

Human cells and the Norwegian Health Research Act

The use of human cells and cell lines in clinical medicine and research is essential to the development of new knowledge and better medical therapies. All such usage must take place in an open and predictable manner. Guidelines should be established making it clear how researchers should act with respect to such research.

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Human cells are frequently used in medical therapies and biomedical research. Generally, immortalised cells are used in research. In Norway, the Health Research Act regulates the use of human biological material for research, although cell lines are not mentioned expressly in the Act or in the preparatory works of the Act. In this article, we discuss the ethical problems associated with collecting and using human cells, and describe how some other countries deal with these issues. Finally, we provide proposals for a code of practice which we believe should be applied in Norway.

Cells and cell lines

In the book *The immortal life of Henrietta Lacks*, which was published in 2010, the author describes the origin of the much-used HeLa cell line and shows the extent to which society's attitude to research and to the use of human cells has changed since the 1950s and up to the present day (1). Biomedical research without the use of human cells is now unthinkable. In other countries, there has been criticism of a practice which treats human biological material as a commercial commodity (2). Such issues have, however, given rise to little discussion in Norway. The Norwegian Health Research Act regulates the use of human biological material in research (3), but neither in the Act nor in its preparatory works are cell lines specifically mentioned.

In order to study living cells, they must be grown in cell cultures. The cells are cultured in special cell incubators where the supply of nutrients, the temperature and the gas composition can be regulated. A primary culture can be defined as a cell culture started with cells, tissue or organs taken

directly from a human. The term «cell lines» comprises cultured cells which are derived from cells in a primary culture and which have been transferred from the primary culture to a new culture (4). Cells in culture will gradually lose their original characteristics and can normally only divide 50–100 times. There is no generally accepted nomenclature for describing cells in culture, but the following terms can be used to categorise them:

- *Primary cells* are cells taken directly from humans and which maintain their functional characteristics as they were in the body. Such cells can normally only divide a few times, but can be carefully frozen and subsequently thawed and used. Red blood cells and bone marrow cells are examples of primary cells which are in widespread, regular use in patient treatment in Norwegian hospitals.
- *Functionally modified (secondary) cells* are cells which were originally taken from humans and which have changed or lost some of their functional characteristics as they were in the body. Functionally modified cells are currently used in therapeutic trials and research. Both genetically modified and genetically unmodified cells are used (5, 6).
- *Immortalised cells* are cells which were originally taken from humans and which have become immortalised, either spontaneously or by means of external manipulation, so that they can be grown indefinitely in culture. In the case of external manipulation, viral genes or a gene (e.g. the hTERT gene) are added, which will cause the cells to continue dividing indefinitely – and thus become immortalised. If viral genes are added, the new cells have modified characteristics (phenotype), but if the hTERT gene is added, the new cells are considered to preserve their original characteristics.

Regulation of use of human cells

In Norway, the use of cells for clinical diagnostics and therapy is regulated by, inter alia, *Behandlingsbiobankloven* (the Act on biobanks for therapeutic purposes) (7); *Blodforskriften* (the Regulations on the withdrawal, testing, processing, storage, and distribution of human blood and blood

components, and on the handling of health data in blood donor registers) (8); and *Forskrift om krav til kvalitet og sikkerhet ved håndtering av humane celler og vev* (the Regulations on quality and safety requirements for the handling of human cells and tissues) (9). Both these latter sets of regulations stipulate that donation shall be based on written, informed consent.

The use of cells for research purposes is regulated by the Health Research Act (3). Neither in the Act nor in its preparatory works is there any mention of cell lines or immortalised cells. The Biotechnology Act does, however, specify that it is prohibited «to carry out research on cell lines derived from human embryos by cloning» (10).

The Act relating to transplantations, hospital autopsies and the donation of bodies etc. states, inter alia, that «the commercial exploitation of organs, parts of organs and cells and tissues as such from humans is

«All collection of cells for research and commercial purposes should be based on written informed consent»

prohibited» (11). This provision concerning the exploitation of organs for commercial purposes has generally been regarded as including the use of cells and tissues in all contexts. The prohibition does not, however, extend to intellectual property rights or services related to the use of human biological material. Issues concerning the commercialisation of human biobanks are discussed specifically in a report from The Research Council of Norway (12).

Our search in the Norwegian biobank registry has revealed only a few research biobanks which deal with cell lines alone. The number of registered research biobanks cannot, in our opinion, be representative

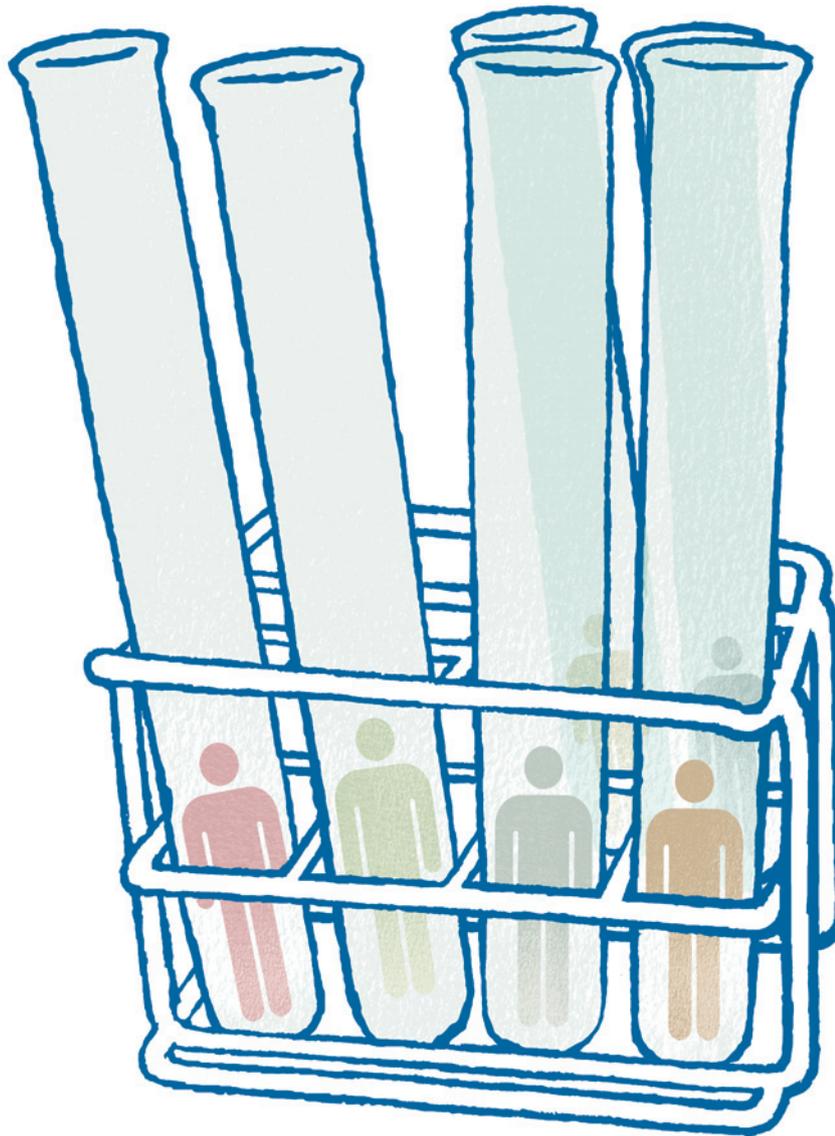


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of the amount of research using cells, including immortalised cells, which actually takes place in Norway. Nor have we been able to locate any views expressed on the ethical aspects of such research by bodies such as the Norwegian Directorate of Health, The National Committee for Medical and Health Research Ethics (NEM), or the Regional Committees for Medical and Health Research Ethics (REC).

Society has a legitimate need for openness and transparency with regard to problems and issues related to research (13). We must expect to see an increase in the use of human cells in both therapies and research. We believe, therefore, that it would be in society's interests to define and clarify the requirements that should be imposed for research on human cells and immortalised cells.

The situation in other European countries

In Denmark, the scope of the current regulations also includes research on cell lines.

If the material comes from previously approved research projects, including projects that have been approved in other countries, it is not, however, necessary to apply for approval for such research (S.P. Jakobsen, Den Centrale Videnskabetiske komité, personal communication). In a new law, which came into force on 1 January 2012, this arrangement will be continued. In addition, the use of anonymous human material, which has been collected in accordance with the laws in the country of collection, will be exempt from the duty to apply for approval to the Danish committees for medical and health research ethics (14).

In Finland, a new Biobanks Act is expected to come into force in 2012. The draft law makes no reference to issues related to cell lines (15).

In Sweden, the National Board of Health and Welfare has made it clear that the current Biobanks Act also covers cell lines (16). In the draft for a revised Biobanks Act, issues have been discussed associated with

the import of biological material and of which types of biological material should come within the scope of the Act (Chapters 6 and 7). Cell lines are considered as covered by the Act – but at the same time there is discussion of where the line should be drawn between the sample material per se and products which consist wholly or partially of human biological material (17). It is thus not clear whether or not immortalised cells will come within the scope of the Act.

In the United Kingdom, guidelines issued by the Medical Research Council stipulate that medical research on human biological material should generally be based on informed consent. Human biological material as such shall not be sold, but intellectual property rights can be sold or licensed in the usual manner. Donor consent must be obtained for the production of cell lines for commercial purposes (18).

Cells and cell lines are not mentioned explicitly in the Council of Europe's Bioethics Convention from 1997 (19). The

European Directive on the legal protection of biotechnological inventions states that patents based on the use of human biological material require informed consent (20).

The situation in the USA

In the USA, the National Institutes of Health have published guidelines for the use of cells and cell lines for research purposes (21). In simplified terms, one may say that the collection of cells from living people for the purpose of conducting research on primary cells or cell lines is considered as medical research on human subjects and requires informed consent. Research on cells and cell lines where the researcher cannot identify the donor is, however, not considered as human subjects research. The same applies to research on cells and cell lines from reputable suppliers, including commercial suppliers, even if the donor information is known, as the research is not considered to be human subjects research because the information is already in the public domain.

With respect to intellectual property rights relating to research on cells, it has been established through judicial decisions that the donor has no ownership of, or control over, biological material donated for research purposes, including commercial purposes (22). In its draft guidance document soliciting public comment on the issue of consent, the US Department of Health recently proposed that it should be permitted to inform donors explicitly that they would have no legal rights or financial interest in any commercial products developed as a result of the research (23).

Proposed Norwegian practice

Despite the fact that the Nordic countries in many ways have similar cultures and comparable regulatory laws, none of them has any clear guidelines on the use of human cells for research. The UK and the USA have different regulations, but they do on the other hand have clear and known guidelines. In the following, we propose how cells and cell lines may be handled in Norway within the existing regulations.

Collection of cells

for research and commercial purposes

All collection of cells for research and commercial purposes should be based on written informed consent. The consent document should state that cell lines may be produced from the donated cells. The document should also state that the donor may not withdraw her consent after the cells have been immortalised, and that she has no intellectual property rights or financial interest in any future commercial products.

Research on primary and secondary cells

Research on primary and secondary cells should as a main rule fall under the provi-

sions of the Health Research Act. This means that pre-approval will be required from a regional committee for medical and health research ethics (REC).

If the material is obtained from another institution in Norway, the researcher should require the sender to submit a declaration stating that the material has been collected in line with Norwegian rules. If the material is obtained from a non-Norwegian institution, the researcher should require the sender to submit a declaration stating that the material has been collected in line with the laws of the country of collection and in line with generally accepted international ethical principles. Such a declaration should be presented to the regional committee for medical and health research ethics when applying for pre-approval.

Research on immortalised cells

Research which exclusively involves the use of immortalised cells should not as a main rule fall under the provisions of the Health Research Act. The researcher should state in the research protocol the method by which the cells have been obtained. If the cells have been obtained from another institution, the researcher should require the sender to submit a declaration of the kind described above.

Summary

The use of cells and cell lines is essential to the development of new knowledge and better medical therapies. Society is served by transparent and predictable regulations and practices on the use of human derived material. The National Committee for Medical and Health Research Ethics should publish guidelines setting out clearly how researchers should act with respect to such research.

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