D2.7: Proposal for an ethical framework for the assessment of genomics technologies and for research in genetics and genomics

[WP2 – Human Genetics and Genomics]

Lead contributor	Mats Hansson, Uppsala University
	E-mail: Mats.Hansson@crb.uu.se
Other contributors	This report is based partly on the SIENNA results reported in 2.2 2.3, 2.4, 2.5 and 2.6, thus with due acknowledgement to contributors to these reports
	Solveig Fenet-Chantereau, Uppsala University
Reviewers	Jantina de Vries, University of Cape Town
	Adam Panagiotopoulos, Trilateral Research

Due date	1 May 2020
Delivery date	1 May 2020
Type	Dissemination Public
Dissemination level	PU = Public
Keywords	Genetics, genomics, research, framework, ethics self-assessment, ethics review

The SIENNA project - *Stakeholder-informed ethics for new technologies with high socio-economic and human rights impact* - has received funding under the European Union's H2020 research and innovation programme under grant agreement No 741716.

Abstract

This SIENNA report 2.7 provides an assessment and integration of key results from SIENNA Reports 2.2, 2,3, 2.4, 2.5 and 2.6. A basic learning from these reports is that one has to acknowledge a need to balance different interests against each other, i.e. important human rights for the protection of basic freedoms against human rights related to the potential of benefiting from scientific advances. The report emphasize that ethics must be an integral reflective part of the conduct of science as well as of clinical practice. A principled approach for such a reflective work is suggested to be part of a framework for ethical assessment both of genomic technologies at large and for research in genetics and genomics. The framework proposes a set of nine ethical principles and questions for ethical self-assessment in genetic and genomics research. For emerging technologies in human genetics and genomics where there is yet not sufficient backing in basic science or animal experiments but a possibility for clinical application within a context of compassionate treatment a special governance structure is suggested with an international organization setting up an institute of a *Patient Ombudsman*.

Document history

Version	Date	Description	Reason for change	Distribution
V1.1	1 March 2020	First Draft		10 March 2020
V1.2	5 April 2020	2nd Draft	Comments by Albena Kuyumdzhieva and Isidoros Karatzas (EC), Stefan Eriksson at Centre for Research Ethics & Bioethics at Uppsala University	6 April 2020
V1.3.X	30.04.2020	Final Version	Final version submitted to the EC	30.04.2020

Information in this report that may influence other SIENNA tasks

Linked task	Points of relevance
5.2 A code of responsible conduct for researchers in genomics	CoC will be based partly on 2.7
7.5 Stakeholder communication and public relations	Communication of ethical framework

Table of contents

Executive summary

An ethical framework for the assessment of genomics technologies and for research in genetics and genomics needs to balance different interests against each other, i.e. important human rights for the protection of basic freedoms against human rights related to the potential of benefiting from scientific advances. To be prepared for what may likely develop in the future is an essential responsibility in research. The essential task is to see what may lie in the continuation of a specific technology or a research project. It is therefore the responsibility of the researcher and needs to be based on specific knowledge about the science as well as the context where science may be applied. A continuous dialogue with stakeholders and researchers can identify different values and interests, accumulate a learning over time and initiate new research projects for assessment of perceived risks.

A characteristic feature of current governance frameworks and regulatory procedures in research ethics is that ethical deliberation is often a non-recurrent engagement at the application phase of research or at the initiation of clinical interventions. It considers ethics and its practice as a *fait accompli*, rather than as an ongoing process that takes new developments, intrinsic or extrinsic to the current practice, into regard. This report acknowledges the need that ethics must be an integral reflective part of the conduct of science as well as of clinical practice. We suggest in this concluding report of the SIENNA work package 2 a principled approach for such a reflective work to be part of frameworks for ethical assessment both of genomic technologies at large and for research in genetics and genomics. It can be instituted by funding organisations at the initiation phase and in association with follow-ups.

The researcher has to his/her help a set of well-established ethical principles and guidelines that are fit for such a recurrent exercise on ethical reflection and self-assessment, to be requested by funding agencies and research councils. A framework for ethical self-assessment is constructed based on the following nine principles:

- The principle of autonomy
- The principle of non-maleficence
- The principle of beneficence
- The principle of Justice
- The principle of respect for privacy
- The principle of reciprocity
- The principle of freedom of scientific enquiry
- The principle of attribution
- The principle of respect for intellectual property

A set of questions are specified under each principle and the researcher may be provided with a protocol for responding to these questions. The CIOMS guidelines from 2016 will provide the researcher with detailed insights on concerns related to all relevant aspects of planning and executing a research project.

For emerging technologies in human genetics and genomics where there is yet not sufficient backing in basic science or animal experiments but a possibility for clinical application within a context of compassionate treatment we suggest a special governance structure with an international organization setting up an institute of a *Patient Ombudsman*.

1. Introduction

1.1 Background

This report is delivered in the context of a European Commission (EC) funded SWAFS5 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-18-20166 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 have fed 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 seventh deliverable completed for Work Package (WP) 2, which addresses the ELSI of Human Genomics. Specifically, this report fulfills the task described in the description of action of the project by the following:

"Task 2.7: Proposal for an ethical framework
Integrating results of Tasks 2.4 through 2.6, we will propose an ethical framework for the assessment of genomics technologies that takes into account the views and judgments of ethicists, scientists, CSOs and citizens. The framework will contain principles, guidelines and criteria for ethical decision-making, and will be flexible in accommodating different contexts in which different moralities and stakeholders are at play."

1.2 Objectives

- Assessment and integration of results from SIENNA Reports 2.2, 2,3, 2.4, 2.5 and 2.6
- Proposal of general principles for the conduct of research
- Proposal of a set of ethical principles and questions for ethical self-assessment in genetic and genomics research
- Proposal of an internationally well recognized set of specific guidelines for biomedical research
- Proposal of a governance framework for emerging technologies in human genetics and technologies

1.3 Structure of the report

The report sets out with a background with some key learnings from SIENNA reports 2.2, 2.3, 2.4, 2.5 and 2.6. It then proposes a set of general principles that can be part of a generic code of conduct in all scientific fields. Well recognized ethical principles in biomedical research provide the structure for an ethical framework with specific questions to be part of an ethical self-assessment by researchers in

human genetics and genomics. A governance structure is proposed for meeting the specific challenges associated with clinical application of emerging, yet unproven technologies in human genetics and genomics.

1.4 Scope and limitations

The focus is on human genetics and genomics, leaving all issues related to research in other areas of life science, e.g. plants, animals etc. out. The report does not deal with military research since this would have needed insights from this field and collaboration with military research disciplines, something that is out of scope for the entire SIENNA project. The report does not discuss forensic use of genetic and genomics technologies since this kind of use is object for specific national and EU-regulations, legal premises that are not covered by SIENNA report 2.2.

2. Methodology

Traditional conceptual and reflective analyses common to bioethics research are used in the report with integration of input from stakeholders and surveys as witnessed in previous SIENNA 2 reports.

3. An ethical framework for the assessment of genomics technologies and for research in human genetics and genomics

3.1 General principles for responsible research and clinical practice

Research and clinical practice in human genetics and genomics share ethical responsibilities of science with other areas. General guiding principles may be summarised in the wordings by WHO. The focus here was gene editing but the principles are common and widely accepted as ethical guidelines for all kinds of scientific research:

a) *Transparency* – a commitment to share information on what is happening, how and why it is necessary;
b) *Inclusivity* – a commitment to draw on the full contributions of all parts of global society, thereby providing diverse points of view, skill sets and additional methods of program management and measurement;
c) *Responsible stewardship of science* – a commitment to rigorous science, to follow ethical practice in scientific and clinical conduct, and strive to maximize potential benefits while minimizing potential harms;
d) *Fairness* – a commitment to fair dealings in relation to all persons and groups, and equitable access to opportunities and potential benefits, and support for efforts to encourage research and development of medical interventions that are appropriate and feasible for the widest possible range of populations; and
e) *Social justice and non-discrimination* – a commitment to celebrate and promote diversity by rejecting patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and disability. (https://www.who.int/ethics/topics/human-genome-editing/WHO-Commissioned-Ethics-paper-March19.pdf)

3.2 The need to balance interests - premises based on human rights and legal frameworks

SIENNA report 2.3 identified key human rights norms and regulatory approaches in different regions that could guide the new and emerging technology in the area of human genetics and genomics. The analysis suggested that in many aspects, the existing human right sources offer a good starting point for further examinations and elaborations. A common theme is the need to balance different interests against each other, i.e. important human rights for the protection of basic freedoms against human rights related to the potential of benefiting from scientific advances. An example in kind is how the founding documents of the European Union emphasize both privacy rights and rights to benefit from medical science and clinical development.

The Charter of Fundamental Rights of the European Union (2010/C 83/02) emphasizes the right of each individual to integrity within the fields of medicine and biology, implying a free and informed consent according to the procedures laid down by law (Article 3). Article 8 of the Charter grants the individual the right to the protection of personal data implying that the processing of such data requires consent of the person concerned or other legally-recognized means. These articles conform with the European Convention for the Protection of Human Rights and Fundamental Freedoms, the Social Charters adopted by the European Union and by the Council of Europe. These rights may be motivated by a fundamental respect of each individual's autonomy and right to have control of matters related to oneself, e.g. in this case, the processing of personal data. They may imply a right to know about genetic and other medical information about oneself but also, as has been frequently discussed in the ethical and legal literature and in the SIENNA report 2.4, the right not to know such information. In addition to these autonomy rights the Charter of Fundamental Rights of the European Union also lays down rights of each individual to social security benefits and social services in cases of illness (Article 34) and the rights of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices (Article 35). As described, the charter of the European Union recognizes both the privacy right leading to requirements of respecting autonomy, obtaining consent etc., and the right to health care and social services in cases of illness as fundamental individual rights, notwithstanding that there may also be societal and public health related interests concerned.

Normally, one considers a right to be empty and rather meaningless if there is no corresponding duty. This is usually the case with rights to health, they require someone to take on the corresponding duty, to provide the necessary means for fulfilling the right and to monitor how the rights to health are recognized. Within the European context these duties will fall on the national governments who will have to provide the resources needed for implementing rights to health, medicine and social services. This will not be part of the EU competencies and the European Commission powers. However, they have both the competence and the powers to lay down the principles that should guide how the balancing of the different rights and interests should be made. This is, for example, the role of the General Data Protection Regulation (GDPR) regarding the protection of privacy. The basic principle in this regard is the principle of proportionality as stated in Recital 4: "The processing of personal data should be designed to serve mankind. The right to the protection of personal data is not an absolute right; it must be considered in relation to its function in society and be balanced against other fundamental rights, in accordance with the principle of proportionality".

This guiding principle reflects indeed very well the need of ethical balancing privacy interests against other interests such as those related to carrying out scientific research and using genetic data for the benefit of current and future patients. This was also one of the conclusions of what international

human rights acquis may offer according to SIENNA report 2.3: "First, there are methods of balancing competing rights and interests, with the principle of proportionality as probably the most common tool. Second, the idea of tripartite state obligations – to respect, protect and fulfil – applied to the key human rights norms from different legal orders, mapped in this report, may be used as a framework to include a wide variety of interests at stake in the face of challenges brought by developments in genetics and genomics. Thirdly, the indivisibility of human rights. For example, the duty to respect freedom of scientific research and the right to enjoy benefits of scientific advances would speak for a more permissive approach with fewer interventions from state and international actors. At the same time the duty to protect, among others, right to the highest attainable standard of health, right to privacy, freedom from discrimination, disability rights or principle of dignity, would allow to express many other ethical, legal and social concerns and set limitations for the duty to respect. Similarly, the duty to fulfil could enable to address concerns about equal access to the highest attainable standard of health, about equal enjoyment of benefits of scientific advances or connected to reproductive rights" (2.3. p. 118).

The need to balance interests in association with research in human genetics and genomics is also well reflected in the public surveys and citizen panels reported in the SIENNA reports 2.5 and 2.6. Even regarding such a relatively, from a European-wide perspective, controversial ethical issue as the research on human embryos a "majority of respondents in the telephone survey in 11 countries thought this would be acceptable if the purpose of this research was to understand 'how to treat or cure severe health conditions" (2.5. p.45). As stated several times in the reports, whether the findings were representative of the general population or not is not possible to say due to methodological limitations, still this is one of the main conclusions that could be drawn. In the same vein, one of the conclusions of the citizen panels conducted in five European countries was that Human genomics technologies (screening and modification technologies) were seen as more beneficial and acceptable when: "they provided a solution to a serious medical condition or improved a patient's quality of life" (2.6. p.52) and somatic gene editing was seen as more beneficial than screening technologies "because it provides a solution to a problem" (ibid. p. 42). Even research use of germline editing was generally seen as beneficial, "because it contributes to curing medial conditions for a range of people" (ibid. p. 46). That autonomy rights should not be overlooked is also evident in that "the use of genomic technologies was more acceptable when voluntary and informed consent was provided" (ibid. p.53).

It is regarded as self-evident that in a political democracy, people's values play an important role. Public surveys were therefore an important ingredient in the SIENNA project. Not only all legislation, but also other policy and regulatory decisions, presupposes some degree of anchorage in the values of the people. Despite this, values do not in themselves constitute good arguments, and from an ethical point of view, it is problematic to take these for granted. The reason is that one sometimes changes one's opinions after having acquired more information about the facts, or having perceived the kind of value conflicts which arise, when some value which one esteems is achieved. One perhaps discovers values which had passed unnoticed and undesirable consequences which had not been anticipated. We tend therefore to agree with George Henrik von Wright's idea that informed preferences should be taken more seriously than the preferences we actually happen to have at the moment (von Wright 1997). "To come into possession of, or experience some X which we wish, increases our welfare provided that we would wish this X if we were informed about the causal relations and consequences which hold both for the totality of which X is part and the totality where not-X is included instead of X "(ibid., 7). von Wright speaks in this connection about people's individual preferences, but it ought to be possible to apply this reasoning also to collective political decisions, for example those which apply to the balancing of values at stake in association with regulation of genomics research and technologies.

3.3 Ethical analysis of specific issues will provide further guidance if based on facts

The scholarly literature on ethical and legal analysis in biomedicine is growing rapidly, a small portion of it is referenced in the SIENNA reports 2.3 and 2.4. This literature may provide valuable guidance to researchers, clinicians and policy makers. The European Group of Ethics is another source of information and guidance, currently working on an opinion on gene editing. Ethical analysis is per definition occupied with identifying and analyzing moral concepts, values and principles for deliberation and decision making. An intrinsic requirement is that conclusions and advices are based on a close understanding and acknowledgement of scientific facts and realistic considerations of contexts for research or practice where ethicists and lawyers work closely together with scientists and practitioners. This implies that foresight analyses where current knowledge and practices are extrapolated in order to predict and discuss likely future scenarios is of limited value since there is no factual evidence available. This was also acknowledged by some of the participants in the foresight workshops organized by SIENNA work package 2 where experts concluded that these kind of foresight analyses

- "focussed more on disadvantages than advantages and that they were ultimately not able to balance ethical reflections between Dystopia and Utopia alternatives;
- 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." (SIENNA Report 2.4, p.95)

To be prepared for what may likely develop in the future is an essential responsibility in research. However, one should not make this into a matter of more or less well-grounded speculations outside of any context. The essential task is to see what may lie in the continuation of a specific technology or a research project. It is therefore the responsibility of the researcher and needs to be based on specific knowledge about the science as well as the context where science may be applied. A good example in kind is how questions about dual use have been managed and it is essential to distinguish between possible and probable risks of harm and to keep the level of uncertainty in mind in order not to end up in mere speculations only serving as a piece of rhetoric used to influence public opinion. From an ethical point of view the distinction falls back upon the morally relevant difference between inflicting harm and imposing risks of harm (Kuhlau, 2013).

A problem can be that a researcher is, for good reasons, narrow minded, focusing on the immediate benefits and risks related to a protocol. In order to widen the horizon, one could initiate an ongoing dialogue with different stakeholders and several relevant competences. A continuous dialogue could, besides identifying different values and interests, accumulate a learning over time, initiate new research projects for assessment of perceived risks etc. If a researcher identifies a perceived risk based on his/her proposed project policy makers/officers could be responsible for initiating the dialogue, create structures and spaces for discussion and deliberation.

3.4 Ethical assessment of genomics technologies in research as well as in clinical contexts and policy making should be a continuous practice

Ethical reflection and deliberation as well as the development of normative guidelines and regulatory frameworks need to be constantly tuned to both developments of science and changes in moral cultures. For both animal and human research there are well established procedures with ethical assessments laid down in national, European and, often also in international law. For clinical applications there are legal premises as well as professional best practices and recommendations available. However, a characteristic feature of all this is that ethical deliberation is often a non-recurrent engagement at the application phase of research or at the initiation of clinical interventions. It considers ethics and its practice as a *fait accompli*, rather than as an ongoing process that takes new developments, intrinsic or extrinsic to the current practice, into regard. Ethics needs to be an integral part of the conduct of science as well as of clinical practice. For example, a researcher using animals in his or her research may be granted permission by an ethics review committee based on an assessment of expected scientific utility versus estimated pain inflicted on the animals or the number of animals needed for the experiment. However, when something unexpected happens there are no or few mechanisms available when the researcher can go back and ask a committee what to do. Ethics need therefore be an integral part of research and ethical reflection a continuous affair. Human studies face similar problems, even if there are some mechanisms in place e.g. data monitoring committees that can intervene and discontinue a clinical trial. Guidelines may be helpful at the onset but one needs to engage a reflective capacity of the researcher, the clinician as well as the policy maker, including those issuing guidelines. The reflective approach we suggest in this report emphasizes the role and the responsibility of the researcher and the clinician for taking due care to the ethics of research and practice. Something that can't and should not be handed over to an ethical committee.

We suggest in this concluding report of the SIENNA work package 2 a principled approach for such a reflective work to be part of frameworks for ethical assessment both of genomic technologies at large and for research in genetics and genomics. It can be instituted by funding organisations at the initiation phase and in association with follow-ups. For certain emerging technologies we will suggest an additional governance structure (see 3.6)

3.4.1 Identifying stakeholders and interests at stake

Göran Hermerén, Senior Professor of medical ethics at Lund University and former Chair of the European Group on Ethics in Science and New Technologies (EGE) (2002-2011), suggested early on that one for the conduct of ethical reflection could apply what he called an "actor perspective" where the first task is to identify those who are stakeholders, the interests that are at stake and potential conflicts between different interests (Hermerén 1986). The researcher, the clinician and the policy maker should start out by asking three questions:

I. Who is a stake holder in this context?
II. What interests are a stake for each stakeholder?
III. How may different interests be in conflict with each other?

For practical reasons one needs to limit the identification of stakeholders to those who are directly concerned and related to the conduct of research and affected by the results of research. In a research context this may be the researcher, someone providing data or biosamples for the research, someone doing statistical analysis, the research subjects and, in case of minors as human research subjects and in genomics research, relatives to research subjects. The funder of research may have interests and

there may be interests related to what becomes an object of research, both with associated ethical issues. However, they are not directly concerned with the conduct of research and policy issues need to be managed at other levels, e.g. as when the European Commission issues calls for exploration of ethical aspects related to emerging new technologies. End users of research results, e.g. public health authorities and industry, may have significant interests that need to be considered. Research colleagues may have issues regarding the focus of research and the selection or use of methodologies but these matters are to be sorted out in different forums, e.g. in peer review, at science conferences or in research seminars. They therefore do not belong to the directly concerned stakeholders. For clinical interventions the directly concerned stakeholders are the patients. Health policy decisions may imply other stakeholders, e.g. when limited resources have to be prioritized between different medical needs and patient groups.

Interests at stake may, e.g. be privacy concerns, the need to improve diagnosis or medical treatment, get an appropriate balance between effects and adverse reactions related to a treatment and the interest to be treated fairly. The identification of interests is by nature context bound. Whole Genome Sequencing (WGS) may in some instances only provide risk information that is not really actionable and may inflict nothing but increased anxiety. In other situations it may provide an avenue to new treatment opportunities as when, e.g. the Swedish Childhood Cancer Fund together with the infrastructure Genomic Medicine Sweden decided to offer WGS to all children with cancer based on a singular case of experimental treatment where gene sequencing for a young boy with cancer revealed a mutation that was focus for a clinical trial in adult patients. The medicine was given to the boy who recovered from his cancer.

It should be observed that it is only a matter of identifying stakeholders, their interests and potential conflicts between the different interests. It is not an invitation or a requirement to engage in lengthy ethical analyses. The first step towards reaching some kind of balance between different interests and different stakeholders require, however, a more sophisticated principled approach.

3.4.2 A principled approach to help researchers identify ethical issues pertaining to their research

Development and application of genomic technologies as well as research projects in genetics and genomics is naturally situated within the broader contexts of biomedical research and biomedicine. Tom Beauchamp and James Childress formulated a set of principles that have since become well accepted both within the biomedical research community and in biomedicine (Beauchamp & Childress 2012). The principles are not like principles used in natural or medical science, such as principles behind gel electrophoresis that determine and explain why molecules move differently in an electric field depending on their size and charge. The principles of biomedical ethics are of a *heuristic* kind, which means that their role is to make us, in the case discussed here researchers, clinicians or policy makers, to ask morally relevant questions to a proposed project or a clinical intervention. They are here intended to help out and give morally relevant guidance in an act of self-reflective assessment. There is, as explained above, always a need to reach a balance between different considerations, but the principle of respect of autonomy has priority, being the basis of morality itself. One of Beauchamp & Childress' main ideas was that the principles proposed would be common to any theoretical premise in moral theory, i.e. provide the common ground for practical reflection by both deontologists and consequentialists. As such they have also gained wide acceptance. See also The World Medical Association Declaration of Reykjavik – Ethical considerations regarding the use of genetics in health care (2019) that is following the same principles. As exemplified in Beauchamp & Childress' book and

in the literature the concept and place of autonomy and its extension into rules of informed consent are still under development. The basic principles for biomedicine and their underlying concerns are:

I. The principle of autonomy
This principle reflects the close connection between respect for persons, self-determination and decision-making in health care and research. It requires assessment of the capacity for autonomy of patients and research subjects and points towards the importance of disclosure of all relevant facts, the attainment of understanding and the securement of voluntariness, all leading to the establishment of a free and informed consent. Following this principle questions for self-reflective assessment may be:

a) Has the research subject sufficient cognitive capacity to understand?
b) If not, is there someone who can act as a trusted proxy?
c) Have you disclosed all relevant facts?
d) Do they understand and how do you ensure that understanding is sufficient?
e) Is participation voluntary and how do you ensure voluntariness?
f) How will your appropriate information and consent procedure look like?
g) Is there an effective means to withdraw participation or medical intervention?

II. The principle of non-maleficence
The principle of non-maleficence is a primary concern dating back to the *Hippocratic* oath *primum non nocere*. It will in practice not be that simple because there are seldom any research projects without any risk of harm, nor any medical interventions that only carry good effects with no risks of adverse events. It is also true that the search for benefits in practice always come first. The researcher has a goal of scientific utility and the advance of science in mind that motivates the project, in the first place whether it is only related to basic science or to clinical application. However, after that stage the first consideration is related to minimizing harm. Following this principle questions for self-reflective assessment may be:

a) Are there any foreseen risks of direct or indirect harms (physical, psychological, privacy related), short-term and long-term, associated with the project/intervention?
b) May these risks be mitigated and, if so, how?
c) Is there a possibility to minimize harm while still answering the research question?
d) Do you see any potential long-term risks related to the new knowledge that will be acquired through the project and, if so, how may these be assessed and mitigated?
e) May an animal for a project be replaced with an animal lower in the animal series, or even by a simulation/computer model?
f) In practice the principle of non-maleficence needs to be balanced against the principle of beneficence and the prospective benefits.

III. The principle of beneficence
Prospected benefits may in some instances justify risks of harm, provided that there is a fundamental respect of autonomy. Benefits may come in terms of, e.g. scientific utility, new biological knowledge, new and better scientific methods, new diagnostic opportunities, better treatments, new treatment modalities or quality of life. The identification of benefits is context-bound and concepts will need clarification but questions posed on a general level may be sufficient for a researcher, clinician or policy

maker to identify, explain and assess what is relevant in a specific context. Following this principle questions for self-reflective assessment may be:

a) What direct and indirect benefits, short-term and long-term, may be expected?
b) Who are the beneficiaries?
c) Are the beneficiaries the same as those facing risks of harm?
d) How may the balance of benefits and risks of harm be justified?
e) How is this communicated to research subjects, patients and concerned parties?

IV. The principle of justice
Fairness or desert is related to what is owed to persons. It can be a question of being entitled to have a say in matters where one's own life, health and quality of life is at stake, to be treated decently and with respect, to receive relevant information in a lay-friendly way that helps understanding. It can also, as has been described extensively in the SIENNA report 2.2., be a matter of respecting certain human rights and freedoms, e.g. pertaining to gender, ethnicity, vulnerable groups. Distributive justice is another matter of justice. It is concerned with the appropriate distribution of benefits and burdens, opportunities and privileges. Both elements of justice are important for assessment in research and practice. Following this principle questions for self-reflective assessment may be:

a) Are there any vulnerabilities that should be observed when selecting subjects for research or medical intervention?
b) Are there subjects who are at the risk of exploitation?
c) May the research or intervention target less vulnerable subjects while still answering the research question?
d) How may risks of exploitation or discrimination be avoided or mitigated?
e) How may the distribution of benefits and burdens be justified?
f) Is there a transparent and open process for the distribution of benefits and burdens?

Specifically, for research projects, there are several principles used in order to ensure fair distribution of opportunities, privileges, costs and gains. Science has to an increasing extent moved from one individual making significant leaps in knowledge towards science as being a collaborative effort with many participating researchers within and across disciplines and national borders. Data and biological samples collected at one site needs to be exchanged and used in collaborative projects with other researchers in order for, at the end, provide meaningful results to patients. Sharing data and bio-specimens is essential for the discovery, new knowledge creation and translation of various biomedical research findings into improved diagnostics, biomarkers, treatment development, patient care, health service planning and general population health. The growing international agreement on the need to provide access to research data sets to optimize their use and fully exploit their long-term value has been articulated in many documents, including the OECD Principles and Guidelines for Access to Research Data from Public Funding, the Toronto Statement, and more recently the Global Alliance for Genomics and Health's White Paper. (Global Alliance White Paper. http://oicr.on.ca/oicr-programs-and-platforms/global-alliance/white-paper, OECD principles and guidelines for access to research data from public funding. http:// www.oecd.org/dataoecd/9/61/38500813.pdf, (Birney 2009).

Ideally, data and bio-specimens should be made widely available to the most inclusive and ethically responsible research community, but there is often resistance by institutions and individuals who fear

that they will not receive recognition for their investment in building collections. Real and perceived risks of discrimination of vulnerable patients' groups because of health-related data sharing also exist and must be considered in any regulatory and ethical framework. Collecting data and storing biological samples in accordance with ethical and scientific standards requires intellectual, institutional and economic resources and, critically, the participation of patients and the wider community including otherwise healthy volunteers. The American College of Epidemiology Policy Committee suggested the following five principles, that we have adapted her to fit a broader context of technological development and research, contributing to the ethical framework for self-reflective assessments. (Ness RB et al., 2007).) In recognition of the collaborative and participatory nature of research and technological development we suggest the wording "custodianship" rather than "ownership".

V. The principle of respect for privacy
Custodianship of data and bio-specimens implies protection of participants' privacy. Privacy protection measures should be in place and informed consent must provide provisions for future as yet unspecified research using data and bio-specimens. Following this principle questions for self-reflective assessment may be:

a) What measures have been taken in order to protect the privacy of research subjects?
b) How are research subjects informed about measures for protection of their privacy?
c) What mechanisms are in place for making sure that data or bio-specimens are not used beyond what is consented?
d) If secondary/further use of data and/or bio-specimens is considered how have research subjects been informed about this?

VI. The principle of reciprocity
Custodianship implies giving back. Feedback of general results should be channeled to institutions and patients. Following this principle questions for self-reflective assessment may be:

a) How will feedback to participants about general research results be executed?
b) How will feedback to institutions and funders making the research possible be executed?

VII. The principle of freedom of scientific enquiry
Custodianship should encourage openness of scientific enquiry, and should maximize data and bio-specimen use and sharing so as to exploit their full potential to promote health. To the need of encourage openness of scientific enquiry responds also the FAIR principles published in *Scientific* Data 2016 (Wikinson et al., 2016). The FAIR principles provide guidelines on how to improve the findability accessibility, interoperability and reuse of data and digital assets. Following the principle of freedom of scientific enquiry questions for self-reflective assessment may be:

a) What measures have been taken in order to make data- and bio-repositories accessible to researchers outside the present consortium?
b) How will you attain an open and transparent discussion of research methods and results?
c) How will you ensure that your research results are in principle and in practice reproducible by other researchers?
d) What will you do in order to adhere to the FAIR principles?

VIII. The principle of attribution
The intellectual investment of investigators involved in the creation of data registries and bio-repositories is often substantial, and could be acknowledged by mutual agreement. Following this principle questions for self-reflective assessment may be:

a) How will you give appropriate recognition of intellectual and substantial contributions to the design of the project?
b) How will you give appropriate recognition of intellectual and substantial contributions regarding collection of data or biological samples?
c) How will you give appropriate recognition of intellectual and substantial contributions regarding preparation and writing of manuscripts for publication?
d) How will you acknowledge contributions regarding the above that are significant but not substantial?

IX The principle of respect for intellectual property
The sharing of data and biospecimens needs to protect proprietary information and address the requirements of institutions and third-party funders. Following this principle questions for self-reflective assessment may be:

a) How will you ensure that intellectual property interests of researchers, institutions and third-party funders are not jeopardized?
b) How will you ensure that important commercial interests conducive to the application of your research results are not jeopardized?
c) How will you attain an appropriate balance between commercial and public interests?

3.5. Guidelines will give directions and help

The SIENNA report 2.2. has provided a detailed oversight and analysis of guidelines for the assessment of genomics technologies as well as research in genetics and genomics (2.2. Section 4). The focus is on human rights and related documents. SIENNA report 2.4 gives an overview of relevant codes and declarations (2.1.3). There is always an issue regarding the justification and legitimacy of guidelines (Smith and Weinstock 2019). For European research involving collection and use of personal data this is not so much of a problem since the GDPR has laid down clear terminologies and legal premises, that in turn are complemented by national law. Concrete guidance is provided in: https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-data-protection_en.pdf

For research in general the situation is not that clear, even if some national jurisdictions have laid down clear premises in law, e.g. the Swedish Ethical Review Act. There is no need here to repeat in this report what is already made available elsewhere. The SIENNA report 2.4 provide information to several other guidelines and supportive documents both for the assessment of genomics technologies in general and for research in human genetics and genomics (Section 2.4).
Of special relevance is: The International ethical guidelines for health-related research involving humans 2016 by The Council for International Organizations of Medical Sciences (CIOMS). These guidelines have been substantially revised since the last version from 2002. There has also been an effort to align with the transnational guidelines issued by the World Medical Association, The Helsinki Declaration from 2013. Of interest for the wider field of genomics technologies is the new emphasis in the CIOMS guidelines regarding the social value of research and the prominent notice of

vulnerable populations. For a thorough discussion of these guidelines see *Bioethics* 2019, Vol. 33, No. 3. In addition, for application in clinical settings see: The World Medical Association Declaration of Reykjavik – Ethical considerations regarding the use of genetics in health care (2019).

The CIOMS guidelines (https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/) include detailed and helpful proposals for conducting research, summarized in 25 guidelines and 2 appendices:

Guideline 1: Scientific and social value and respect for rights

Guideline 2: Research conducted in low-resource settings

Guideline 3: Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research

Guideline 4: Potential individual benefits and risks of research

Guideline 5: Choice of control in clinical trials

Guideline 6: Caring for participants' health needs

Guideline 7: Community engagement

Guideline 8: Collaborative partnership and capacity-building

for research and research review

Guideline 9: Individuals capable of giving informed consent

Guideline 10: Modifications and waivers of informed consent

Guideline 11: Collection, storage and use of biological materials and related data

Guideline 12: Collection, storage and use of data in health- related research

Guideline 13: reimbursement and compensation for research participants

Guideline 14: Treatment and compensation for research-related harms

Guideline 15: Research involving vulnerable persons and groups

Guideline 16: Research involving adults incapable of giving informed consent

Guideline 17: Research involving children and adolescents

Guideline 18: Women as research participants

Guideline 19: Pregnant and breastfeeding women as research participants

Guideline 20: Research in disasters and disease outbreaks

Guideline 21: Cluster randomized trials

Guideline 22: Use of data obtained from the online environment and digital tools in health-related research

Guideline 23: Requirements for establishing research ethics committees and for their review of protocols

Guideline 24: Public accountability for health-related research

Guideline 25: Conflicts of interest

Appendix 1 Items to be included in a protocol (or associated documents) for health-related research involving humans

Appendix 2 Obtaining informed consent: essential information for prospective research participants

These guidelines are openly available on line and recommended for specific guidance regarding concerns related to genomics research and technologies.

3.6. Emerging technologies will use the same principled approach and the same guidelines but a different governance structure

It may be believed that some genomic projects and technologies require other ethical and legal approaches due to their complexity or novelty. Gene therapy, preimplantation genetic diagnosis, whole genome sequencing or gene editing may be candidates in kind. They have all stirred intense ethical discussions when they first were presented in scholarly journals and conferences or reported in public media. Some early research applications with these technologies were indeed premature and should have awaited better evidence but, after some progress and more scientific evidence about benefits and risks, they will all belong to main stream medical science. At each stage they will all benefit from the same principled self-reflective approach suggested here but, for reasons explained, novel and emerging technologies need a different governance structure.

New technologies in genomics and genetics emanate from basic science long before any dedicated project proposals are developed. Later they are tested in animal models and sometimes in experimental treatment procedures, long before any formalized clinical trials following regulatory approvals are initiated. Research projects involving patients or healthy volunteers are fairly well

regulated across the globe. The use of animals as experimental models is also well regulated. Experimental treatments of human patients are not that well-regulated and they may sometimes be based on a doctor's privilege to use a vital indication for treatment or compassionate treatment of a patient in a clinical circumstance in order to save the patient's life. Other terms used are innovative, novel, unproven, unvalidated, non-standard, and unlicensed treatments (Nuffield Council of Bioethics, Briefing Note 2018). In practice there is a grey zone and the balance between estimated benefits and risks is not based on scientific evidence.

It should be clearly acknowledged that experimental treatment a such may indeed be justified, being in the best interest of an appropriately informed patient and in accordance with professional codes of conduct. However, there is a grey zone and some of the emerging technologies in genomics and genetics have initiated experimental treatments and clinical introductions that have been criticized for being premature.

Gene therapy was proposed as a promising new technology forty years ago and treatment for alpha 1 antitrypsin deficiency was one of the first treatments. Later came treatment of severe combined immune deficiency syndrome (SCID). The context matters since for antitrypsin one didn't need to reach a precise amount of the protein in order to get an immune response. 10% was still an improvement. For SCID the problem was that the treatment as a side-effect triggered oncogenes in the treated children. The professional societies issued different regulatory frameworks, e.g. research protocols that involved specified animal experiments in the whole animal series up to primates. Forty years later there are several clinical trials with gene therapy and the technology is moving into main stream medical science governed by ordinary regulatory frameworks for clinical trials.

The development of preimplantation genetic diagnosis (PGD) has received a lot of attention since its commencement at the beginning of the 1990's, not only in the fields of reproductive medicine but also among lawyers, philosophers and politicians. Parliamentary committees and ethics committees specially assigned for dealing with issues related to PGD assumed the task of balancing the interests and values believed to be at stake. Patients undergoing PGD had experienced repetitive miscarriages, they had previously given birth to affected children or they had experienced serial terminations of pregnancy. The technology has provided significant opportunities of benefit to these women and couples. Governance structures look differently around the globe. Normally PGD requires a serious condition in order to warrant treatment. In the beginning *ad hoc* ethical committees were set up for deciding who would be eligible for treatment with no clear guidelines for making these decisions. A still contested issue is who shall be in judge about what is to be considered a serious disease. A governance framework for PGD need to find an answer to the question if ethics committees or the women and the couples themselves are best suited to assess their situation, what burdens they are willing to bear, and how serious the condition is.

Following rapid progress in genome sequencing, genetic information will to an increasing degree be relevant in clinical settings in order to provide more precise and personalized diagnosis and treatment for patients. However, with this progress comes the obligation to ensure that providing patients with genetic risk information leads to patient benefit. Recent development in high-throughput genetic health care technologies is capable of generating large volumes of genetic risk information, including information about unsolicited findings. This development gives rise to hopes of individualized health advice and selection of optimal treatment and prevention. However, being diagnosed with a risk of genetic disease can also evoke negative emotions like guilt of passing the condition on to your children, worry about future events and cognitive confusion about genetic testing and diagnosis. Understanding

and dealing with genetic information is influenced by cultural and educational differences, and the public in general have limited understanding of genetic information which makes the introduction of next generation sequencing into clinical every day practice a challenge and emphasize the need of ensuring patient benefit, and to this end, appropriate governance structures.

Gene editing using CRISPR-Cas9 technique or other techniques is a fairly new technology. It holds significant possibilities to knock out disease genes or modify genetic elements, e.g. changing HLA type of iPS cells to be transplanted. Also, here there has, however, been examples of experimental treatment that was clearly premature. A Chinese scientist used a gene-editing procedure (CRISPR-Cas9) to rewrite the DNA in two girls' embryos. The scientist claimed the modifications would make the children immune to HIV by turning a gene called CCR5 into a mutant form that prevents the virus from invading cells. However, there was no scientific evidence backing this and no appropriate estimate if the expected utility was balancing foreseen risk. The scientist was sentenced to three years in prison for violating medical regulations. There is, clearly, need of some governance structures, but also important to ensure continuous development of the gene editing technologies.

In conclusion, regarding these four examples one needs both to ensure scientific progress in the field but also prevent premature experimental treatments. Scientists should engage in self-reflective assessment following the proposed principled framework but there is a need of clear governance structures. There is EU Regulation in place regarding compassionate use of unauthorized medicines. (Ref: Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency). For advanced therapies, such as stem cell and gene therapies, there is a requirement of a centralized European marketing authorization, granted by the EC following assessment by the EMA, before they can be supplied in the UK and Europe.

Setting up governance frameworks for experimental treatment using novel genomics and genetics technologies on a local level at each hospital is not feasible since there will not be many cases. Even on a national basis a specially assigned monitoring and governance system would not have much to do. We suggest that e.g. EMA, WHO, OECD could play an important role and we would like to invoke the idea of setting up an institution with a *Patient Ombudsman*. It is when these technologies are first set up on an experimental basis with intervention at a singular patient or small group of patients that the ethical concerns become prominent. It is also in association with such interventions that previous cases of premature introduction of novel, experimental technologies have entered the public debate. A scientist planning such an intervention could turn to the *Patient Ombudsman* for external review and advice. The scientist would be requested to fill out a self-reflective ethical assessment as described above and be informed about any regulatory premises applicable.

The *Patient Ombudsman* could also be an institution where patients could appeal when they have been denied PGD by a national authority or ethics committee. There would not be any legal effects of such an appeal but patients' rights would be strengthened and an advice could be brought back to the national authority or ethical committee. Three examples from Sweden where patients have been denied PGD may illustrate the need of a possibility to appeal. A couple with a child with galactosaemia, an autosomal recessive disorder, asked for PGD. They love their child and take full parental responsibility for it but they strongly feel that they would not manage to have another child with the same disease. A 38-year old woman with a history of several miscarriages strongly feels that she will not manage a child with Down's syndrome. She wants to take part in a PGD programme. A 36-year-old

father suffering from hereditary prostate cancer, an autosomal dominant disease but with no genes yet identified and characterised, requests PGD. He is infertile and suffering from incontinence. There are frozen sperms available. A son would have a 50% risk of getting the same kind of cancer while a daughter would have a 50% risk of being a carrier. The father strongly feels that he cannot pass on such a condition to his son. Taking the available rules and guidelines into consideration, all three cases mentioned would be disqualified for PGD.

4. Conclusion

Research on genetic and genomics technologies give rise to concerns on ethical issues that are discussed widely at many levels across the globe. In this report we conclude that the best way forward in this field regarding research ethics is to acknowledge the primary responsibility of the researcher who by knowing the factual circumstances is well equipped to identify and assess the benefits and risks associated with the research. The researcher has to his/her help a set of well-established ethical principles and guidelines that are fit for a recurrent exercise in ethical reflection and self-assessment, to be requested by funding agencies and research councils. For emerging technologies in human genetics and genomics where there is not yet sufficient backing in basic science or animal experiments but a possibility for clinical application within a context of compassionate treatment we suggest a special governance structure with an international organization setting up an institute of a *Patient Ombudsman*.

References

Ballantyne A, Eriksson S (eds.) Special Issue: Research Ethics Revisited, *Bioethics* **33** (3) March 2019.

Beauchamp TL & Childress JF, *Principles of Biomedical Ethics* 7th edition, Oxford University Press 2012.

Birney, Prepublication data sharing, Toronto International Data Release, *Nature* 461:168–170.

CIOMS Guidelines 2016: (https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/.

Global Alliance White Paper. http://oicr.on.ca/oicr-programs-and-platforms/global-alliance/white-paper

Hermerén G, Kunskapens pris: forskningsetiska problem och principer i humanioras och samhällsvetenskap, Stockholm : Humanistisk-samhällsvetenskapliga forskningsrådet (HSFR) 1986.

Kuhlau F, *Responsible conduct in dual use research towards an ethics of deliberation in the Life Sciences,* Acta Universitatis Upsaliensis, Uppsala 2013.

Ness RB. on behalf of the American College of Epidemiology Policy Committee: biospecimen "ownership": point. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 188–189.

Nuffield Council of Bioethics, Briefing Note 2018.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004.

https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-data-protection_en.pdf

http:// www.oecd.org/dataoecd/9/61/38500813.pdf

Smith J, Weinstock D, Political legitimacy and research ethics, *Bioethics Bioethics* **33** (3): 312-318, 2019.

The World Medical Association Declaration of Reykjavik – Ethical considerations regarding the use of genetics in health care (2019).

The Charter of Fundamental Rights of the European Union (2010/C 83/02)

von Wright, Georg, Henrik, The Good of Man, i: Carson, Thomas, L., Moser, Paul, K., (eds.) *Morality and the Good Life*, Oxford University Press, New York 1997, s. 147-163.

Wilkinson MD, et al., Comment: The FAIR Guiding Principles for Scientific Data Management and Stewardship, *Scientific Data* 3:160018 doi: 10.1038/sdata.2016.18 (2016).

(https://www.who.int/ethics/topics/human-genome-editing/WHO-Commissioned-Ethics-paper-March19.pdf).