WP 2: Proposal for operational guidelines for ethical self-assessment of research in genetics and genomics

[WP2 – Human Genetics and Genomics]

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Introduction

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 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 and the clinician. The reflective approach suggested here 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.

A principled approach for such a reflective work is to be part of a framework for ethical self-assessment regarding research in genetics and genomics. It can be instituted by funding organisations at the initiation phase and in association with follow-ups. Reference material are provided to help the researcher elaborate on specific issues.

1. Identifying stakeholders and interests at stake

The first task is to identify those who are stakeholders, the interests that are at stake and potential conflicts between different interests (Hermerén 1986):

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.

Task 1 in ethical self-assessment: identify stakeholders and their interests

I. Identify those current and future parties who may be stakeholders in relation to your research.

II. Identify and describe the interests of each defined type of stakeholder.

III. Identify and describe if and how interests may come into conflict with each other.

2. A principled approach for reaching a balance between different interests of different stakeholders

Development and application of 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 and clinicians, 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

Task 2 in ethical self-assessment: consider 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 respond to the following questions and explain the reasoning behind your response:

I. Has the research subject sufficient cognitive capacity to understand?

II. If not, is there someone who can act as a trusted proxy?

III. Have you disclosed all relevant facts?

IV. Do they understand and how do you ensure that understanding is sufficient?

V. Is participation voluntary and how do you ensure voluntariness?

VI. How will your appropriate information and consent procedure look like?

VII. Is there an effective means to withdraw participation or medical intervention?

Task 3 in ethical self-assessment: consider 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 respond to the following questions and explain the reasoning behind your response:

I. Are there any foreseen risks of direct or indirect harms (physical, psychological, privacy related), short-term and long-term, associated with the project/intervention?

II. May these risks be mitigated and, if so, how?

III. Is there a possibility to minimize harm while still answering the research question?

IV. 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?

V. May an animal for a project be replaced with an animal lower in the animal series, or even by a simulation/computer model?

Task 4 in ethical self-assessment: consider the principle of beneficence

In practice, the principle of non-maleficence needs to be balanced against the principle of beneficence and the prospective benefits. 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 or clinician to identify, explain and assess what is relevant in a specific context. Following this principle respond to the following questions and explain the reasoning behind your response:

I. What direct and indirect benefits, short-term and long-term, may be expected?

II. Who are the beneficiaries?

III. Are the beneficiaries the same as those facing risks of harm?

IV. How may the balance of benefits and risks of harm be justified?

V. How is this communicated to research subjects, patients and concerned parties?

Task 5 in ethical self-assessment: consider 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 be a matter of respecting certain human rights and freedoms, e.g. pertaining to gender, ethnicity, vulnerable groups. Distributive justice is another aspect 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 respond to the following questions and explain the reasoning behind your response:

I. Are there any vulnerabilities that should be observed when selecting subjects for research or medical intervention?

II. Are there subjects who are at the risk of exploitation?

III. May the research or intervention target less vulnerable subjects while still answering the research question?

IV. How may risks of exploitation or discrimination be avoided or mitigated?

V. How may the distribution of benefits and burdens be justified?

VI. Is there a transparent and open process for the distribution of benefits and burdens?

Task 6 in ethical self-assessment: consider 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 un-specified research using data and bio-specimens. Following this principle respond to the following questions and explain the reasoning behind your response:

I. What measures have been taken in order to protect the privacy of research subjects?

II. How are research subjects informed about measures for protection of their privacy?

III. What mechanisms are in place for making sure that data or bio-specimens are not used beyond what is consented?

IV. If secondary/further use of data and/or bio-specimens is considered how have research subjects been informed about this?

Task 7 in ethical self-assessment: consider the principle of reciprocity
Custodianship of data and samples implies giving back. Feedback of general results should be channeled to institutions and patients. Following this principle respond to the following questions and explain the reasoning behind your response:

I. How will feedback to participants about general research results be executed?

II. How will feedback to institutions and funders making the research possible be executed?

Task 8 in ethical self-assessment: consider the principle of freedom of scientific enquiry
Custodianship of data and samples 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 this principle respond to the following questions and explain the reasoning behind your response:

I. What measures have been taken in order to make data- and bio-repositories accessible to researchers outside the present consortium?

II. How will you attain an open and transparent discussion of research methods and results?

III. How will you ensure that your research results are in principle and in practice reproducible by other researchers?

IV. What will you do in order to adhere to the FAIR principles?

Task 9 in ethical self-assessment: consider the principle of attribution
The intellectual investment of investigators involved in the creation of data registries and bio-repositories is often substantial, and should be acknowledged by mutual agreement. Following this principle respond to the following questions and explain the reasoning behind your response:

I. How will you give appropriate recognition of intellectual and substantial contributions to the design of the project?

II. How will you give appropriate recognition of intellectual and substantial contributions regarding collection of data or biological samples?

III. How will you give appropriate recognition of intellectual and substantial contributions regarding preparation and writing of manuscripts for publication?

IV. How will you acknowledge contributions regarding the above that are significant but not substantial?

Task 10 in ethical self-assessment: consider 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 respond to the following questions and explain the reasoning behind your response:

I. How will you ensure that intellectual property interests of researchers, institutions and third-party funders are not jeopardized?

II. How will you ensure that important commercial interests conducive to the application of your research results are not jeopardized?

III. How will you attain an appropriate balance between commercial and public interests?

3. Guidelines and references for further reading and assistance

3.1. General guidelines and references for tasks 1-5

Further reading about a principled approach in ethical assessment see:
Beauchamp TL & Childress JF, Principles of Biomedical Ethics 7th edition, Oxford University Press 2012. 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.

Of special relevance for research in genetics and genomics are *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* ***Ballantyne A, Eriksson S (eds.) Special Issue: Research Ethics Revisited, Bioethics 33 (3) March 2019.*** 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, available on-line:

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

G**uideline 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

3.2 Guidelines and references for tasks 6-10

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, Prepublication data sharing, Toronto International Data Release, Nature 2009, 461:168–170.*

Ideally, data and bio-specimens should be made widely available to the most inclusive and ethically responsible use by the 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 ethical reflection. 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 five principles specified in tasks 6-10. See Ness RB. on behalf of the American College of Epidemiology Policy Committee: biospecimen "ownership": point. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 188–189.

The European Commission has provided further guidance on use of personal data following GDPR in: https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-data-protection_en.pdf

3.3. 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 formalised 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 authorisation 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 centralised European marketing authorisation, 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.