profiling, automated decisions, and special categories of data involved in such activities. In the GDPR, 'profiling' is defined as "*any form of automated processing of personal data consisting of the use of personal data to evaluate certain personal aspects relating to a natural person, in particular to analyse or predict aspects concerning that natural person's performance at work, economic situation, health, personal preferences, interest, reliability, behaviour, location or movement*"[308]: When applied to human genomics, AI systems clearly fall under these definitions[309]. In Europe, data subjects are thus "*entitled to receive meaningful information about the logic involved, the significance and the envisaged consequences of automated decision-making and profiling*", which obliges data controllers (in this case, research institutions, hospitals and physicians) to provide meaningful information to patients about the use of such systems[310]. There is still work to do to define what it means to inform a data subject about the logic and significance

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[301] Machamert, Darden, and Craver, "Thinking About Mechanisms".

[302] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ 2016 L 119/1 ('GDPR').

[303] GDPR, Section 39.

[304] Selbst and Powles, "Meaningful Information and the Right to Explanation".

[305] Wachter, Mittelstadt, and Floridi, "Why a Right to Explanation of Automated Decision-Making Does Not Exist in the General Data Protection Regulation".

[306] Ibid.

[307] Ibid.

[308] GDPR, art 4(4)

[309] Andrews, Bonta, and Wormith, "The Recent Past and near Future of Risk and/or Need Assessment".

[310] Ferretti, Schneider, and Blasimme, "Machine Learning in Medicine : Opening the New Data Protection Black Box".

of an AI system, especially using ML in the context of genomic research or healthcare.

Moreover, the disclosure of detailed information about medical treatment to patients—a fundamental tenet of medical ethics—requires that the doctors themselves grasp at least the fundamental inner workings of the devices they use. Considering the complexity of both genomic medicine and AI systems, such requirement may raise issues in terms of training for physicians.

- **Autonomy:** As more diagnostic and therapeutic interventions become based on ML, the autonomy of patients in decision processes about their health and the possibility of shared decision-making may be undermined. This would happen, for instance, if reliance on automated decision-making tools reduces the opportunity of meaningful dialogue between healthcare providers and patients or if payers consider ML recommendations as a precondition for reimbursement and refuse to cover treatments when the ML recommends against them.

- **Communication of results:** Patients generally prefer a human to communicate information about their diagnosis with them, since they perceive humans to be better at tailoring information to their level of understanding or for delivering difficult news[311]. Perceived risks to using AI in healthcare include: the loss of human contact and opportunity to discuss options for care, errors arising from a lack of access to relevant or accurate information, and the inability to explain how and why a technology has arrived at a specific outcome.

- **Privacy:** Privacy refers to the right of an individual to keep his or her health information private. **Confidentiality** refers to the duty of anyone entrusted with health information to keep that information private.

  o Privacy issues related to genomic data are already addressed both in research and clinic[312]. Patients[313] and the public[314] feel strongly about the need for further information or controls around data that are personally identifiable, which is potentially the case with genomic data[315].

  o In the GDPR, the processing of genetic data, biometric data, data concerning health

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[311] Vayena, Blasimme, and Cohen, "Machine Learning in Medicine : Addressing Ethical Challenges".

[312] Nordal, "Privacy".

[313] Kaye et al., "Ethical Implications of the Use of Whole Genome Methods in Medical Research."

[314] Gaskell et al., "Publics and Biobanks: Pan-European Diversity and the Challenge of Responsible Innovation."

[315] Homer et al., "Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays"; Gitschier, "Inferential Genotyping of Y Chromosomes in Latter-Day Saints Founders and Comparison to Utah Samples in the HapMap Project".

are considered personal data[316]. When applied to genomics, data intensive systems like ML (or other AI technologies) thus rely on personal data that require specific protection. Data curators and controllers thus have a duty to secure genomic data.

- **Commercial access to patient data:** Patients, the public and healthcare professionals generally do not support the use of patient data by data-driven technologies *solely* for commercial activities such as direct marketing, which are not perceived to offer patient, system or societal benefit[317].

7.3.3 Security and Democracy

Since they have been developed, in the 1980s, forensic DNA profiling technologies have occupied an increasing place in criminal, security, and mass disaster investigations[318]. Sequencer technology is now being introduced into routine criminal investigations and raises collective discussions about their social impact, especially since they have facilitated the introduction of a wide range of novel social institutions (such as forensic DNA databases and their governing bodies) as well as new stakeholders (such as the commercial providers of DNA hardware, software, and DNA analysis services) in the realm of surveillance and security.

7.3.3.1 DNA technologies in crime management and prosecution

As was shown in D.2.1, advances in forensic DNA profiling and the creation and maintenance of DNA databases contribute to the ever-growing scientific toolbox available to law enforcement in order to detect and convict criminal suspects[319]. DNA databases and DNA-profiling technologies are alleged "*to further enhance the capacity of the police to use genetic information to detect suspects quickly and unequivocally*"[320] with the aim to improve public safety [321].

> "*Acceptance of this argument by legislators and criminal justice agencies has led to a significant increase of biological samples — from crime scenes and individuals — being taken, stored, and used in those jurisdictions permitting the adopting of various kinds of DNA technologies. This increase has been accompanied by a widening of the categories of individuals subject to forensic profiling and analysis, and the expansion of jurisdictions' adoption of DNA technologies globally. A further development under this perspective — fueled by the potential investigatory gains that may result from cross-border exchanges — is the emerging routine sharing of DNA profile data across national*

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[316] GDPR, art 9(1).
[317] Ipsos, "The One-Way Mirror: Public Attitudes to Commercial Access to Health Data".
[318] Williams and Wienroth, "Social and Ethical Aspects of Forensic Genetics: A Critical Review".
[319] Fraser and Williams, *Handbook of Forensic Science*.
[320] Williams and Wienroth, "Social and Ethical Aspects of Forensic Genetics: A Critical Review".
[321] Townley and Ede, *Forensic Practice in Criminal Cases*.

boundaries".[322]

The efficiency and reliability of DNA methods is however questioned since data have proven to be difficult to capture and hard to interpret[323] for well-established technologies, and even more for more recent innovations (such as familial searching, the use of ancestry-informative markers, and those that seek to infer externally visible characteristics from DNA samples)[324].

DNA profiling may also be used to provide expert evidence in support of prosecution or defence cases in criminal trials but determining whether this type of evidence is legitimate is challenging the courts. Pressing issues address the representation of minorities in forensic databases[325] and the use of assumptions about the relationship between genetic and phenotypical characteristics.

7.3.3.2 Genetic surveillance

The expansion of forensic DNA profiling and databases also supports new forms of biological surveillance of citizens, residents, visitors, migrants and minorities[326]. Databases established with the purpose of criminal surveillance or defence against terrorism may indeed serve other purposes and allow governments to track minorities or immigrants.

In a recent case, published in *The New York Times*[327], Chinese authorities have been accused of creating comprehensive DNA databases in order to chase down minorities. The Uighburs, a predominantly Muslim ethnic group, is known to be one of the targets of the Communist Party, who seeks for their servility. Not only are they put in "re-education camps" (condemned by human rights groups), they are also the victims of a "genetic surveillance", thus raising important ethical questions on the global governance of science.

First, under the pretence of criminal surveillance, ministry researchers have worked on ways to sort people by ethnicity by screening their genetic makeup. They took genetic material from Uighurs with no insurance of their informed consent and compared it with DNA from other ethnic groups, from both Chinese databases and publicly available data from the 1000 Genomes Project, a public catalogue of genes from around the world.

Knowing the highly tensed political situation between Uighurs and Chinese authorities, "*this sharing of data could violate scientific norms of informed consent because it is not clear whether the Uighurs volunteered their DNA samples to the Chinese authorities*"[328].

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[322] Williams and Wienroth, "Social and Ethical Aspects of Forensic Genetics: A Critical Review".

[323] Williams and Weetman, "Enacting Forensics in Homicide Investigations".

[324] Williams and Wienroth, "Social and Ethical Aspects of Forensic Genetics: A Critical Review".

[325] M'charek, "Technologies of Population: Forensic DNA Testing Practices and the Making of Differences and Similarities".

[326] Toom, "Bodies of Science and Law : Forensic DNA Profiling , Biological Bodies , and Biopower"; Nelkin and Andrews, "DNA Identification and Surveillance Creep"; Duster, "The Molecular Reinscription of Race: Unanticipated Issues in Biotechnology and Forensic Science".

[327] Wee, "American DNA Expertise Helps Beijing Crack Down".

[328] Ibid.

Considering the role that international databases play in this practice, one could question the ethical implications of having cutting-edge knowledge publicly available, in particular in countries, which do not hold the same ethical standards. Other aspects of this question relate to the fact that international cooperation, which may me linked to the fact that China is one of the most important markets for gene-sequencing technologies and other genomics-supporting equipment, not only allows for such practice but somehow may legitimate it.

In Europe, anthropologists of science Amade M'charek, Katharina Schramm and David Skinner have questioned how DNA databases may be used at a time when the threat of terrorism accentuates security matters, to monitor migrants' circulation within European Union. They show that through a network of distributed technologies of governance that include criminals' DNA databases and migrants' databases, a Muslim identity has created as a "phenotypic other" from the European citizen and in the same time a potential enemy that requires constant monitoring.[329].

7.3.3.3 Focus on military uses of genomics

Ethical discussion of the military uses of genomics was requested by the European Commission after the SIENNA project had already began and without this topic being included in the grant call, nor in the grant agreement. This section is based on an informal literature review and on the results of a session with experts at the Goteborg workshop (p.18) devoted to discussing these aspects.

Genomic applications in the military field are not vastly addressed in the literature and a review of the literature on PubMed and Google Scholar with the key terms "genomics" and "army" OR "military" in the last decade mainly leads to discussions about genomic medicine within the army, ie. mainly how screening for genetic conditions can be provided to soldiers[330]. Although this provision of care may benefit soldiers and their families, it also raises ethical questions in terms of potential employment discrimination and breach of privacy for potential or present soldiers. One could imagine that (potential) soldiers carrying a genetic condition perceived as potentially impeding their ability to commit to their military duty could be excluded, while applicants could be screened and only those carrying gene variants perceived as supporting soldiers' qualities (for instance: capacity for obedience and discipline; aggressiveness and lack of empathy) would be selected. Not only would this genetic profiling be discriminating for individuals, it could also diminish the diversity of recruited soldiers and hinder the mission for peace.

Military use of genomics also refers to the use of genomic knowledge and genetic engineering for biological warfare, which could have serious implications for international peace and security. Any

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[329] M'charek, Schramm, and Skinner, "Topologies of Race: Doing Territory, Population and Identity in Europe".

[330] De Castro and Turner, "Military Genomics: A Perspective on the Successes and Challenges of Genomic Medicine in the Armed Services"; Mehlman and Li, "Ethical, Legal, Social, and Policy Issues in the Use of Genomic Technology by the US Military"; De Castro et al., "Genomic Medicine in the Military".

such misuse of biology is actually prohibited by the 1975 Biological and Toxin Weapons Convention[331] (BTWC). Article I of the Convention states:

> "*Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:*
> 1. *Microbial or other biological agents, or toxins whatever their origin or method of production, of types or in quantities that have no justification for prophylactic, protective or other peaceful purposes.*"

The italicized section, known as '"General Purpose Criterion", does not refer to any particular activity but to the intent of any activity. This prohibition accepted by over 140 States Party still applies today and will apply in the future[332]. There is thus a large scope of scientific activities covered by this prohibition that includes the use of genomic knowledge and genetic engineering. However, States Party could not agree to effective verification procedures, to ensure that they live up to their obligations, especially at the time the BTWC was negotiated (during Cold War)[333]. And non-governmental organizations (NGO) dedicated to upholding prohibitions against biological warfare, like the former Sunshine Project[334], have since then denounced offensive military programs that should be prohibited by the BTWC.

Genomic knowledge and genetic engineering could be used for biological warfare and to enhance[335] soldiers:

i.   Biological Warfare (BW) involving genomics and genetic engineering

BW can be defined as the capacity for armed groups (whether states, terrorist groups or criminal organizations) to deliberately launch outbreaks of disease through the manipulation and distribution of pathogens with the intention of disrupting societies[336]. This definition shows a. that these disease-causing agents do not necessary target human beings but any living organism and b. that they are not necessary lethal but are used in order to provoke general disruption and anxiety. **Biological warfare is particularly threatening because today, "*nearly all countries have the technological potential to produce large amounts of pathogenic microorganisms safely*"[337], which means that**

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[331]https://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument

[332] Fraser and Dando, "Genomics and Future Biological Weapons : The Need for Preventive Action by the Biomedical Community".

[333] British Medical Association, *Biotechnology, Weapons and Humanity*.

[334] http://www.virtualbiosecuritycenter.org/organizations/the-sunshine-project/

[335] The notions of enhanced and enhancement in the context of military uses are to be understood as an increase in performance rather than as a moral progress.

[336] Jansen et al., "Biological Warfare, Bioterrorism, and Biocrime".

[337] van Aken and Hammond, "Genetic Engineering and Biological Weapons. New Technologies, Desires and Threats from Biological Research".

biological weapons pose a technically greater threat since they could be as lethal as nuclear weapons, yet are actually easier to obtain.

As stated by expert in genomics C. Fraser and in peace studies M. Dando, there are several main "advantages" of BW:

> "*(i) they are easy to manufacture (ii) the starting materials, such as bacterial and viral strains and plasmids, can be easily obtained by requesting them from the scientists working with them or from culture repositories and (iii) the ever-expanding microbial genome databases now provide a parts-list of all potential genes involved in pathogenicity and virulence, adhesion and colonization of host cells, immune response evasion and antibiotic resistance from which to pick and choose the most lethal combinations*"[338].

There is a long history of biological warfare[339] but the question here is how recent genomic knowledge – of the biology of pathogens (viruses, bacteria, toxins), of the defence immune system, of infectious disease mechanisms in humans, crops and livestock – and how the new genomic technologies enabling analysing and specifically changing an organism's genetic material may be used to increase the threat of biological warfare.

Genomics can be used in two main ways to support the development of biological warfare:

    a. Lethal weapons targeting human beings

The threat usually associated with the development of "genomic weapon" is one of genetically engineered "superbug" that would be highly lethal and resistant to environmental influence[340]. According to Jan Van Aken and Edward Hammond, involved in the former Sunshine Project[341], this scenario would likely be based on the genetic enhancement of classical pathogens[342]. Although some natural pathogens are already deadly, they may be difficult to acquire and may not fill in the conditions required to be useful in war: being produced in large amounts, acting fast, being treatable or having available vaccines to protect one's own soldiers. A minority of natural lethal pathogens are thus suitable for military purposes[343]. But the development of genetic engineering makes the artificial synthesis of agents and the new combination of agents possible in order to reach these conditions and to "tailor" warfare agents and to make them harder to detect, diagnose and treat.

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[338] Fraser and Dando, "Genomics and Future Biological Weapons : The Need for Preventive Action by the Biomedical Community".

[339] Frischknecht, "The History of Biological Warfare. Human Experimentation, Modern Nightmares and Lone Madmen in the Twentieth Century"; Szinicz, "History of Chemical and Biological Warfare Agents".

[340] van Aken and Hammond, "Genetic Engineering and Biological Weapons. New Technologies, Desires and Threats from Biological Research".

[341] http://www.virtualbiosecuritycenter.org/organizations/the-sunshine-project/

[342] van Aken and Hammond, "Genetic Engineering and Biological Weapons. New Technologies, Desires and Threats from Biological Research".

[343] Ibid.

"This danger was highlighted last year by a worrying article in Science: a research team at the State University of New York in Stony Brook chemically synthesized an artificial polio virus from scratch[344]. They started with the genetic sequence of the agent, which is available online, ordered small, tailor-made DNA sequences and combined them to reconstruct the complete viral genome. In a final step, the synthesized DNA was brought to life by adding a chemical cocktail that initiated the production of a living, pathogenic virus. (…) In principle, this method could be used to synthesize other viruses with similarly short DNA sequences. This includes at least five viruses that are considered to be potential BW agents, among them Ebola virus, Marburg virus and Venezuelan equine encephalitis virus."[345]

The enhancement of existing pathogens for warfare purposes could also be used to target particular groups and for 'stealth' viruses that could be introduced covertly into the genomes of a given population and then triggered later by a signal[346]. This threat was for instance one of the main reasons for some ethnic groups to refuse to participate to the Human Genome Diversity Project[347], so that the genetic variants that are most common within their populations would not be known and potentially targeted again. This is still today one of most pressing ethical issues in researching population genetics[348].

Although these manoeuvres relying on the ability to tag the genome of a given population would be especially dangerous, there are two main reasons to doubt of their feasibility: firstly, although genetic susceptibility to infectious diseases has been described, the human genetic sequence is not the only determinant for disease susceptibility and secondly, research in population genetics has not revealed any polymorphism that could be used to absolutely define an ethnic group[349].

b. Non-lethal weapons targeting material, staple crops and livestock.

Although there is a global norm against biological weapons, "the moral barrier" seems to be lower for 'non- lethal' weapons targeting materials, livestock and plants[350]. According to militants from the

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[344] Cello, Paul, and Wimmer, "Chemical Synthesis of Poliovirus CDNA: Generation of Infectious Virus in the Absence of Natural Template".

[345] van Aken and Hammond, "Genetic Engineering and Biological Weapons. New Technologies, Desires and Threats from Biological Research".

[346] Fraser and Dando, "Genomics and Future Biological Weapons : The Need for Preventive Action by the Biomedical Community".

[347] Dodson, Williamson, and South, "Indigenous Peoples and the Morality of the Human Genome Diversity Project".

[348] Ilkilic and Paul, "Ethical Aspects of Genome Diversity Research: Genome Research into Cultural Diversity or Cultural Diversity in Genome Research?"

[349] Fraser and Dando, "Genomics and Future Biological Weapons : The Need for Preventive Action by the Biomedical Community".

[350] van Aken and Hammond, "Genetic Engineering and Biological Weapons. New Technologies, Desires and Threats from Biological Research".

Sunshine project, the US military for instance has worked on various uses of biotechnology for warfare scenarios, which would weaken their enemy while avoiding civilian victims, among which material-degrading microorganisms to destroy fuel, constructional material or stealth paints and genetically engineered fungi that would degrade a variety of materials, such as plastics, rubber and metals[351].

Genetic engineering would be used to make these organisms more powerful and focused. Limited genomic variation in staple crops and livestock would also make agriculture a vulnerable target for biological attack[352].

ii.   Enhanced Soldiers

Genomic technologies and in particular genome editing could be used to enhance soldiers by genetically engineering the gene variants that may be more useful for soldiers: those susceptible to reinforce the sense of obedience, authority and discipline; those susceptible to support athletic capacities, sensory acuity, resistance to pain and discomfort; those susceptible to enhance aggressive behaviours and to ponder empathy. Although this scenario is far from our scientific ability at the moment, the threat of genetically engineered super-soldiers through gene editing techniques is one of the reasons advanced for closely monitoring this research field and its applications. One of the CRISPR pioneers, Jennifer Doudna wrote herself that she was afraid of the military implications and feared gene editing could come to the world's attention, as atomic power did, in a mushroom cloud[353].

One should consider how genomics could be used to set up countermeasures against biological warfare development:
- through the development of more rapid methods for detecting biological agents
- through the development of new vaccines benefitting from the availability of pathogen genome sequence information
- through a better understanding of infectious mechanisms and defence systems, design of new antibiotics and anti-microbial compounds

7.3.4   Infrastructures

Herein we address how genomics could be used in general infrastructures such as home, hospitals and cities and the related ethical issues one could envision from these. Indeed, this is one of the areas that, to date, has barely, if at all, been addressed in the literature, so the discussion remains general.

i.   Health smart homes and hospitals

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[351] Ibid.

[352] Fraser and Dando, "Genomics and Future Biological Weapons : The Need for Preventive Action by the Biomedical Community".

[353] Doudna and Sternberg, *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*.

Health smart homes and smart hospitals are infrastructures integrating smart health design and can be defined as follows:

- Health "Smart" homes provide health care services for people with special needs who wish to remain independent and living in their own home. The large diversity of needs in a home-based patient population requires complex technology.
- Smart Hospital are highly interactive environment saturated with ubiquitous interconnected devices in charge of collecting and analysing patient data.

"Smart health"[354] typically integrates advancements in ubiquitous computing applications with the use of a sophisticated intelligent sensor (e.g., temperature, heart rate, blood pressure, blood and urine chemical levels, breathing rate and volume, activity levels etc.) to monitor, predict and improve patients' physical and mental conditions. "Smart health" can thus be considered a high-tech medicine that relies "big data" and aligns with the goals of P4-medicine (preventive, participatory, predictive, and personalized)[355].

In this project, omics-data (including data from genomics, epigenomics, meta-genomics, proteomics, metabolomics, transcriptomics, epigenetics, microbiomics, fluxomics, phenomics[356]) are required to refine diagnosis and support personalized decision for healthcare professionals through big data analytics[357].

However recent advances in -omics along with web technologies have led to a dramatic increase in the amount of available complex data sets which challenge not only our ability to make sense of them but also our capacity to regulate their circulation and ultimately protect them[358]. This is particularly important in "smart" homes (or "smart" hospitals), where objects create a social network autonomously, with minimal or no human intervention. Imposing rules to protect user privacy becomes them crucial through data access control mechanisms and data management policies[359].

ii.   Surveillance technologies in "smart cities".

A "smart" city uses different types of electronic sensors to collect data and the use these data to manage assets efficiently. For surveillance purposes, DNA and biometric scanning technologies may be integrated in "smart" cities for intimate monitoring and "classifying of individuals into the spaces

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[354] Chen, Compton, and Hsiao, *Smart Health*.
[355] Hood and Galas, "P4 Medicine : Personalized , Predictive , Preventive , Participatory A Change of View That Changes Everything".
[356] Chen, Compton, and Hsiao, *Smart Health*.
[357] Streeter Jr., Beron, and Iyer, "Precision Medicine: Genomic Profiles to Individualize Therapy".
[358] Femminella et al., "Networking Issues Related to Delivering and Processing Genomic Big Data".
[359] Porambage et al., "The Quest for Privacy in the Internet of Things".

and times where they 'belong'"[360]. Coupled to national and commercial DNA databases, these technologies would underpin surveillance systems and be of used for tracking criminals or migrants. They would also bear a serious threat to the liberty of movement, which is one of the fundamental human rights.

7.3.5   (Commercialization of) companionship

In this section, we review ethical issues related to less common areas of ELSI studies. We analyse two seemingly mundane uses of direct-to-consumer genomic services that highlight how genomics invades everyday life. Although these may not appear as sensitive questions as those raised in research setting, in clinical practice or in relation with surveillance, they also entail ELSI, plus they question the ever-growing attributed legitimacy of genomics in our everyday decisions and provide interesting illustrations of the geneticization of our societies.

7.3.5.1. Direct to Consumer: genomics-based dating apps

Genetic matchmaking refers to the idea of matching couples for romantic relationships based on their biological compatibility. It is based on a hypothetical correlation between attraction and genes of the major histocompatibility complex (MHC), which code for proteins on the surface of cells that help the immune system recognize invaders, that was first developed in a 1976 study showing that mice tended to select female mice with dissimilar MHC genes[361]. The mice supposedly detected this DNA diversity through scent. Researchers' hypothesis for this selection ranges from the prevention of inbreeding to promoting offspring with greater diversity of dominant and recessive genes[362].

This assumption was tested on humans in 1995 through the famous "sweaty T-shirt" study, which showed that women sniffing the sweaty garments recently worn by males favoured the scent of those whose immune response genes were different from their own [363]. This first study has been followed by other scientific work looking for human pheromones but most research on the topic is subject to major design flaws: "*common problems include small sample sizes, an overestimate of effect size (as no effect can be expected), positive publication bias and lack of replication*" [364].

Despite the controversial science behind human sex scents, several companies are offering genetic matchmaking services: DNA Romance[365], GenePartner[366], Instant Chemistry[367], Pheramor[368]…

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[360] Graham, "Spaces of Surveillant Simulation: New Technologies, Digital Representations, and Material Geographies".

[361] Yamazaki et al., "Control of Mating Preferences in Mice by Genes in the Major Histocompatibility Complex".

[362] Ipsos, "The One-Way Mirror: Public Attitudes to Commercial Access to Health Data".

[363] Wyatt, "The Search for Human Pheromones: The Lost Decades and the Necessity of Returning to First Principles".

[364] Mansky, "The Dubious Science of Genetics-Based Dating. Is Love Really Just a Cheek Swab Away?"

[365] https://www.dnaromance.com/ (Consulted on 03.07.2019)

[366] https://www.genepartner.com/ (Consulted on 03.07.2019)

[367] https://instantchemistry.com/ (Consulted on 03.07.2019)

[368] https://www.pheramor.com/ (Consulted on 03.07.2019)

These are internet mediated platforms that look to genetics to test the compatibility among current partners or "dating apps", i.e. mobile phone application where a person can add their profile to connect with other people and arrange a date in the perspective of being in a relationship with this person.

Pheramor belongs to the latter category and provides an example as to how this market works. For $15.99, its members receive a saliva DNA test kit, which they then send back for sequencing. Pheramor analyses the spit to identify 11 genes that relate to the immune system. The company then matches this new member with people who are suitably genetically diverse. It is worth noticing though that Pheramor, like other companies, does not just look at genetic diversity. Metadata from other social media footprint are pulled to identify common interests and as members swipe through the app, each profile includes compatibility estimations based on an algorithm that takes into account both genetic differences and shared common interests.

Although the market of genetics-based dating is not health-related, it thus raises various ethical concerns already highlighted in existing DTC genetic testing:

i. Potentially misleading advertising

As is common for genetic research related to complex human behaviours (such as attraction, love, romance and long-term relationship), the data supporting genetic attraction is highly inconsistent. A scientific review of the literature about the influence of MHC on the choice of mate in humans concludes that "*the mixed evidence … makes it difficult to draw definitive conclusions, [even though] the large number of studies showing some MHC involvement suggests there is a real phenomenon that needs further work to elucidate*" [369]. The research to date thus does not support quantifying the impact of genetic attraction, while "*SingldOut claims that genetic tests can identify up to 40 percent of the chemistry of attraction between two people*" [370].

ii. Terms of Service agreement vs. Informed consent

As commercial companies, providers of DTC commonly make use of Terms of Service agreements rather than informed consent procedures. However, to protect consumers from the potential harms associated with personal genome testing and to promote autonomous decision-making with regard to the testing offer, current practices of information provision are insufficient. A procedure of informed consent should be proposed to meet both the norm of providing sufficient information and the norm of providing understandable information so as to allow customers to know the limitations, risks and implications of personal genome testing and to give them control over the genetic information.

iii. Privacy and confidentiality:

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[369] Marchant and Stevens, "I Love Your Genes! Online Dating Sites Use DNA to Make Perfect Matches. Does It Really Work?"
[370] Yamazaki et al., "Control of Mating Preferences in Mice by Genes in the Major Histocompatibility Complex".

Purchasing genetic testing services in an online commercial marketplace raises significant privacy concerns, as consumers may turn over their DNA and other personally identifiable information to companies without a clear understanding of the privacy risks and without clear guidance as to their legal and regulatory rights in this area.

- **Sensitivity of genetic information:** Warnings and overall information given by DTC companies may be misleading about the risks associated with analysis and storage of genetic information. For instance, the website of Pheramor emphasizes that: "*the ONLY portion of your DNA that is sequenced by Pheramor is called your HLA genes. These only tell us about who you will be attracted to. From our DNA test we do not know your gender, race, hair colour, height, etc.*". But HLA genes analysis may result in much more information than just attraction-related data, including health information and identifying information. Because an individual's genetic information is so personal and specific, it is vital to protect it from any unwarranted access or use. Whenever DNA samples are collected and stored, there is a risk that violations of genetic privacy may follow.

- **Lack of governance:** The methodology by which this information is secured is essential (measures to protect information and biological samples from unauthorized access, use, disclosure, alteration or destruction), yet without standards and oversight there is no assurance that the requirement to protect privacy is giver proper consideration. At present, there are still no clear guidelines with respect to the protection of customer privacy by the direct-to-consumer genetic testing industry. Consent forms and privacy policies vary widely within the industry and without standards can be unclear and often subject to change. Safeguards should include physical, technical and administrative measures to protect information and biological samples from unauthorized access, use, disclosure, alteration or destruction.

- **Ramification of personal and potentially sensitive information:** As shown with the example of Pheramor, customers, when using these apps, allow search engines to look for different kinds of personal data and compile them into a "matching algorithm". Customers are also often not limited to providing a DNA sample but are also offered a variety of surveys, blogs and other tools where they can provide personally identifiable information. The provision of different kinds of personal data, their storage and possible ramification, compilation or triangulation threatens the privacy of customers.

- **Lack of control on DNA submitted by customers:** Considering how simple surreptitious collection of individual DNA can be, it is not hard to imagine how political, social and personal motivations could compel an individual to submit DNA samples from someone else. At present, commercial personal genomics companies do require customers to confirm they have the legal authority to submit DNA samples. Yet, few controls are offered beyond such statements to ensure that customers are actually complying with this requirement. No offer of proof is requested beyond the statement.

iv.   **Commercialization and Research uses and of genomic data**

- **Ownership and Third Party Disclosure of Customer Data:** One significant unresolved issue relating to the DTC industry is exactly who owns the customer's data. Most DTC companies do not explicitly address this issue in their privacy policies. If the DNA sample and other information submitted by the customer are the property of the company, the company is free to sell or otherwise transfer that information to a third party. Many DTC companies have adopted this approach as part of their business model without sufficiently explaining to customers the extent to which this may occur, what type of data is being transferred and the potential negative consequences.

- **Research uses:** DTC tend to blur the lines between the commercial service they provide and their research activities. Some even advertise their connexion to research, making the ability to contribute to contribute to research an ulterior benefit for customers. In a company like Pheramor for instance, there is an obvious link between individual purchase and altruism (possibility to participate to donor registries or contribute to research) and even activism (against hetero-normativity):
    * With their app, users are indeed given the option to register as potential bone marrow donor[371].
    * Although the research on genetic-based matching has mainly focused on heterosexual couples, Pheramor is open to all sexual preferences. Although this could be advanced as an argument to discuss the algorithm of compatibility for people identifying as LGBTQ and radically question the relevance of those apps for non-heterosexual couples, the lack of data from this community is turned into an opportunity to contribute to research and more precisely, to contribute to sexual orientation diversity on the subject in an otherwise hetero-normative field of research [372].

In this example, it is obvious that DNA provided for a commercial transaction will be used along with other personal information (e.g. sexual orientation) for research purposes. But customers are transformed into research participants without further notice as to who will carry research, for how long their DNA and associated data will be used and for which specific purpose, if there is an option to opt-out and destroy their samples, what would happen in case of secondary findings and for how long their biological material and associated data will be kept.

v.   Geneticisation and genetic determinism

The invasion of genomic arguments in everyday life and mundane decisions questions how such practices will interact with notions of genetic determinism and how they will make us perceive the

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[371] See Pheramor website: https://www.pheramor.com/activism. Consulted on 03.09. 2019.
[372] Niemiec, Kalokairinou, and Howard, "Current Ethical and Legal Issues in Health-Related Direct-to-Consumer Genetic Testing".

place of non-genetic factors. In this sense, one can also question how this affects people with disabilities, ethnic minorities, issues of stigmatisation, etc.

Although they seem trivial and dedicated to entertaining purposes only, companies that offer direct-to-consumer genetic testing service to help determine compatibility in intimate relationships are yet other contributors to an already complex data environment where genetic information, among other types of personal data, are traveling without a clear sense of ownership, responsibilities and implications.

7.3.5.2. Pets' genomics

Pets can be defined as domestic animals procured for companionship and pleasure. In Western countries, pets are mainly cats and dogs. So far, the development of pets' genomics has led to the publication in 2007 of an initial draft of the genome of an Abyssian cat, as an achievement of the Cat Genome Project [373] and to a global effort on genome sequencing in dogs (see for example the NHGRI Dog Genome Project[374] and the Dog 10k Genome project[375]).

Pets' genomics has several purposes:

- exploring the evolutionary history of cats and dogs, so as to better understand the genotype to phenotype relationship, the genetic changes associated with domestication, the phylogeny of mammals in general;

- investigating loci involved in feline and canine susceptibility to disease, particularly among certain breeds, in veterinary genomics research and clinic [376]

- contributing to both the veterinary and human medicine, especially concerning cancer research, since the canine disease genes are often the same or related to ones causing disease in humans [377]

- monitoring surveillance of veterinary infectious agents for both animal and human health: hazard-specific surveillance (pathogen identification and typing) and early-warning surveillance (pathogen discovery) [378]

- developing cat and dog genetic fingerprinting for use in forensics, since hair from domestic animals found on the site of criminal scenes can provide a source of transfer evidence for criminal investigations [379];

- understanding natural variation of morphological traits in cat and dog populations (e.g. skull shape, body size, leg length, and fur length, colour and curl) for breeding purposes;

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[373] Caulfield et al., "Harm, Hype and Evidence: ELSI Research and Policy Guidance".

[374] https://research.nhgri.nih.gov/dog_genome/

[375] http://www.dog10kgenomes.org/

[376] Evans et al., "Deflating the Genomic Bubble".

[377] Stark et al., "Integrating Genomics into Healthcare: A Global Responsibility".

[378] Mathew et al., "Inclusion of Diverse Populations in Genomic Research and Health Services: Genomix Workshop Report".

[379] Møller and Hovig, "Our Genes, Our Selves: Hereditary Breast Cancer and Biological Citizenship in Norway".

-    confirming identity and parentage of pets, to validate their registries;

-    organising genotype disclosure among breeding companies to practice genomic enhancement of animal selection using SNP markers while avoiding inbreeding, co-ancestry and emergence of recessive disorders [380].

The applications of pets' genomics thus concern pet owners, vets and breeders but also society at large considering that pet's genomics may provide useful resources for research on human health and forensics.

Pets' genomics, and in particular pet's genetic testing, is also a growing part of an already global industry devoted to pets and estimated to be about $109 billion per year [381]. There are today 19 laboratories worldwide providing tests for more than 100 different diseases (including cancer, heart disease, diabetes and epilepsy) with a soon to come option for whole genome sequencing and even gene editing for pets [382]. **These offers, of course, question our priorities when, according to UNICEF, 22,000 children under five are dying each day, mostly from causes preventable with low-cost, and proven interventions**. But, independently of these general remarks on global justice and interspecies relationships, the market of pet genomic testing itself raises concerns, due to the absence of specific regulation. As for any market, there is a need to pay attention to potential conflict of interest since a genomic database used for breeding for instance could also be used to notify pet owners when specific pet foods (made by the same company), screening tests (performed by the company's clinical lab) or exams (performed at the company's vet clinics) in general could become available without assessed validity or utility. Considering the specificity of genomics and its use for diagnostics, there is also a need to create an ad-hoc governance, since regulatory mechanisms for pets have so far focused on research and treatments but not diagnostics. Neither the US Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) has stated on quality standards for pets' genomics[383].

We have learnt from human genomics, that candidate gene studies do not provide enough evidence to designate a genetic variant as "disease causing" [384] and that validation of genomic testing is a cumbersome scientific process [385]. As an example of a response to these challenges, every clinical variant (i.e. genetic variants linked to medical phenotype) is now scored from 'pathogenic' to 'benign' on a five-point scale, collaboratively defined by representatives of industry, academia,

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[380] Solbrække et al., "Our Genes, Our Selves: Hereditary Breast Cancer and Biological Citizenship in Norway".

[381] Gripsrud and Solbrække, "Scientific Supremacy as an Obstacle to Establishing and Sustaining Interdisciplinary Dialogue across Knowledge Paradigms in Health Medicine".

[382] Weerts and Freed, "Public Engagement and Organizational. Identity in US Higher Education".

[383] Wilsdon and Willis, *See-through Science: Why Public Engagement Needs to Move Upstream*.

[384] Schot and Rip, "The Past and Future of Constructive Technology Assessment".

[385] Barben et al., "The Handbook of Science and Technology Studies".

physicians and patients [386]. But many of the pet's genomic tests are based on only a single small candidate-gene study and have not been reassessed so carefully.

In absence of serious regulation, companies may sell products providing inaccurate information and that could be potentially misleading. In such situation, not only would pets and their owners be exposed to needless suffering, their disappointing experience may also feed societal distrust in genomics in general, (veterinary) medicine and science. Moreover, opportunities would be lost not only to improve pet health, improve publics' knowledge of genetics and genomics but also to leverage studies in dogs and cats that benefit human health.

Through this example, we show how genetics in non-human animals may also have an important impact on publics' with respect to genetics and genomics and such examples should also be considered when studying novel technologies in genomics, since they stand to be much more accessible to larger audiences.

7.4 Genome editing

7.4.1 Introduction

In deliverable 2.1 "State of the art review", we explained types of genome modification approaches (gene/genome editing, mitochondrial replacement, and gene therapy using viruses as vectors to deliver DNA; please see deliverable 2.1 and the glossary of this report for explanations). We then focused on gene editing (also called genome editing; GE) technology and described basic technical aspects and applications of this technology. Herein, due to time and space constrains, we will focus, as in in the 2.1 deliverable, on gene editing, which currently seems to raise the most profound and contentious ethical issues, many of which overlap with issues related to the other genome modification approaches. We focus herein in particular on approaches that would use tools like CRISPR-Cas9 to achieve the desired editing. Such a tool allows for faster, more precise, efficient and cheaper modifications of DNA than many of the previous approaches (see 2.1 deliverable for details). We refer the reader to 2.1 deliverable, which provides explanation of how the technology works and broadens the context of the reflection on ethical aspects presented below.

There are two main types of applications of GE, that is, germline and somatic. Germline gene editing (GLGE) is performed on germline cells such as oocytes and sperm, (that is, cells whose genetic material will be passed on to next generation) as well as on embryos. Therefore, changes introduced by GLGE can be passed on to future generations (children of persons who would undergo GLGE). Somatic refers to any other type of cells whose genetic material will not be passed on to next generation such as skin cells, blood cells, cells of internal organs etc. Ethical, legal and social problems relevant to somatic GE overlap with issues related to other types of gene therapy and include, among others, questions such as: will all persons have access to this therapy? Are current

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[386] Guston and Sarewitz, "Real-Time Technology Assessment".

process of marketing approval is adequate for somatic GE therapies? What risks are acceptable in the context of somatic GE? Which healthcare professionals will be responsible for provision of this therapy? How can we ascertain and manage any risk of unintended editing of germline cells (when applying somatic GE)? .

In this section, we focus mainly on GLGE applications since they raise arguably more profound and contentious ethical problems than somatic GE. Importantly, as we note below, some problems discussed herein are relevant to both contexts of somatic and GLGE (e.g. issues related to whole genome sequencing conducted within GE studies). We briefly also tackle issues related to uses of GE in gene drive approach on animals in the context of security. The issues related to infrastructure do not seem to be relevant to GE at this time. We refer the reader to deliverable 2.1 for the ethical concerns of commercialization and do-it-yourself uses of GE, or alternatively to section 7.3 where these have been addressed for genomic testing and are similar in nature..

In the sections below we firstly summarise the main uses of the technology (in research, in the clinic and for security purposes) and then discuss related ethical issues.

7.4.2 Summary of GE applications to date

7.4.2.1 Research on GLGE

To date, at least six instances of using GE technology in human embryos in the research context (that is, where embryos have not been used to establish pregnancy) have been reported in the academic literature (Table 10). The first study involving GLGE aimed to modify β-globin gene (which if mutated causes β-thalassemia)[387]. In three other studies, the researchers attempted to correct disease-causing gene variants[388]. In the experiment of Kang et al. (2016)[389] an allele increasing resistance to HIV was introduced. Fogarty et al. used CRISPR-Cas9 to investigate the function of a gene in embryogenesis[390].

7.4.2.2 Clinical GLGE

In November 2018 at the Human Gene Editing Summit in Hong Kong, He Jiankui, a Chinese scientist, presented an experiment in which he edited the genomes of embryos which were subsequently implanted to establish a pregnancy and which resulted in the birth of twins called Lulu and Nana[391].

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[387] Liang et al., "CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes".

[388] Liang et al., "Correction of β-Thalassemia Mutant by Base Editor in Human Embryos"; Ma et al., "Correction of a Pathogenic Gene Mutation in Human Embryos."; Tang et al., "CRISPR/Cas9-Mediated Gene Editing in Human Zygotes Using Cas9 Protein".

[389] Kang et al., "Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR / Cas-Mediated Genome Editing".

[390] Fogarty et al., "Genome Editing Reveals a Role for OCT4 in Human Embryogenesis".

[391] Krimsky, "Breaking the Germline Barrier in a Moral Vacuum".

The goal of the experiment was to edit gene *CCR5* to increase resistance to HIV in children who were conceived with sperm of a man who was HIV-positive. He Jiankui announced that the on-target and intended modification of *CCR5* was achieved, which was confirmed in genomic sequencing after birth. Moreover, He noted that there were no off-target effects (unintended modifications in the genome). Although the scientist explained that he submitted a manuscript to a journal describing this case, no article has been published to date, and it is yet to be confirmed whether He's claims are completely true[392].

Currently, GLGE is illegal in many countries and the majority of scientific community considers any attempts to apply GLGE in clinic as premature[393]. In March this year eighteen researchers from seven countries called for moratorium on GLGE[394]. We discuss ethical issues related to the first clinical application of GLGE in the section below.

[392] Ibid.
[393] Brokowski, "Do CRISPR Germline Ethics Statements Cut It?"; Lander et al., "Adopt a Moratorium on Heritable Genome Editing".
[394] Lander et al., "Adopt a Moratorium on Heritable Genome Editing".

	Year	Authors	Title	Aim	Embryos used
Clinic	2018	He Jiankui (unpublished, presented at the International Summit on Human Gene Editing, Hong Kong, 2018)	Developing a CCR5-targeted gene editing strategy for embryos using CRISPR/Cas9	Modification of CCR5 gene to increase resistance to HIV infections	Embryos created with sperm of men who contracted AIDS. Two embryos were implemented to establish pregnancy which resulted in two babies born, as claimed by the scientist.
Research	2017	Ma et al.	Correction of a pathogenic gene mutation in human embryos	Correction of a mutation that causes hypertrophic cardiomyopathy	Viable embryos created for the purpose of the research (over 100 embryos were created)
	2017	Tang et al.	CRISPR/Cas9-Mediated Gene Editing in Human Zygotes Using Cas9 Protein	Correction of a mutation in *HBB* gene causing β-thalassemia and a mutation in *G6PD* gene related to a common enzyme deficiency	Viable embryos created using surplus oocytes and sperm from patients undergoing IVF and non-viable tripronuclear embryos
	2017	Liang et al.	Correction of β-thalassemia mutant by base editor in human embryos	Correction of a mutation in the *HBB* gene which causes β-thalassemia	Non-viable embryos obtained in parthenogenesis
	2017	Fogarty et al.	Genome editing reveals a role for OCT4 in human embryogenesis	Study of the function of the pluripotency transcription factor OCT4 during embryogenesis	Viable surplus embryos created in clinical IVF procedures
	2016	Kang et al.	Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-Mediated Genome Editing.	Introduction of an allele of the gene CCR5 associated with a resistance or slower progression of HIV infections	Non-viable tripronuclear embryos
	2015	Liang et al.	CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes	Modification of *HBB* gene, which when mutated causes β-thalassemia	Non-viable tripronuclear embryos

Table 10: List of studies using gene editing in embryos

7.4.2.3 Somatic GE: research and clinical applications

As of 2017 there were at least seventeen clinical trials in which GE approaches were used; among these four trials involved CRISPR-Cas9 approach. The diseases targeted in these trials include cancers (e.g. bladder cancers, renal cell carcinoma), HIV, and haemophilia, among others[395].Somatic GE is also used in drug discovery research and recently has been developed for diagnostic purposes since CRISPR-Cas9 proteins have ability to precisely recognize genetic sequences. Such CRISPR-based diagnostic tools could be used to detect, for example, oncogenic mutations that occur in cancer development or nucleic acid of viruses to diagnose an infection[396].

7.4.2.4 CRISPR-based gene drives in animals and security issues

The background of genomic technologies uses for military purposes is presented in the section 7.3.3. Genomic modifications, in particular GE, can potentially be used to create biological warfare or to affect in another negative way a given population as already outlined in 7.3.3.3. section. In addition, CRISPR-Cas9 has recently been used along with gene-drive approaches, which change the inheritance pattern of a given gene, and allow for very rapid spread of the introduced variant. Gene-drive technologies used to spread particular variants (e.g. a variant conferring infertility) have the potential to lead to the extinction of a population as was shown in laboratory conditions for mosquitos that carry malaria[397]. Such an approach has the potential to limit the spread of malaria, however, it raises very serious issues regarding among others, the downstream effects of wiping out entire populations of insects in the ecosystem (see section below). Potential military uses of gene drives have been discussed; the fact that the US Military's Defence Advanced Research Project Agency is the main funder of gene drive research indicates that potential military uses of gene drive technology are seriously being considered[398].

7.4.3 Ethical aspects of human GLGE research and clinical applications

In the deliverable 2.1, in the context of social impacts (which have also ethical dimension), we discussed the following concerns pertaining to research and clinical applications of GLGE; we develop these topics further in the sections below:

7.4.3.1   Scientific uncertainties of GLGE

7.4.3.2   Potential negative impact on societies: justice and potential social disparities

7.4.3.3   Instrumentalization of embryos in GLGE

7.4.3.4   Impact on persons with disabilities

We discuss also ethical issues which were not addressed in the deliverable 2.1. Below we reflect on:

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[395] Shim et al., "Therapeutic Gene Editing: Delivery and Regulatory Perspectives".

[396] Foss, Hochstrasser, and Wilson, "Clinical Applications of CRISPR-Based Genome Editing and Diagnostics".

[397] Kyrou et al., "A CRISPR-Cas9 Gene Drive Targeting Doublesex Causes Complete Population Suppression in Caged Anopheles Gambiae Mosquitoes".

[398] African Centre for Biodiversity, ETC Group, and Third World Network, *Synthetic Gene Drives – Genetic Engineering Gone Wild. Briefing for CBD Delegates*.

7.4.3.1 Scientific uncertainties of GLGE entail ethical aspects

<u>What we don't know about safety</u>

Currently GE still suffers from a lot of technical and safety-related uncertainties; such techno-scientific matters are intimately related to ethical dimensions, since they are ultimately included in a cost-benefit calculation of using an approach or not. These uncertainties include off-target events (alterations in the DNA at sites other than the desired site), mosaicism (not all cells of the organism having the desired alteration) and unknown epigenetic effects (alterations to the system surrounding the DNA but not to the actual DNA sequence). Basically, each of these technical issues may result in unanticipated effects or consequences for the person in which GLGE would be performed. From American recommendations, Ormond et al. (2017) highlight that*: "the magnitude of the potential risks of off-target or unintended consequences are yet to be determined.*"[399] They go on to explicitly state:

> "*(m)oving with less haste also limits reliance on early and often inadequate models of cause and effect in our understanding of genetic inheritance and could mitigate the impact of decisions based on unsubstantiated notions of genetic determinism.*" [400]

Moreover, we are still mostly in the dark about gene-gene interactions, and gene-environmental interactions that may result from GLGE, as well as other "unknowns"/struggles that we need to overcome before we could even envisage the responsible application of GLGE in the clinic.

The notion of criteria for "safe-enough" for use in the clinic is very appealing yet there are currently no reliable foundations to answer such a question robustly. What would these criteria be based on, and who would decide? Such questions highlight the labyrinthine nature of a problem that is not just a scientific issue, but also an ethical and political matter. Indeed, the European Group on Ethics in Science and New Technologies suggests that:

> "*the question of whether, if ever, germline engineering of human embryos would be precise enough to guarantee a successful outcome (…) is still an open one.*" [401]

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[399] Ormond et al., "Human Germline Genome Editing".

[400] Ibid.

[401] European Group on Ethics in Science and New Technologies (EGE), "European Group on Ethics in Science and New Technologies (EGE) Statement on Gene Editing".

Uncertainties for the first children born with GLGE, their future generation, and society as a whole

A very important point to realise is that the safety evaluation of the technique if applied in clinical settings would likely need to include life-long monitoring of any child born with GLGE. The ethics group of the European Society of Human Genetics addresses some of the difficulties in this context including questions of children's and their families' privacy and the need for funding for such long-term follow-up[402]. Highly contentious issues regarding consent (of the parents and/or of the child) also exist: can parents decide for a child that s/he will be a life-long research participant? Even if children are given the chance to "re-consent" (or not) at the age of majority, could this step really be done freely given all that rides on the participation? Without doubt the autonomy of the prospective child born with GLGE may be challenged if life-long monitoring was mandatory. Other authors go as far as suggesting that GLGE is not acceptable "*because the results of such studies could not be evaluated effectively in an acceptable timeframe.*"[403] Indeed, the issues surrounding scientific safety and potential harms go beyond the individual who would undergo GLGE, and include also his/her descendants and potentially a society as a whole. Friedmann et al. further specify the related problems:

> "*Because research subjects would include not only embryos but also future generations, the difficulties of long-term follow-up raise ethical, practical, and scientific hurdles. The requirement that the results of an experiment be susceptible to analysis and characterization before further applications are undertaken cannot be met with human germ-line modification with current methods, because the results of any such manipulation could not be analyzed or understood for decades or generations—a situation incompatible with ethical imperatives and with the scientific method.*"[404]

Reduced Genetic Diversity
The potential problem of reduction of genetic diversity (e.g. the possibility that human genetic diversity decreases if GLGE is used) is raised by the Nuffield Council[405]. The underlying problem being that if human genetic diversity is reduced (i.e. we have less different variants for each trait, like skin colour), it could leave humans less capable of adapting to changing environmental conditions (e.g. more intense sun light). This could result in humans being less 'fit' (in the Darwinian sense) to

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[402] Wert et al., "Responsible Innovation in Human Germline Gene Editing . Background Document to the Recommendations of ESHG and ESHRE †‡".
[403] NHS Science and Technology Committee, "Genomics and Genome Editing in the NHS - Science and Technology Committee - House of Commons".
[404] Friedmann et al., "ASGCT and JSGT Joint Position Statement on Human Genomic Editing".
[405] Nuffield Council on Bioethics, *Genome Editing and Human Reproduction*.

survive. While such a situation of reduced variation and fitness, if even possible, would not be noticeable before many decades will pass, it does expose once again the magnitude of uncertainties raised by GLGE as well as the fact that they could manifest in very concrete ways only much later on for future generations. This then raises the question of what are today's stakeholders' responsibilities towards future generations?

7.4.3.2 Potential negative impact on societies: justice and potential social disparities
Equal Access to technology?

While the worry that not all persons will have equal access to certain expensive approaches or technologies is certainly not specific to GLGE (should it ever come to be used in the clinic), it remains, nonetheless, a very important factor when weighing the pros and cons of potentially allowing its use beyond research. Indeed, it would be a poor use of public resources to try to push a technology to the clinic (with all the resources this entails) and then have that technology only be affordable to a small privileged minority. The costs of performing GLGE (or somatic GE) are expected to be considerable and the worry is that only the rich (countries and/or persons) will have access to the therapy/treatment/cure and thus creating different classes of groups in society with respect to health care: those who can afford to pay to access GLGE and those who cannot.

Not all created equal?
Another concern relates to the possibility that the "creation" of "genome edited" persons leads to a new system of castes, where some groups will be the "creators", others the "created" in a "lab" via GLGE, and then a group who are neither of these. Different stigmas and discriminations based on a hierarchy could result for all three groups, the full detail of which we cannot address herein. However, it is easy to conceive how these differences could be used for gain of some of the groups at the expense of the others.

7.4.3.3 Instrumentalization of embryos in GLGE
The other issue pertains to use of embryos in GLGE both in research and the clinic, which in the procedure of GLGE are destroyed. Again, this is not specific to gene editing, and embryo research is conducted for other purposes, but given the very high number of experiments that would be needed to address all the questions (of safety for example) of GLGE, this is certainly a very important aspect. In the research context all embryos have to be destroyed according to the fourteen day rule (which is encoded in law or recommended by guidelines in many countries)[406], which states that embryos used in research have to be discarded two weeks after fertilization. Clinical GLGE on embryos would have to take place in the context of *in vitro* fertilization (IVF), whereby in order to increase the efficacy of the procedure, more embryos are created than are then implanted in uterus to establish pregnancy.

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[406] Hyun, Wilkerson, and Johnston, "Embryology Policy: Revisit the 14-Day Rule".

Pacholczyk, when discussing IVF stated: "*It (IVF) dehumanizes embryonic children, treating them as objects to be frozen, manipulated, abandoned or de-stroyed*"[407]. Indeed an embryo is human life at the earliest and most vulnerable stage of its development.

The issue of instrumentalization of human life may be even more profound in the context of potential uses of GLGE for enhancement purposes. Sandel raised the following concerns related to procedures which allow to obtain a child with traits desired by its parents:

> "*(i)n caring for the health of their children, parents do not cast themselves as designers or convert their children into products of their will or instruments of their ambition. The same cannot be said of parents who pay large sums to select the sex of their child (for nonmedical reasons) or who aspire to bioengineer their child's intellectual endowments or athletic prowess.*" [408]

Cussins and Lowthorp drawn attention to the link between IVF and eugenics when discussing GLGE stating that IVF "*has a widely unacknowledged legacy of eugenics*" [409] The same authors explain:

> "*We cannot talk about NGT or gene editing in embryos as tools that would only mitigate disease propensity. There is significantly more social baggage than that. Ethical concerns about children's right to an open future, and for the parent/child relationship not to be reduced to an overt commercial transaction, do not hinge on intended use of modification technologies.*" [410]

7.4.3.4 Impact on persons with disabilities

There is great concern regarding the potential impact of the uses of genomic approaches on the perception and treatment of persons with disabilities[411]. Genetic or genomic testing of embryos or foetuses to detect diseases generates information that can be used to select embryos and terminate pregnancies respectively. Such practices can be considered as "sending" a message that persons with certain diseases are not desirable in society and that it is best that their births be avoided[412]. Indeed, the use of GLGE to avoid disease (for generations) could also be perceived in the same light as these practices. The difference between genetic/genomic testing and GLGE is that in the latter approach embryos or foetuses are not eliminated, but rather they would be "cured" (if the technology will

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[407] Pacholczyk, "Gene-Edited Babies and the Runaway Train of IVF".

[408] Sandel, *The Case against Perfection: Ethics in the Age of Genetic Engineering*.

[409] Cussins and Lowthorp, "Germline Modification and Policymaking: The Relationship between Mitochondrial Replacement and Gene Editing".

[410] Ibid.

[411] Wert et al., "Responsible Innovation in Human Germline Gene Editing . Background Document to the Recommendations of ESHG and ESHRE †‡".

[412] Kellogg et al., "Attitudes of Mothers of Children with down Syndrome towards Noninvasive Prenatal Testing".

work correctly). Nevertheless, the result of avoiding, or "eliminating" the birth of persons with a disability and/or disease remains and the impact of this should be addressed seriously. Of note, in case of clinical GLGE in embryos, such procedure would very likely involve discarding some embryo which do not develop properly or in which GE was not successful.

A very important aspect of this discussion is that many persons with disabilities evaluate their life as of good or excellent quality[413]. Furthermore, authors also point out that the elimination or avoidance of sick and/or disabled people would lead to less opportunities to learn and express compassion in society or cause other unexpected social changes[414].

The ESHG and ESHRE recommendations raise these issues and go on to state that:

> *"(t)he disability rights critique forcefully reminds society of its responsibilities towards people with disabilities, more particularly its obligation to remove barriers for inclusion, but it should not be used as an argument against the development of medical therapies, including gene editing, irrespective of whether it concerns somatic gene editing or GLGE."*[415]

Of note, on this topic are the results of the quantitative survey conducted within the SIENNA project (deliverable 2.5). We posed the following question to a total of eleven thousand respondents, 1000 from each of seven European countries and four non-European countries:

> "*Suppose that over time more and more women choose to terminate their pregnancy due to the result of a genetic test. How likely do you think that this would result in disabled people being less accepted in society?*"

The choice of answers were: very likely, fairly likely, not very likely, not at all likely. Based on an average across all countries, two thirds of respondents (67%) answered that they thought it was likely that disabled people would be less accepted by society if more and more women choose to terminate their pregnancy due to the result of a genetic test. Within this group, about one third said this would be very likely (33%) and one third said it would be fairly likely (34%). One third (29%) answered that this would be unlikely to happen: 20% not very likely and 9% not at all likely.

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[413] Albrecht and Devlieger, "The Disability Paradox: Highly Qualified of Life against All Odds".

[414] Dance, "Better Beings?"

[415] Wert et al., "Responsible Innovation in Human Germline Gene Editing . Background Document to the Recommendations of ESHG and ESHRE †‡".

Furthermore, when we asked if they thought that prospective parents would feel pressured to have their unborn child tested if testing becomes increasingly common (see exact question in footnote)[416], 80% said it was likely that this would happen.

While these empirical findings on publics' views and beliefs on hypothetical questions are not about GLGE per se, they are certainly salient concerns for GLGE. Moreover, while the results do not confirm that this would be the case in reality, they offer good indicators of trends to watch for in the future and they provide weighty material of what publics may be concerned with regarding the use of genomics.

7.4.3.5 Issues related to egg procurement from women for GLGE experiments

As shown in table 10, different types of human embryos may be used in research, yet, the experiments on viable embryos created specifically for use in research may be seen as advantageous for a number of reasons. First, in order to conduct an experiment on correcting a particular mutation, scientists must be able to manipulate an embryo with that mutation, and this can most easily be achieved by creating embryos with the needed gametes which have the desired genotype. Secondly, if an embryo is created in an experiment, it allows for the introduction of the CRISPR-Cas9 system at an early stage of embryo development, even at the moment of fertilization. This was the case in the study of Ma et al., who reported that such an approach may help avoid mosaicism[417]; that is, a situation where not all cells of an embryo or an organism have the same DNA (in this case, due to not all cells being modified). In order to develop a viable GLGE procedure, which could be potentially used in a clinical setting, scientists would have to generate enough data to evaluate its safety and efficacy[418]. Therefore, many such experiments involving "freshly" created embryos using gametes from donors, would have to be performed.

Importantly, such research poses a specific set of concerns, the main of which include 1) instrumentalization of embryos which are destroyed in such research (in the study of Ma et al. over hundred embryos were created and destroyed); and 2) the burden placed on women who donate oocytes (eggs) for such research. As the first aspect regarding embryos is tackled in the section above, herein we will discuss the second problem, that of procurement of oocytes from women.

For GLGE experiments, scientists often want to use embryos with a specific genotype (i.e. disease-causing variant); for this, they need to use gametes (sperms and/or eggs) that have such a variant. Such gametes, theoretically could be obtained from women and men who undergo IVF; women have their eggs extracted for the purpose of IVF and it may happen that there are leftover eggs and/or

[416] "*Now suppose that genetic testing on unborn babies becomes increasingly common. How likely do you think that this would result in parents feeling pressured to have genetic testing done on their unborn baby*?"
[417] Ma et al., "Correction of a Pathogenic Gene Mutation in Human Embryos."
[418] Marx, "A Rocky Road for the Maturation of Embryo-Editing Methods".

embryos which are not used for attempting to establish a pregnancy. These, if consented by the donor, could be used in a GLGE study. It may be problematic, however, to find already donated oocytes or embryos with the desired genotype(s). Therefore, to enable a GLGE study on a specific disease, recruitment of gamete donors is likely to be necessary.

The burden and risk to women who donate oocytes for GLGE experiments

Oocyte extraction is an invasive procedure involving inconveniences and serious health risks for women. It requires a procedure of suppressing ovaries, followed by ovarian stimulation which are both achieved by daily administering (by injections) of medications over the course of a few weeks and frequent visits to a doctor's office to monitor the procedure. When eggs have matured, they are retrieved in a surgical procedure under conscious sedation. The most common side effects associated with these procedures include, among others things, physical discomfort, nausea, vomiting, headaches, and bleeding between menstrual periods. Rarer but more dangerous risks include ovarian hyper-stimulation syndrome, which in a worst-case scenario, can cause death. Indeed, in the informed consent form for oocyte donation used in the study Ma et al.[419], the risk of death was mentioned three times in the context of different procedures involved in oocyte procurement[420]. There may be long term risks involved as well, such as, increased risk of breast cancer. Schneider et al. go as far as suggesting that egg donor registries should be created to enable a follow up of women who donate oocytes and assess long-term risks of this procedure[421].

Given all these risks and inconveniences to which women are exposed, a question arises as to how or whether such type of research can be ethically acceptable. Magnus and Cho, when discussing oocyte donation in the context of stem cell research, highlight this issue as follows:

> *"These women are not pursuing the procedure for any reproductive or medical benefit to themselves; rather, they are exposing themselves to risk entirely for the benefit of others. If we were to think of them as simply clinical patients, their physician's fiduciary obligations would seem to require counsel against undergoing such a procedure for no benefit."*[422]

Moreover, in the context of GLGE, the benefit for others is questionable[423]; there are alternative approaches to help couples at risk of having a child affected with a genetic disease, and the cases of couples who would need and be interested in GLGE are speculative (see section below on medical need). All things considered, the question of whether it is justifiable to place women at serious risks

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[419] Ma et al., "Correction of a Pathogenic Gene Mutation in Human Embryos."
[420] We obtained informed consent form at our request from a coauthor of the study of Ma et al. (2017); the form is not available online.
[421] Schneider, Lahl, and Kramer, "Long-Term Breast Cancer Risk Following Ovarian Stimulation in Young Egg Donors: A Call for Follow-up, Research and Informed Consent".
[422] Magnus and Cho, "Issues in Oocyte Donation for Stem Cell Research".
[423] Lander et al., "Adopt a Moratorium on Heritable Genome Editing".

to continue ethically questionable research is urgent, yet currently not adequately addressed. Many guidelines and recommendations suggest continuation of research of GLGE to evaluate its safety and efficacy, yet they do not acknowledge the costs of such experiments to women. The comment of Dickenson, made in the context of stem cell research involving egg donation, seems even more pertinent when it comes to GLGE research involving oocyte donation:

> "*In most commentaries and debates, the women from whom the ova are taken have virtually disappeared from view.*" [424]

Stakeholders in genomics, and in particular those who are interested and engaged in the debate on genome editing, should recognise the burden which will be placed on women if such studies continue. Furthermore, they should reconsider the need and recommendations for such experiments or at least ensure a better framework to protect women donors.

Adequate informed consent and undue inducement

If such GLGE studies involving procurement of oocyte continue, it should be ensured that women give informed consent to the participation in the experiments, and that the wider policy context of GLGE is well explained, as Magnus and Cho emphasise:

> "*Their vulnerability and the risks of oocyte donation make it imperative that prospective donors are adequately counseled and that risks are weighed carefully against a realistic assessment of benefits before allowing research to proceed.*"[425]

Of note, there is another set of issues which may influence or, indeed, undermine informed consent for GLGE research participants; the compensation offered to oocyte donors may be considered problematic. In the study of Ma et al., egg donors received 5,000 USD for participation in the study. Arguably, such a sum is not inflated considering all the risks and inconveniences to which egg donors are exposed. On the other hand, it is not difficult to imagine that such money will attract women in financially vulnerable situations, thereby appearing as an undue inducement to research. Indeed, one may question whether satisfying both conditions of offering fair compensation and avoiding undue inducement is ever possible.

7.4.3.6 Issues related to genomic sequencing of gametes and embryos in research and the clinic

One of the main shortcomings of the current GLGE approaches are off-target effects, that is unintended changes in DNA caused by CRISPR-Cas9 (or any editing tool) at sites in the genome other

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[424] Dickenson and Dickenson, "The Lady Vanishes: What's Missing from the Stem Cell Debate".

[425] Magnus and Cho, "Issues in Oocyte Donation for Stem Cell Research".

than the desired targeted sequence. To ensure that the desired on-target modification is achieved and that no unwanted (and potentially harmful) edits occur, genomic sequencing has to be performed on embryos. In the study of Ma et al., sequencing was performed, among others, on research participants' (gamete donors) blood DNA (whole exome sequencing) and embryos' blastomeres to control for off-target effects (whole genome sequencing)[426]. This quality checking procedure faces scientific challenges as it is difficult to achieve such a depth of sequencing that would detect all potential unintended modifications[427].

Furthermore, genomic sequencing introduces a set of ethical considerations both in research and the clinical settings, which are discussed at length mostly in the context of sequencing adults, children and more recently also foetuses for diagnostic purposes[428]. These issues include, among others: what sequence information should be provided to patients/research subjects, and how it should be explained to them in the informed consent process; how sequencing data is stored and who can access it. As explained by Tabor et al.: "… *researchers should consider whether participants should be told specifically about ES/WGS during informed consent in order to maintain transparency and trust in the research enterprise.*"[429] Indeed, research participants should be explicitly informed that all their DNA will be sequenced and how the genomic data will be handled and used, as it is suggested for any other types of studies involving genomic sequencing.

Having genomic sequencing conducted in the context of gene editing, in a way exacerbates some of these ethical issues related to sequencing. In some ways, these sequencing ELSI seem to be overshadowed when sequencing is just one part of a larger study, which also happens to be ethically contentious and facing a plethora of ethical concerns.

7.4.3.7 Alternatives to the use of GLGE and the limited medical need for GLGE

In Table 11 we present three situations in which GLGE could be considered for clinical use. Importantly, in all these contexts the goal of using GLGE would be to *obtain a genetically-related child* for a given couple, and this child would have a certain feature (e.g. first row, s/he would not be affected by a disease his/her parents carry or have; and in the second row, it is the case of enhancing a trait for the child).

In the first case, the context involves couples who are carriers/heterozygous for a recessive disease or heterozygous for a dominant disease; currently pre-implantation genetic diagnosis (PGD) and embryo selection can be used to prevent passing a disease to their offspring. In this approach,

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[426] Ma et al., "Correction of a Pathogenic Gene Mutation in Human Embryos."

[427] Marx, "A Rocky Road for the Maturation of Embryo-Editing Methods".

[428] Pinxten and Howard, "Ethical Issues Raised by Whole Genome Sequencing"; Borry et al., "Current Ethical Issues Related to the Implementation of Whole-Exome and Whole-Genome Sequencing".

[429] Tabor et al., "Genomics Really Gets Personal: How Exome and Whole Genome Sequencing Challenge the Ethical Framework of Human Genetics Research".

genetic testing is performed on embryos created by *in vitro* fertilization to check if they have a disease-causing genotype and to select the embryos which do not have such a genotype to establish a pregnancy. The embryos with disease-causing genes are discarded or donated for research.

It should be recognized that PGD also raises a set of ethical issues, which are discussed in the 7.3. We do not have the intention of simply suggesting that it is an option without objections for some, only that it is a current alternative to GLGE, which for many people is much less ethically contentious (as long as one accepts IVF and the destruction of embryos), and is better established and can act as a guide or point of comparison when discussing the less established GLGE.

In the second situation, where all the offspring of a given couple would be affected by a disease (Table 11), there is no option of pursuing PGD and selecting a "healthy" embryo. For such couples, GLGE could be the only option of having a genetically-related child not affected by a given disease. However, this situation, to our knowledge would be incredibly rare. One would have to not only have persons with already rare diseases find each other to form a couple, but that couple with these diseases, would then have to be healthy enough to physically support a pregnancy.

In this and the previous case, it is important to carefully reflect on and weigh the *potential* benefits of having genetically-related child, free from a given disease, and the risks and concerns involved in the development of GLGE technology (see section 7.4.3.1). This is especially true when alternatives, like PGD exist to help parents conceive a healthy child. Furthermore, the couples described above have additional options; they could give birth to an affected child, decide not to have children or adopt a child. Having one's own biologically-related child is of great value and we do not question this here. Yet, it cannot be seen as an absolute right, which should be achieved at any cost, including all the concerns mentioned above such as the uncertain risks of the technology and the risks to the first "gene edited" babies; the exacerbation of inequalities in access to the technology; the instrumentalisation of embryos; the burdening of women and exposing them to serious health risks; the potential negative consequences for persons with disabilities, and for society both socially and biologically etc. All these "costs" must be carefully and thoughtfully weighed against this "wish" for a healthy biologically related child.

Goal	Group concerned	Alternative approach	Example
Genetically-related child not affected by a specific disease	Prospective parents are carriers/heterozygous for a recessive disease or heterozygous for a dominant disease; *a portion of their offspring* would be affected by the disorder	Preimplantational genetic diagnosis and embryo selection	Recessive disorders: sickle cell disease, cystic fibrosis, phenylketonuria Dominant disorders: Huntington's disease, familial hypercholesterolemia
	Both prospective parents homozygous for a recessive disorder or one parent homozygous for a dominant disorder; *all their offspring* would be affected by that disorder	No alternative approach to have genetically-related child; adoption is an option to have non genetically-related child	
Genetically-related child with enhanced features	Any couple	Depending on a trait in question, the "need" for it could be reconsidered. There may also be enhancement approaches which could be applied in childhood or in adult life.	Modification of CCR5 gene to increase resistance to HIV

Table 11: Contexts in which clinical GLGE could be applied

7.4.3.8 Issues related to the first case of GLGE – for enhancement purpose

Surprisingly, the first known, or at least claimed, clinical application of GLGE was not related to any of these above explained scenarios; it was an application which may be qualified as enhancement. He Jiankui used CRISPR-Cas9 to enhance the future offspring's resistance to HIV and reported that the edited embryos were used to establish pregnancy which resulted in birth of twins. He Jiankui sought to justify his experiment referring to a need of a means to prevent contracting of AIDS by children whose father was HIV-positive.

Yet, it is well known that currently, to avoid passing AIDS to children sperm of father can be washed to remove the virus[430]. Hence, there was no medical need for clinical application of GLGE performed by He and the experiment exposed the children to unnecessary and unknown risks. It was also indicated that *CCR5* gene may play other biological roles than the one in HIV infection, therefore, modification of this gene to increase resistance to HIV may also have undesired consequences[431]. Furthermore, to understand the biological consequences and safety aspects it would be necessary to collect data from experiments on animals before applying such intervention on humans, which He failed to do[432].

Informed consent forms did not adequately address the risks involved in the experiment, and were written using technical language making them difficult to understand for a person not familiar with genetics[433]. Additionally, the couple who took part in the experiment was offered compensation equivalent of around 40 000 USD; such a sum may have unduly influenced the research participants[434].

Finally, He did not inform his university about the research, forged the ethics approval form, did not comply with the rules for clinical trials as well as violated international consensus that GLGE should not yet be conducted[435]. Krimsky summed up He's experiments in these words:

> "I contend that the ethical infractions in this work are among the most egregious that have been recorded in modern medical history since the Second World War. There is every reason for researchers across the world to be embarrassed and for the scientific community to speak of this work as "reckless.""[436]

There is an ongoing investigation conducted by Chinese authorities to understand what happened and whether and how He violated the law. In the meantime, statements condemning the study were

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[430] Krimsky, "Breaking the Germline Barrier in a Moral Vacuum".
[431] Cyranoski, "Baby Gene Edits Could Affect a Range of Traits".
[432] Krimsky, "Ten Ways in Which He Jiankui Violated Ethics".
[433] Krimsky, "Breaking the Germline Barrier in a Moral Vacuum".
[434] Ibid.
[435] Ibid.
[436] Krimsky, "Ten Ways in Which He Jiankui Violated Ethics".

issued by various groups. Questions arise in this context regarding how future abuses can be prevented and what should the criteria be for similar experiments to be allowed.

7.4.3.9 Calls for public engagement on GLGE: potential role and challenges

Many professional societies (in their guidelines) as well as individual authors have called for public input/engagement and/or social consensus on potential applications of (mainly) GLGE[437]. Given that GE (technologies) may potentially have an important impact on society (especially in case of heritable GE, which can be passed on to future generations), and that research on GE is often funded from public sources, (i.e. via public taxation), from democratic perspective citizens' opinion on how GE should (not) be applied should be considered when deciding and setting policies on these issues.

The scope of, and depth with which guidelines on GLGE have addressed public engagement vary; most often, however, documents provide very limited and general perspectives on this issue. A few documents emphasised that public engagement should be inclusive[438]; some specified which groups should be included in the discussion: scientists, experts in medical humanities, clinicians, patients and their families, lay people, policymakers[439]. Furthermore, some documents indicate what form such discussions/engagement should have (deliberative democracy, community-based participatory research, citizen juries)[440] and what topics should be addressed, e.g. "*rights, needs, interests, and values affected by this rapidly advancing science*" [441], "*the risks, benefits, alternatives, unknown consequences, and access*"[442]. Some authors addressed the question about the goal of public engagement outlining, for example, that public engagement "*will inform the frameworks to enable ethical uses of the technology while prohibiting unethical ones*"[443].

In some guidelines related to public engagement notion of societal consensus is present[444]. The Federation of European Academies of Medicine stated that public engagement should "*enable both the research community and society to agree on whether, and if so how, these scientific*

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[437] Brokowski, "Do CRISPR Germline Ethics Statements Cut It?"; Lander et al., "Adopt a Moratorium on Heritable Genome Editing".

[438] Wert et al., "Responsible Innovation in Human Germline Gene Editing . Background Document to the Recommendations of ESHG and ESHRE †‡"; Ormond et al., "Human Germline Genome Editing"; European Group on Ethics in Science and New Technologies (EGE), "European Group on Ethics in Science and New Technologies (EGE) Statement on Gene Editing".

[439] Ormond et al., "Human Germline Genome Editing"; Wert et al., "Responsible Innovation in Human Germline Gene Editing . Background Document to the Recommendations of ESHG and ESHRE †‡".

[440] Ormond et al., "Human Germline Genome Editing".

[441] Friedmann et al., "ASGCT and JSGT Joint Position Statement on Human Genomic Editing".

[442] Ormond et al., "Human Germline Genome Editing".

[443] Ibid.

[444] Friedmann et al., "ASGCT and JSGT Joint Position Statement on Human Genomic Editing".

developments should be taken forward in Europe."[445]. In the recent call for a moratorium on clinical uses of GLGE published in March 2019 by Eric Lander (and seventeen other researchers and ethicists from seven countries) it is stated that one of the conditions for allowing clinical application of GLGE is "*broad societal consensus in the nation on whether to proceed with human germline editing at all, and on the appropriateness of the proposed application.*" Unlike most documents, the authors continue by explaining what they mean by societal consensus:

> *"the concept does not mean unanimity or simple majority. Societal consensus on germline editing is something that must be judged by national authorities, just as governments make political judgements about their citizens' views on other complex social issues."* [446]

In principle the idea of public engagement (i.e. obtaining publics' views) on issues related to science is laudable and there are good reasons to pursue it as explained earlier in section 5. Results from the SIENNA survey conducted in spring 2019 show that a significant part of the respondents recognized the importance of understanding more about genetics or DNA (see deliverable 2.5)[447]. Nevertheless, many problems arise from these calls for public engagement, including among others: the vagueness of the call regarding the definition of public engagement, goals and methods as well as how the input will be used (if at all) in any downstream decision making or planning. Furthermore, we outline additional challenges below, which should be carefully addressed when discussing and/or considering to conduct public engagement activities.

Firstly, it is known that health literacy, including in genetics and genomics among certain groups of public is low[448]. Therefore, to conduct a meaningful public engagement activity, the educational needs of publics in a given topic should be addressed. Educational activities should be adjusted to the current knowledge and general education/literacy of publics in question. Importantly, an appropriate amount of time should be allocated for such educational sessions to be useful. Specifically, it should be ensured that the vocabulary used when discussing the subject in question is understandable. Genomics, including GE, is a complex matter and often not easy for a lay person to become familiar with. Indeed, problems in communication about genomics were identified, for example, in the

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[445] Federation of European Academies of Medicine, *Human Genome Editing in the EU*.

[446] Lander et al., "Adopt a Moratorium on Heritable Genome Editing".

[447] The respondents were asked: "How important do you think it is for the general public to understand more about genetics or DNA?" On average 87% of 11 000 surveyed answered that it is very or fairly important. Please see SIENNA deliverable 2.5 for details.

[448] Lea et al., "Communicating Genetic and Genomic Information: Health Literacy and Numeracy Considerations".

context of informed consent for genomic sequencing[449]. Efforts to identify appropriate language to talk about genomics, which could help to familiarise with the topic and engage in discussion lay audience have been taken[450].

Secondly, also related to literacy (or lack thereof), it is important to recognize and be vigilant about the possibilities of abuses of public engagement processes. People who are not thoroughly educated in a given matter may be prone to accepting misleading information or be unduly biased by an "expert" point of view. This aspect is especially important to recognize if there are stakeholders which may have (financial) interest in increasing public acceptability of genomic technologies. It is important to keep in mind that public engagement process can be manipulated in such a way that desired outcome (e.g. decreased resistance, increased acceptability, increased consumption) of a given technology is achieved. This is, of course, also related to the type of engagement activity held and its uses. Indeed, some stakeholders may also try to use a public engagement activity as a mere "check mark" or symbol of having been seemingly "responsible" or accountable to publics.

Lastly, but certainly not least, the role or purpose of public engagement must be explicitly and clearly stated. Out of 11 000 persons surveyed, only 12% (on average) indicated that (lay) public should be the stakeholder group with the most responsibility for making decisions about how genetic technologies are used (see SIENNA deliverable 2.5 for details). Such a result may be related to the relatively low knowledge of the topic and such a perspective could change if the public was more educated. On the other hand, general publics will never reach the level of expertise of scientists or other groups which have been investigating given topics for a long time, which should be kept in mind.

In conclusion, although the concerns of general publics should be considered when debating on policies, it may not be prudent to (only) consider the opinion of a majority (or of a consensus) as an answer to policy questions. The issue of how exactly public should be engaged on the issue of new technologies is one of the topics which could be further addressed in the coming SIENNA deliverables and future SWAFs calls.

7.4.4 Ethical issues related to CRISPR-based gene drives in animals and security

In addition to the issues explained in section 7.3.3, the problems specific to use of CRISPR-based gene drives in animals can be considered. Gene drive can be used to allow for the propagation of a specific genetic variant through a population very rapidly. Depending on the variant in question, gene drive could relatively quickly suppress a population of a wild species, which would lead to changes in the whole ecosystem, including interactions between pests, pollinators, and crop production and

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[449] Niemiec, "Readability of Informed Consent Forms for Whole-Exome and Whole-Genome Sequencing".
[450] Parry and Middleton, "Socialising the Genome".

ultimately human life. This may impact food security, create niche in an ecosystem which may be taken by other potentially more harmful species, and cause unpredicted changes in the populations to come[451]. Indeed, such a tool could be used to develop very powerful "weapons", "weapons" which may be difficult to "turn off" and/or confine to any geographic area. The ethical guidelines on this topic recommend taking appropriate confinement, containment and mitigation strategies when conducting the experiments on gene drives[452]. Furthermore, the importance of public engagement especially involving the communities who would be affected by the release of modified organisms was recognized[453]. Of note, in 2016, over 170 civil society organisations from various countries signed the call for moratorium on both further experiments involving gene drives and environmental release of modified gene drive organisms[454].

In closing, the ethical analysis of gene editing in this section focused on a number of overlapping issues, most of which pertain to germline gene editing which seems to pose most serious ethical issues (comparing to other applications of gene editing, such as somatic gene editing). Our analysis touched upon values and principles such as value of human life and health (in particular of human embryos and women who donate oocytes for germline gene editing research), value of having genetically-related children, and principles of justice, informed consent/autonomy, as well as issues related to public engagement. Our analysis indicated the stakeholders groups who would likely be affected by germline gene editing application in the clinic: the couples who desire to have a genetically-related child not affected by a given disease, children on which gene editing would be performed at the embryonic phase of their development, women who donate oocytes for research, disabled persons, and human embryos, among others. We discussed also the role of public engagement, problems and questions related to public engagement activities, which could be potentially further addressed in the ethical framework in the deliverable 2.7. We also described the potential applications of gene drive technology based on gene editing on animals, some of which can become a threat to security or used for military purposes.

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[451] The African Center for Biodiversity, *Gene Drive Organisms. What Africa Should Know about Actors, Motives and Threats to Biodiversity and Food Systems*.

[452] Akbari et al., "Safeguarding Gene Drive Experiments in the Laboratory: Multiple Strategies Are Needed to Ensure Safe Gene Drive Experiments"; Committee on Gene Drive Research in Non-Human Organisms, Board on Life Sciences, and National Academies of Sciences Engineering and Medicine, *Gene Drives on the Horizon*.

[453] Committee on Gene Drive Research in Non-Human Organisms, Board on Life Sciences, and National Academies of Sciences Engineering and Medicine, *Gene Drives on the Horizon*.

[454] Civil Society Working Group on Gene Drives. "Common Call for a Global Moratorium on Genetically-engineered Gene Drives" 2016. http://www.synbiowatch.org/wp-content/uploads/2016/12/CBD-Gene-Drive-Sign-on-Letter-English.pdf

8. Conclusion

This report is part of the ethical analysis of human genomics (and related technologies and approaches) in the SIENNA project; it follows a specific set of steps as developed by the project coordinator (cf. p.17). After describing the social and ethical impacts of genomic technologies in deliverable D.2.1 and before addressing further questions related to an ethical framework in human genomics in task 2.7, we propose, in the present report, an overview of the ethical, legal and social implications (ELSI) of emerging and future genomic technologies, based on their applications, namely in studying the genome (e.g. genomic sequencing) and modifying the genome (e.g. gene editing)

After conducting the work in this task, we can report that although the proposed ethical analysis of human genomic technologies has been done in parallel with, and has benefitted from continued discussions from the analysis of AI & Robotics and Human enhancement, we question whether the SIENNA approach as described currently, is the most optimal approach for the assessment of ethical issues for genomic technology. That being said, we have herein been able to discuss a large number of salient ELSI of human genomics, including among others, the "usual suspects" of privacy, confidentiality, consent procedures, justice, etc… We have also been able to raise relatively less common aspects such as those pertaining to the use of genomics for military purposes, in infrastructures and regarding companionship.

The SIENNA approach for ethical analysis can be defined as: foresight-orientated and empirically informed, requiring stakeholder engagement. Rather than taking these features of ethical analysis for granted, the compatibility of the different methods and investigations developed in SIENNA (for instance, the complexity of merging public opinion studies and media studies from different countries, as well as foresight studies with experts), their theoretical relevance to ELSI of genomics and actual execution in SIENNA have been discussed with experts in genomics and ELSI of genomics during two workshops. As a result we can say that:
- Experts have questioned the benefits of foresight analysis in ELSI of genomics, pointing to the risk of tipping into speculative discussions that would hardly lead to actionable measures.
- Experts have also criticized the execution of empirical work in SIENNA. They have especially warned against the risk of over interpretation of the results due to several weaknesses in the execution of both the surveys and focus groups with lay people.
- Experts have eventually questioned the relevance of a unique framework for ethical analysis of different technologies which may share important evolution at the moment and have significant economic, social and ethical impact, but may not require the same ethical approach.

In particular, in human genetics and genomics, so much work has already been completed on the ELSI that stakeholders may be looking for specific guidance, which is usually handled by professional societies (like the ESHG and the ACMG), rather than the general discussions and global perspectives cultivated in SIENNA. An interesting nuance may however be brought up considering two distinct areas of technology development – technologies looking at the genome and technologies modifying the genome – since those are not at the same stage of development at the moment. ELSI referring to

sequencing technologies rather question the limits and accommodations surrounding their implementation and use in different areas in society. ELSI referring to genome editing are still formulated in terms of drastic interdictions and raise the question of a research moratorium. Indeed, based on the analysis of ethical issues pertaining to germline gene editing there remains serious ELSI to be addressed before widespread use of this approach should be used, especially in the clinic, but also in research. Among others, one has been under addressed in a potentially vulnerable group, namely, the burden and risk of harm to women who donate oocytes for experiments that would be needed to even attempt to verify if gene editing could be used in the clinic .

Our choice to focus on these two approaches or areas of technology development (i.e. the study of the genome (sequence), and modification of the genome), rather than on specific genomic technologies is motivated by two reasons:

- As illustrated with the example of the various contexts of uses for a sequencing machine and as was shown with the multiple potential uses of CRISPR9 in ethical analysis of gene editing, it is not the technological product that raises issues but its applications.
- Focussing on specific technologies, in the sense of specific products, may also soon make ethical analysis irrelevant, since these technological products are in constant evolution. For genome sequencing, when NGS will become obsolete, third generation sequencing will take on (e.g. D.2.1), and for genome editing, CRISPR9 can also be expected to be replaced by another tool. Independently of the products themselves that are constantly changing, the area of technology development deserves continuous scrutiny in order to track changes and continuity in our relation with genomics.

For these reasons, contrary to D.3-4 and D.4-4, we did not opt for the three-level approach of 'technology', 'artefact/product' and 'application' inaugurally proposed in SIENNA and rather focussed on areas of technological development and domains of applications for the ethical analysis of genomics. This 'one-size-does-not-fit-all' attitude regarding the ethical analysis of (new) technologies may be an important generalisable point/result in SIENNA.

On a larger scale, this work already leads us to raise the question of whether future grants on the ELSI of these technologies (like this SWAF grant) may be better spent with individual grants per technology area (ELSI). Following such work, or included in the calls (for parallel grants on the ELSI of different technologies) there could be specific tasks around comparing and contrasting the analyses performed and the results obtained (including any frameworks and codes). This approach would remedy many of the time and decision-making challenges faced to date in SIENNA.

Based on this report, the next step of ethical analysis (D.2.7) will thus further question the type of framework to be developed to address the stakeholders' concerns about the development of genomic technologies and their uses.

Acknowledgments

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Annexes

Annex 1: Description of Foresight Workshop and List of Participants

Genomics: Future impacts and ethical issues

18th January 2019, 09.30-1700

Venue: Hilton London Kensington,

179-199 Holland Park Avenue, London, UK, W11 4UL

Human Genetics and Genomics Foresight Workshop Date Friday January 18th	
09h00-09h30	Registration and welcome
09h30- 10h00	Introduction to the SIENNA project, aims of the workshop & overview of agenda
Foresight Activity 1: Scenario Discussion	
10h00-10h10	Introduction Foresight Session and Instructions
10h10-11h10	Group discussion session on 3 scenarios Fields of foresight discussion: Whole genome sequencing & Genome editing
11h10-11h25	Break
11h25-11h45	Prepare group presentations
11h45-12h30	Plenary presentations and discussion of group results
12h30-13h30	Lunch
Foresight Activity 2: Short Story Discussion	
13h30-14h30	Short Story reading Group discussion: Connect Foresight narrative and ELSI Prepare group presentations
14h30-15h00	Plenary presentations and discussion of group results
15h00-15h30	Break
Foresight Activity 3: Discussion on Foresight	
16h00-17h00	Plenary discussion: Use of foresight in Bioethics
17h00	End of workshop

This day consists of 3 main activities; 1 in the morning and 2 in the afternoon. For each activity, there will be a reflection and discussion stage and a presentation stage.

You will be separated into three groups. You will have ten minutes to gather as a group, meet your group-members and select among the members of the group:

a moderator: who makes sure that everybody in the group shares their views and speaks up

a time-keeper: who makes sure that activities are done in time and follow the schedule

an observer: who will keep track of the larger dynamics of the group and who keeps notes of themes raising consensus and dissensus during discussions.

a presenter: who makes sure that there is a content to present and presents it.

FORESIGHT ACTIVITY 1

The scenarios below are intended to provide stimulus for you to consider the ethical, legal and social issues that we may face in the coming 5-10 years in the area of genomics. In order to consider more concrete questions and provide credible analyses, we ask each group to work on scenarios that highlight specific issues.

It is important to stress that the scenarios are not necessarily predictions of what may happen, or anticipations of likely problems or eventualities per se. The scenarios are intended to illustrate and dramatize potential futures to provoke debate and discussion.

Scenario 1:Genome sequencing

In the near to medium term future, technological advances have continuously changed genome sequencing from an expensive and burdensome undertaking to a rapid and less costly option for many purposes. The validity of genomic testing has been found to establish the molecular diagnosis for hundreds of genetic disorders, to assess pharmacogenomic variants, including to identify treatable targets of malignant tumors. With the aim that the availability of genomic information will provide clinical benefit to individuals and provide anticipatory insights for their future health care, whole genome screening of foetuses is proposed to all new pregnant women from week 10.

Scenario 2: DIY sequencing

In the near to medium term future, mini DNA sequencers are available at affordable prices – these are small devices which can sequence DNA, including entire exomes or genomes. They can be connected to a computer and a "user-friendly" software can analyse the sequence and give information about the type of organism sequenced. If the DNA is human, the software can give information about disease predisposition, physical traits e.g. eye colour, as well as ancestry. The software can also allow users to connect to different existing DNA databases, and potentially allow for the identification of the individual whose DNA was sequenced.

Scenario 3: Germ line gene editing

In the near to medium term future, technical aspects of germ line gene modification have been further studied and in some countries, the safety-benefit ratio has been deemed acceptable to allow for clinical trials to take place; some countries are already at the stage of rolling out germ line gene editing as a pilot treatment programme both from the "traditional" public health care system as well as from private providers. In such countries, parents with a chance of passing on a severe disorder to their child could be eligible for the treatment. The criteria for being offered such a treatment are still heterogeneous between countries and are still being worked out.

*For details and explanations about the above technologies, please refer to the following link or to the SIENNA deliverable that was sent to you.

Basics of DNA and Genome Sequencing:

https://www.labroots.com/trending/videos/11397/the-basics-of-genomic-sequencing

Basics of gene editing or genome modification:

https://geneticliteracyproject.org/2017/08/04/understanding-crispr-works-basics/

INSTRUCTIONS:

Each group has been assigned a scenario. These scenarios are purposefully generic so that they lack in detail and specificity. We would like you to discuss the ELSI emerging in the scenario your group has been assigned and complete it with whatever specific details you need to be able to advance your discussion.

You may want to detail some technicalities, give a geographic/financial/political/legal/religious background to the discussion, imagine varying social structures etc. You may want to have only one scenario to work on or to create different scenarios.

In a first instance (A) the scenario(s) will be "completed"/created, labeled and briefly described; in a second instance (B) the three questions will be discussed and answered. Each group will present the results of this discussion from 11h45 to 12h30.

BUILDING UP ON THE SCENARIO

1. COMPLETE SCENARIO

Add time frame and whatever contextual clue, such as geographic/financial/political/legal/religious, to this scenario that would give substantial meaning to how different trends and countertrends

might unfold and interact and what the implications would be of variations from the standard account of these developments. At this step, it is likely that several scenarios may emerge from the one given to you.

2. NAMING YOUR SCENARIO(S)

Here we would like you to characterize the scenario(s) developed by your group. One way in which this can often be assisted is to come up with a "name" for each scenario and then succinctly describe it.

A- QUESTIONS

QUESTION 1
We would like you to comment on any ways the domain of health, and society in general would be transformed according to each scenario. In particular focus on: the social impacts, impacts to society, to individuals being screened or "gene-edited", to those not being screened or "gene edited".
[Suggested: 20 minutes]

QUESTION 2
We would like you to list and comment on the greatest potential benefits and risks of each scenario. Please use the green and red sheets, to list each ones respectively
[Suggested: 20 minutes]

QUESTION 3
We would like you to work through and comment on the main ethical issues associated with your scenario above and beyond what you may have answered for 1 & 2 above. Please use the flip chart to identify the issues that you consider most important.
[Suggested: 20 minutes]

The answers to these three questions may be overlapping – answers to some questions may contain answers to others. These questions are here to help you develop the reflection, you do not have to strictly organize your presentation around these questions.

C- SUMMARY – PRESENTATION PREPARATION [7-10 minutes per group]
Please prepare a brief presentation of your reflections by following this plan:
1. Describe your extensions of the primary scenario according to contextual clues in ways that the other groups can rapidly grasp - kicking off with the names of the scenarios and the list of ELSI associated with each one.
2. Present the responses to the questions by explaining which ones were consensual and which ones were discussed.

FORESIGHT ACTIVITY 2

The Oracle is a story hat raises moral issues according the use of an innovative genomic technology for medical use.

1. **INDIVIDUAL READING AND REFLECTION**
   a. Please read or re-read the text (suggested time: 12 min.)
   b. Make a list of the ELSI raised in the text (suggested time: 15 min.)
      - You may want to take a look at the questions in n#2 below to see how well you have captured some details of the text
   c. "Tour de table": Give us a specific ELSI and an overarching ELSI raised by the text? (suggested time: 15 minutes, so 1 min per participant)

2. **GROUP READING**
(suggested time: 10 min.)
After having read the Oracle, you may want to further familiarise yourself with the story by considering the following questions. These are NOT the questions we want you to discuss and present in the end; they are simply questions to help you recall and further grasp some important aspects of the story. Should you decide to go through these as a group, please take no more than 10-15 minutes. If you decided not to discuss these questions, please move on directly to the next point: Group discussion (right?)

From the perspective of Big Data and AI
   o At the time when the story starts, how long has the technology of the Oracle been used?
   o How does its role evolve in the family's everyday-life during the course of the story?
   o How does *The Oracle* work? On what kinds of data are the predictions based? What kind of knowledge does it produce?
   o What kind of advice does the Oracle give?
   o After the lawn incident, what does the Oracle control in the child's life?
   o Is there any evidence, any hints in the story of how the rest of society is using (or not using) the Oracle?
   o Are there any other important details from this perspective that you think should be highlighted? If so, which?

From the perspective of Health Care
   o How does the family GP relate to the Oracle?
   o What type of disease is Fünder disease?
   o How is the gene-environment interaction presented for this disease?
   o What are the devices used in the story to get health information and track health data?
   o How is health measured within this story?
   o are there any other important details from this perspective that you think should be highlighted? If so, which?

From the perspective of Parenting
   o What is the child deprived from during childhood? Are the parents also deprived from something?

- o According to the narrator, what harm would be done by not complying with the Oracle?
- o At what age is the child "diagnosed" and when does the story end?
- o Have the parents evolved in their position towards the Oracle along the time?
- o What, would you say are the ethical perspectives of what constitutes a child's best interest defended by the narrator and the child in this story?
- o Are there any other important details from this perspective that you think should be highlighted? If so, which one?

3. GROUP DISCUSSION
(Suggested time: 20 minutes)

Use this short story for further discussion of ethical issues that you may find interesting. Please, pick one or several of the following questions to discuss within your group.

1. Who are all of the moral agents in this story? Who are the subjects of moral worth?
2. How would discussions on assent and consent play in this story?
3. Ethical parenting is responsible caregiving, requiring of parents enduring investment and commitment throughout their children's long period of dependency. Is there a responsibility to provide the best care out of evolving knowledge and new data? How does this kind of discussion relate with prenatal diagnosis and vaccines?
4. Can a probabilistic knowledge be deterministic?
5. What role should health technology play in the moral decision making of parents insofar and with respect to limiting or expanding choices available for a child? Is this intrusive and how is it different from other intrusive third parties (teachers, Family GP…)
6. Or your own ethical question.

4. PRESENTATION

Please share your reflections (8-10 minutes) on the ELSI and wider questions raised in the text. Did you find the text interesting? Did it raise interesting discussions within the group? What was discussed? What topic(s) did you discuss in the end?

FORESIGHT ACTIVITY 3

We would like to discuss if/how foresight methods and scope deserve a dedicated place in Bioethics or Ethics of technologies studies. We hope that you had some interest in today's activities but we are really interested in your critique. Could you thus please take the first 15 minutes to answer the following questions, with your neighbor?

A. Questions to discuss in pairs

1. Do you think that today's activities are useful/not useful for ELSI analysis?
2. How is it similar and different from what you have done before?
3. Did you know anything about foresight methods before today?
4. Do you think that today's activities correspond to a foresight approach?

B. Plenary session: Discussion (16h15-17h00)
You now can share some thoughts in plenary discussion based on the discussions in pairs; you may also share your thoughts on the questions below.

1. Do you think that the foresight activities conducted today? Or do you really mean the approach in general, which would go beyond what we did today. Does it bring something new, relevant, and useful in bioethics?
2. How could we have improved today's activities?

List of participants: In addition to Consortium members, the following experts contributed to the workshop:

Name	Institution
Group 1	
1- Álvaro Mendes	Centre for Predictive and Preventive Genetics, Portugal
2- Jonathan Roberts	Cambridge University Hospital, UK
3- Dorota Adamska	Institute of Biochemistry and Biophysics Polish Academy of Sciences, Poland
4. Marie Gaille	CNRS, France
5- Karolina Snell	University of Helsinki, Finland
Group 2	
4- Mahsa Shabanni	Interfaculty Centre for Medicine and Law, UK
5- Paolo Corsico	University of Manchester, UK
6. Clémence Guillermain	Université Paris IV, France
7- Mauro Turrini	Université de Nantes, France
8. Oliver Feeney	Centre of Bioethical Research and Analysis, Ireland
Group 3	
9- Gemma Chandratillake	University of Cambridge, UK
10- Anne Cambon-Thomsen	INSERM, France
11- Virginie Bros-Facer	EURORDIS, UK
12- Alessandro Blasimme	ETH Zürich, Switzerland

Annex 2: Description of ELSI of Genomics Workshop and List of Participants

Day 1: Friday 14 June 2019	
Location: Högåsplatsen 2, behind the Göteborg Art Museum, see below for maps (nb: on Saturday the meeting is at the towers by the ESHG)	
12:00	Registration and lunch
12:45	**Welcome and introduction to SIENNA, overview of goals of workshops** Heidi Howard, Uppsala University
Session 1: SIENNA approach and Task 2.4 Chair: Heidi Howard, Uppsala University	
13:00-13:30	**The SIENNA approach for "ethical analysis"** Heidi Howard, Uppsala University Please refer to the document called "SIENNA Handbook"
13:30-14:40	**Ethical Analysis of Human Genomics (2.4): What about AI, enhancement and military uses?** Alexandra Soulier, Uppsala University Short presentation and group work
14:40-15:00	Coffee/Health Break
Session 2: Empirical Work in Sienna: what, how and a few results Chair: Deborah Mascalzoni, Uppsala University	
15:00-15:45	**Survey of publics (n=11000, yes, 11000!) and a few results** Heidi Howard and Emilia Niemiec
15:45-16:15	**Focus-groups with lay people** Emilia Niemiec and Heidi Howard
16:15-16:30	Coffee/Health Break
Session 3: What do we do with the empirical data? Was it really engagement? Chair: Emilia Niemiec, Uppsala University	
16:30-17:00	Discussion in groups
17:00-17:45	Presentations of groups discussions, plenary discussion
17:45-18:00	Recap of the day

Day 2: 15 June 2019	
Location: Hotel Gothia Towers, Mässans gata 24	
8:30-9:00	**Welcome and registration**
Session 4: Ethical Framework (2.7) and Code of Responsible Conduct (5.2)	
9:00-9:15	Recap of Friday sessions
9:15-9:30	Presentation of 2.7, our questions
9:30-9:50	Presentation of 5.2 (and briefly 2.3 and 5.1 which are related), our questions

9:50-10:30	Work in groups, groups will discuss either 2.7 or 5.2
10:15-10:30	Break
Session 4 Conclusion	
10:30-11:30	Each group presents results of the discussions, plenary discussion
Thank you!	
11:30-11:45	Thank you!
11:45-12:00	Lunch bags
Workshop ends	

List of Participants

Name	Organisation
Layla Afkhami	Viapath, UK
Pascal Borry	KULeuven
Oliver Feeney	National University of Ireland, Galway
Vera Frankova	Charles University, Prague
Caroline Gallant	Uppsala University, Sweden
Katie Hasson	Center for Genetics and Society, Berkeley, CA, USA
Wannes van Hoof	Sciensano, Belgium
Heidi Howard	Uppsala University, Sweden
Leigh Jackson	University of Exeter, UK
Hülya Kayserili	Koc University, School of Medicine, İstanbul, Turkey
Samantha Leonard	Natera, USA
Deborah Mascalzoni	Uppsala University, Sweden
Amal Matar	Uppsala University, Sweden
Chloé Mayeur	Sciensano, Belgium
Emilia Niemiec	Uppsala University, Sweden
Virginia Romano	Uppsala University, Sweden
Vigdis Stefánsdottir	Landspitali University hospital Reykjavik, Iceland
Jane Tiller	Monash University, Australia
Danya Vears	KULeuven, Belgium
Jantina de Vries	University of Cape Town, South Africa

Annex 3: Instructions for country reports

Task 2.4: Analysis of current and future ethical issues in Human Genomics
Lead: UU | Contributors: all partners | Months 6-23

What do we expect from all SIENNA partners?

– All partners have at least 0,3 person month, that means 6,6 days, per each task (2.4/3.4/4.4). That means 19,8 days for the three tasks together.
– Please conduct in your 19,8 days a national search of relevant documents in the three SIENNA areas, following the instructions in this document
– Please prepare a report of your national search. See template reports for each area of technology. Please state your country and the name of the person who conducted the national search for your organization in the heading line. The report will constitute:
  ✓ all the completed TABLES (you will find them in the template report)
  ✓ Plus brief summary reports (see instructions in template report)
– **Deadline for draft 1 week feb 4ᵗʰ – feb 11ᵗʰ 2019**
– **Deadline for final draft due BEFORE for the Corfu meeting April 9-10ᵗʰ**
– Send the report 2.4 to Emilia.niemiec@crb.uu.se
  o Report 3.4 to s.r.jensen@utwente.nl and <saskia.nagel@humtec.rwth-aachen.de>
  o Report 4.4 to p.h.jansen@utwente.nl
– Please Keep all your literature review work in 1 file (2.4 country name) divided into 3 subfiles, 1 per tech, and Upload your saved files in SharePoint.

Partner	Country	Contact person	Task 2.4	Task 3.4	Task 4.4
UT	Netherlands	Philip Brey, Philip Jansen Saskia Nagel, Sean Jensen	0,3	7 (lead)	6 (lead)
TRI	UK	Rowena Rodrigues	0,3	1,3	2,45
UU	Sweden	Heidi Howard,	7,7 (lead)	0,3	0,3
HFHR	Poland	Zuzanna Warso	0,3	0,3	0,3
EUREC	Germany	Lisa Tambornino	0,3	0,3	0,3
UGR	Spain	Javier Valls	0,3	0,3	0,3
IONIO	Greece	Maria Bottis	0,3	0,3	0,3
Science Po	France	Robert Gianni Anaïs Rességuier	0,3	0,3	0,3
UFRJ	Brazil	Marcelo de Araujo Clara Dias	0,3	0,3	0,25
DUT	China	Wang Qian	0,3	0,3	0,25
UCT	South Africa	Jantina de Vries	0,6	0,3	0,25
Berkman	USA	Adam Holland	Brey	Figures	out
Chuo	Japan	Hiroshi Miyashia	Brey	Figures	out

Table 12: Division of person month and contact persons

Timeline

1- Finalising approach
   a. Proposed country approach (2.4, 3.4) shared with all partners week Nov. 6th
   b. Discussed with all partners in Warsaw last day,
   c. Feedback from partners in writing by week Nov. 12th
   d. Final proposal for approach sent out by Friday Nov. 23rd[th]
2- Partners work on country reports from Nov. 23rd[th]-
3- Each WP schedule an email/call in mid January to check in with all partners on work for X.4
4- **Partners first draft due week feb 4th – Feb 11th 2019**
5- **Partners final draft due BEFORE for the Corfu meeting April 9-10th**

Summary of document:

   The approaches below outline searches for:
   I- academic literature
   II- popular media: academic media studies, and if possible newspaper search
III- Use of results from X.3 to pull out ELSI

I Goal: Overview of academic discourse on ethical ELSI aspects of Human Genomics & Genetics (HG), in country X

(Time suggestion: 25-30%-40% of time, depends on how much you find here)

Research question: What ELSI are being discussed specifically with reference to HG HE, AIR and/in country X?

How will this be used in larger 2.4 work?
- the summary section will be included in the X.4 report. So, the summary you will write for each section is very important.
- the raw work will be included in the annex (see how we did it with task X.3)
- the results will provide a list of ELSI which may or may not overlap with those already addressed in the larger ELSI analysis of X.4
- this is not meant to be systematic or exhaustive search, but rather provide an idea of the ELSI being discussed in your country that could help the SIENNA ELSI analysis overall, so X.4, as well as X.7 and work in WP5.

SEARCH STRATEGY

Database: Suggested to use Google scholar, if you use another database, try to make sure it/they are inclusive of many different sources of academic literature AND MAKE SURE TO BE EXPLICIT ABOUT THE DATABASE IN YOUR REPORT
- log out of your google account if you use Google Search

Time Period restrictions (if any):
Human Genomics
- Default instruction: run the search without any time period restrictions
- quickly scan the first 100 results to get an idea of how many results you will be able to include
- OPTION
  - If manageable, and you think you may find something interesting based on time, you can rerun the search 2- 4 x and group results by category:
  - By 10 year span: 1999-2008, 2009-2018
  - Or by 5 year span: 2013-2018, 2008-2012, 2003-2007, 1998-2002
  - if you have time to the latter step, when reporting issues addressed in your country, frame around time period as is relevant
  - of course, you can also just look at the year of articles you report on…

By Keywords
Human Genomics
Ethical, Legal or Social + country + (human genomic or human genetic)
        Ethic* + country + (human genomic or human genetic)
                Debate country + (human genomic or human genetic)
                (legal or law) + country + (human genomic or human genetic)
                Social + country + (human genomic or human genetic)

        (ethic* or law or legal or social) + country + (genomic or genetic)

Optional: Depending on what you find using the above (i.e. a lot or little, and how much time you have), you can also use in the last bracket: Gene , Gene therapy, Genetic test, Genetic screening, Pharmacogenetics or pharmacogenomics, Patents, Biobank, databank, direct-to-consumer genetic testing

Remember to provide us with the key words you have actually used in your report

Ideally, this search should lead you to be able to comment about whether ethical issues were raised specifically on the following questions: (See instructions p.9 + tables to fill in)
Could you comment specifically in your summary on the following? (i.e. were these domains mentioned in your search? Anything particularly interesting to say about them?) :

      i. Human germline gene editing? In research? In clinic?
      ii. Genetic testing?
      iii. Genetic screening?
          1. Prenatal screening and/or testing?
          2. Newborn screening?
      iv. Direct-to-consumer genetic testing and advertising?
      v. Databanks? Biobanks?
      vi. Patents?

Language(s): local language(s), and/or English (Please specify in your report which language used)
Inclusion criteria: by reading title/ overview of article, keep only articles that specifically address:
Human Genomics

a) specifically to do with genomics or genetics
    a. if you did extra keyword search, we accept also anything related to: Gene , Gene therapy, gene editing, Genetic test, Genetic screening, Pharmacogenetics or pharmacogenomics, Patents, Biobank, databank, direct-to-consumer
    AND
b) some ELSI (not just law, if only law, discard, or if very relevant, and you did not report in X.2, you can mention here but note that we don't want to focus on the legal per se)
    AND
c) specific to country X (so not just an article published by UK or USA authors…) but the content is specific to country X (either a section of the article or the entire article addresses specific ELSI in country X; only use what is specific)
d) Only include what you have full access to, but keep track of what you do not have access to
e) If you find a book, you need to be explicit about what you were able to review (all, table of contents etc..), remember you should only use parts specific to country X

ANALYSIS
Human Genomics
A- For ALL article meeting inclusion criteria, insert the following information in the template

i.   author, year, title, link in table for all
ii.   from this list you will choose top 10-15 (from google scholar search) to answer questions in the template
iii.   please note that you will need to state (in table 3) how/why you choose these articles, why they are relevant/important in table

B- For the 10-20 results found in Google scholar that meet inclusion criteria, and are the most relevant keep the PDF, label file with 1st author last name, and year, keep in folder which you will upload to share point.

     - If possible squeeze in title in both original language and English, even if you have to make font small (for one) if not possible, just put English translation.

C- Complete analysis of articles by filling in **table 3 in reporting document** (copy table for as many articles as you include, up to a max of 20)

D- After all analyses have been done, you will write a summary, please keep time for this as this will be included in the results section of the X.4 report and needs to be informative, a reflection of all your results and well written. Please see instructions below.

B- For the 10-20 results found in google scholar that meet inclusion criteria, and are the most relevant, keep the PDF, label file with 1st author last name, and year, keep in folder which you will upload to share point

C- Complete analysis of articles

Fill in analysis using tables 3.1 to 3.3 for all articles meeting inclusion criteria to report on AI & robotics

II Goal: provide overview of media studies on technology area X in country X

Main Research question: what do media studies (in the academic literature) report on for technology area X in Country X?

Sub-Research questions (if you have time, or if you had no results in the academic search for I or II): What ELSI are raised in the popular media about technology area X?

Search strategy

A- conduct a search of the literature using parameters below
Search Strategy
     Database: google scholar

     Language: national language and/or English

     Keywords:

Human Genomics

Human Genomics: Media AND (genetics or genomics)

Media coverage AND (Genetics or genomics) AND (ethic or legal or social)

- you can use additional keywords from above, as you please, depending on your time

Analysis

Human Genomics Analysis: fill in tables 4 and 5

B- OPTIONAL: Choose the largest/most important national newspaper (so not regional) in Country X

- Time limit
- explain why you choose this newspaper over others
- search the newspaper for keywords (see below)
- no year limit or year limit, just specify
- Only select articles that specifically address genomics or genetics
- **Analysis: conduct content analysis looking for ELSI.**
    - **Fill in table __ in reporting doc (for Genomics, it would be table 6)**

Keywords
Human Genomics

(Genetics or genomics) and/or (ethics)
(use key words from above)

III- Goal: overview of ELSI of genomics and genetics addressed by other organisations and institutions in country X

Go back to X.3 and see what you would pull out as ELSI.
Add list of ELSI to table ____ (for Genomics it is table 7)

REPORT: see instructions on reporting documents or below

1- **Fill in all tables (see reporting document)**

2- **Write 1.5 page summary: Please keep adequate time to write up a thoughtful and informative summary as this will be the first interface we use for insight into the ELSI of your country.**

Based on your findings (including what is in the table, but not just a copy of the table), write a short summary (1 page results summary + max 0.5 pages for methods) on the ELSI of genomics in your country as found through all searches (try to be specific from which search you found which ELSI) Here are the types of questions we are interested in having answers to

ii. Based on your searches, what were the main ELSI that were addressed in the academic literature specific to your country?

    a. For example for genomics, could you comment specifically on (i.e. were these domains mentioned in your search? Anything particularly interesting to say about them?:

        i. Human germline gene editing? In research? In clinic?

        ii. Genetic testing?

        iii. Genetic screening?

            1. Prenatal screening and/or testing?

            2. Newborn screening?

        iv. Direct-to-consumer genetic testing and adverstising?

        v. Databanks? Biobanks?

        vi. Patents?

        vii. Direct-to-consumer genetic testing

iii. According to your experience, do these seem the same or different than issues discussed in other countries/Europe/America/Asia-wide?

        i. If the same/different, why do you think that is? What contextual factors play a role here?

iv. Can you contextualise these ELSI in the larger cultural, financial, religious, political or societal context of your country?

v. Are there themes that are surprising to find? Surprising not to find

vi. Did you find a preponderance on one issue and nothing on many others? Can you explain why this is?

vii. Can you glimpse a trend based on years (2018-2013; 2012-2008 etc…)?

viii. What do you think are the most important ELS issues for SIENNA to know about/focus from your country that would help for the larger task X.4 (ethical analysis) and even tasks X.7 (ethical framework proposal)

Annex 4: Summary of Foresight Survey Results with Experts

	1. According to you, what are the important upcoming technological developments in the field of human genetics and genomics?	2. Why did you choose to tell us about this technology?	3. At what stage of development the technology is?	4. How soon the technology is likely to be implemented?	6. In which fields do you have expertise?	7. In which country do you work?
#30	Panel/genome analysis prenatal/ carrier set up	Social implications for prenatal care/health risk perception, partnership and family identity/values	It has been implemented recently	In the next 5-10 years	Genetic counseling as a clinical geneticist, cytogenetic laboratory	Germany
Answer #29	Federated networks in genomic data sharing	The importance of secure and broad access to the genomic data makes developments around genomic data sharing and access very important.	It has been implemented recently	It has been recently implemented	Ethics, law and policy	
Answer #27 (a)	Ongoing innovation and application of CRISPR technology within the field of human genetics and genomics.	CRISPR represents an interface of rapid scientific and technological innovation with equally significant ethical and social factors that will continue to pose a	Other – Write In: This area of S&T is well advanced but its use may well be hidden and that, in and of itself, is of great import.	It has been recently implemented	Economics and public policy applied to health care, public health and population health	Canada

		major questions for science and society in the coming years.			
Answer #27 (b)	The application and ongoing innovation at the interface of genomics and the Artificial Intelligence (machine Learning, Natural Language Processing…)	This has the ability to transform human genetics and genomics research in heretofore unknown ways, thereby advancing innovation at a speed and in directions that are not easily understood at this time.	Advanced research	Within the next 5 years	
#27 (c)	Nanotechnology	Potential impact on the field deployable sensors, personal medical devices has the potential to transform the detection, surveillance and research into many diseases that are strongly influenced by humanities genome and the genomes of other parts of our world such as the microbiome.	Advanced research	Within the next 5 years	

#26 (a)	Circulating tumor DNA analysis (liquid biopsy)	- Could be used to identify genetic changes that can guide treatment in tumours where access to tissue for analysis is difficult e.g. due to location, due to origin being unknown, due to inability to remove much tissue, etc - Could be used for "fuller picture" of genetic changes in tumour than that obtained from surgical tissue - Could be used for monitoring tumour recurrence - Could be used for screening "healthy" individuals for earlier tumour detection	Other – Write In: All of the above	It has been recently implemented	Genetics, Genomics, Genetic Counseling, Implementation of genomic technology in healthcare setting, Product development, Genomic Education.	UK
#26 (b)	Epigenetic marked detection (liquid biopsy with detection of	- Similar reason to circulating tumor SNA but utility beyond	Transnational stage	Within the next 5 years		

	epigenetic markers)	cancer application e.g. in disease diagnostics.				
#26 (c)	CRISPR/Cas9 (or other gene- editing technology such as zinc fingers) coupled with induced pluripotent stem cell technology	Potential to engineering a patient's own cells to correct a genetic disorder. E.g. http://www.sciencemag.org/news/2017/11/boy-rare-disease-gets-new-skin-thanks-gene-corrected-stem-cells	It has been implemented recently	It has recently been implemented		
#26 (d)	Single cell DNA and RNA sequencing i.e. advances in microfluidics that make this possible e.g. https://www.10xgenomics.com/solutions/single-cell/	There are lots of presentations about it at ASHG this year!	Other- Write In: This is a technology that is really been utilized by the research community so in that sense is has been implemented but not in a health care setting	-		
#25 (a)	Germline gene editing	Because of its potential to intervene/influence/modify in future generations	Advanced research	In the next 5-10 years	Psychological and social aspects of genetics Genetic Counselling	Portugal

					Pre-symptomatic testing	
#25 (b)	Whole genome sequencing	Because it has the potential to be implemented, and mainstreamed, in health systems (or, in some cases, already is being implemented)	It has been implemented recently	Within the next 5 years		
# 23	FAIR (Findable, Accessible, Interoperable, Reusable) data applied to genomics	The implementation of such technology will enable to share and reuse genomic datasets derived from publicly funded research	Advanced research	Within the next 5 years	Biomedical Informatics	Spain
#22 (a)	WGS whole genome sequencing	Reduce the %age of undiagnosed patient with suspected genetic disease, way to diagnosis might also be faster. Incidental findings will become common, and their management will be a big challenge.	Transnational stage	Within the next 5 years	Genetic counselling	France
#22 (b)	NIPD non invasive prenatal diagnosis	This is a technology with many different test	Other-Write In: some test are	In the next 5-10 years		

		possible. NIPD fetal trisomy testing NIPD fetal fine caryotype (microdeletion/ microdupplication NIPD fetal mutation screening	recently available, other under research			
#22 (c)	Gene therapy	Letal or very severe condition might become curable. A very few disease can be treated by gene technology actually, but success in these pathology could concern much more disease and much more patients maybe in few years.	Advanced research	In the next 10-20 years		
#21 (a)	WGS on foetal DNA in maternal blood	Whole genome sequencing is one of the most challenging technogy in genetics because: 1) we still don't know everything about the	Advanced research	Within the next 5 years	Genetics Counselling	France

		DNA 2) it is still very challenging to classify plenty of " variation of unknown significance" 3) do we really want to know about adulthood deseases at a 8 weeks pregnancy stages ? 4) it will be very hard to not slip on eugenism				
#21 (b)	CRISRP-Cas9	It is a very effective technology for gene editing and it is very cheap. So it must be very tempting to use it in Gene Therapy!	It has been implemented recently	It has been recently implemented		
#19	Web-based decision support tools for Pharmacogenomics	-	Translational stage	Within the next 5 years	Pharmacogenomics	Greece
#18 (a)	Point of care genotyping for CYP alleles prior to prescription of new drug	Adverse drug reactions are a huge problem on both clinical and economical basis. Rapid identification of those likely to experience reactions or simply	Translational stage	In the next 5-10 years	Human genetics and Genomics Genetics Health professional and public education	UK

		those for whom the drug will not work would allow more focused and efficacious treatments.				
#18 (b)	Polygenic/ genome risk score assisted IVF. Using multiple genomic loci to predict disease risk and assist in choosing the most health embryo for implantation.	As a natural extension to expanded carrier screening, this technology potentially using millions of loci for a given condition will give insight into disease risks over and above the existing monogenic context. Some GRS have found risk ratios equivalent to monogenic variants.	Advanced research	In the next 5-10 years		
#16	In my opinion technology that will become increasingly important is the analysis of the epigenome.	I think that's what's missing in our interpretation of the results. This may also explain the clinical variations.	idea	In the next 5-10 years	Clinical genetics	Belgium
#15 (a)	Crispr- cas	Somatic therapy for genetic disease, will change how we view	Early research	In the next 10-20 years	Social research/implem entation research	NL

		and consequently may have impact on other domains (reproductive decision making etc.)				
#15 (b)	NIPT	Fetal DNA and RNA, opportunities ot screen for health/ disease in fetus beyond common aneuploidies but also for foetal maternal risk factors (preeclampsia)	Translational stage	Within the next 5 years		
#14	Single cell genomics/transcriptomics	Single cell genomics is important because it helps to better understand function of cells in complex environment. It is especially important in heterogeneous cellular systems like cancer, stem cell differentiation, immune system.	It has been implemented recently	It has been recently implemented	Microfluidics, biomedical engineering, physics, medical diagnostics, biochemistry, genomics.	United Kingdom