In molecular epidemiology of cancer where many studies are genetic in nature and they are done among healthy people, ethical issues require special consideration. Genetic information differs from other health care information in that it is predictive in nature, and it always involves at least family members, but in some genetically very homogeneous populations even a wider group. General discussion of the potential good and harm should be encouraged more, so that it would be possible for lay people to make informed decisions. Personal involvement of scientists in education of public, general discussion and considering their own studies from the point of view of the study subject and their family is in the end the only way to ensure that the spirit of international regulations of ethics are realized in practise.

Introduction

Molecular cancer epidemiology is a multidisciplinary field combining molecular biology methods and epidemiological study design embracing also such fields as cell biology, biochemistry and statistics (1,2). It aims at developing molecular markers to aid in revealing exposures, setting diagnosis, detection of early disease, follow-up of treatment and individual susceptibility of diseases (3). In molecular epidemiology, research is done in many cases among healthy people with one of the main aims being to reveal individual risk, and studies are often genetic by nature. Consequently, there are important ethical aspects to consider on one hand to protect people, and on the other hand, to increase understanding of the positive implications of such studies (Figure 1) (4–7).

For several reasons, the ethical issues especially in genetic research are complex (7): molecular genetics is new with constant flow of evolving information and all implications of which may not be clear, yet. Genetic information differs from other health care information in that it is predictive in nature, although the degree of certainty varies, and it always involves at least family members, but in some genetically very homogeneous populations even a wider group. In addition, the world is culturally heterogenic and the significance and meaning of genetic information varies from one culture to another (7,8). The special nature of genetic information and the importance of the ethical aspects in genetic studies are stressed by the fact that UNESCO published in 1997 a Universal Declaration on Human Genome and Human Rights (9). Both the spirit of this Declaration and other authors (10) stress the dignity of human beings as individuals who are more than just a mere machinery orchestrated by the genome and the danger of such a shrinking view of humanity.

Ethics involves the principles of conduct governing an individual or a group, and conforming to accepted professional standards of conduct is usually regarded as morally sufficient. However, ethics can also be understood as a reflection on existing moral principles. If this is accepted, laws and moral principles are necessary but not sufficient for good ethics (6) (Figure 2). In addition, personal involvement of the scientists in the continuous process towards better conduct in their research field is necessary. The fact that official guidelines are not enough is very well illustrated by the fact that an official research policy in Germany requesting an unambiguous consent from subjects in biomedical research since 1931 was in effect at the time of Nazi atrocities (11). Since ethics is concerned with moral and personal values, it cannot be value-free. This applies also to research ethics. Molecular epidemiology especially is a field where risk of false conclusion about the hypothesis may have social consequences and thus non-epistemic values should be taken into consideration (12). For instance, molecular epidemiology of smoking and lung cancer (13) has direct social consequences depending on whether authorities in different countries regard the evidence convincing enough to ban smoking.

Genetic analysis in molecular epidemiology

The special interest on the gene level in molecular cancer epidemiology is based on the realization that the process of carcinogenesis involves the accumulation of genetic damage and that inborn genetic damage, like a mutation in a certain tumor suppressor gene, may carry a susceptibility to cancer (1,14). The results of the Human Genome Project (15) have established the platform for large-scale studies on such susceptibilities and there is currently great pressure for utilizing the existing sample sets in addition to the creation of new ones (16,17). The pressure comes from the interest of basic research, from the possible clinical usefulness of the information as well as from commercial possibilities for genetic tests.

At best, the analysis for putative individual susceptibility, e.g. analysis of drug metabolism polymorphisms or germ line mutations of tumor suppressor genes, protects individuals by warning about potential health risks and helps to seek early diagnosis and treatment. However, not all conditions are curable, not even treatable and testing may cause harm to the individual. Potential harm includes discrimination in health insurance policies and employment, stigmatization, psychological distress in deciding whether to know or not to know of the susceptibility and strain in the relationship with the family (18–20). Potential discrimination has been recognized by legislators, for instance in the USA, and consequently, laws prohibiting the use of genetic information exist (21,22).

The aim of the genetic research is ethically relevant. As pointed out by, for example, Pelias and Markward (23), aiming at clinical diagnosis and treatment are, without an argument, beneficial. Predictive testing has different implications.
Many new methods used in molecular epidemiology studies are labor-intensive and under development (3,5,14). This makes it difficult to study populations big enough for good epidemiology. At the same time there is a need to carry out mega studies with tens of thousands of people. Thus, there is pressure to use methods that summarize results from several studies either using meta-analysis (a summary of results from published papers) or pool and re-analyze original data from published and unpublished sources. The latter approach has the possibility to bring into light unpublished studies, which are common in molecular epidemiology because there is a quick turn-over of fashionable markers and many smaller studies are left unpublished (31). In such studies questions of the use of old samples for new purposes and the form of consent emerge. Recently, journals are making an effort to publish well-done studies with negative results, e.g. (32), which will help to resolve some publication bias in molecular epidemiology of cancer.

Sample and databanks and sample identification

According to the principle of autonomy (33) people have the right to decide how their body, tissues and information on their health are used. This includes the right to privacy regarding sensitive health information (5). In molecular epidemiology, both computerized databases and the storage of samples may endanger privacy. In the literature, the terminology about labeling samples varies and sometimes causes confusion of the meaning. Table I presents a proposal for harmonizing this detail. It can be argued that anonymous samples without possibilities for identification could be used for validation of molecular epidemiology markers without consent, because no personal harm can be caused to an individual (5,6,8). This requires a sample collection big enough so that the combination of age, sex and disease/condition do not reveal the identity of a person. On the other hand, in genetic studies, the possibility of a link to disease revealed in future studies and thus, a possibility to help them, has been presented as an argument for retaining personal information.

Regarding health information of some serious diseases, information has been already collected for a long time in national registries in many countries by law without any consent from the individual. The data from these are usable by scientists after permission from the authorities. As to samples, big collections of tissues, usable for DNA isolation, already exist in pathological archives and clinical laboratories (23,34). Whether and how these existing information and samples can be used and combined for further molecular epidemiology studies is an important question. Their use would certainly benefit the studies by saving time and money. Since they have been collected for clinical purposes, their use with

| Table I. Proposed definitions for the terminology on the level of identification of tissue and DNA samples |
|---------------------------------|---------------------------------|
| **Identifiable** | Name and/or social security number on the sample. |
| **Coded** | A sample does not have identification, only a code, but the person is identifiable with relative ease. |
| **Encrypted** | A sample does not have identification, only a code, and it requires extra effort to identify the person. |
| **Anonymous** | No possibility to link data from the sample to a person. |

depending on the age of the individual to be tested, treatability of the disease and the developmental stage of the test. Defining genetic susceptibility to environmental cancer may aid in decisions about the level of ADI (acceptable daily intake) value for the carcinogen to protect also the most sensitive individuals in a population. However, the same information could be used to discriminate against an individual by employers (20,22,24,25).

Important practical considerations are the relevance of the marker used, the specificity and sensitivity of the assay, and the prevalence of the risk factor in the population, which all affect the proportion of true positives (26). Most methods of current molecular epidemiology are still developmental and cannot be reliably used in screening for individual susceptibility (2,5,27,28). In principle, a very simple task of detecting 1 base difference in a short strand of DNA, nevertheless resulted in highly variable results among three test laboratories analysing TP53 codon 72 polymorphism (29). The reliability of the data is a central ethical aspect due to the persistent nature of genetic information. Such information is also more far-reaching in the society than many other types of health information, because close relatives may have the same trait (8,30). Whether, and how, to distribute the knowledge of the potential risk has to be resolved in molecular epidemiology studies on a case-by-case basis with a special emphasis on the effects for sensitive groups (children, minorities). A well-established procedure, including the establishment of benefits and relative lack of harmful effects, to register drugs for clinical use exists. Eventually, a similar system is, no doubt, necessary for genetic tests and molecular markers to be used in public health.
There is also an incentive for opening existing, stored tissue banks within the large, prospective national epidemiological studies in addition to collecting new large sample sets. Decisions and plans for nationwide banking of DNA already exist in several countries (Table II). The need for coding or anonymizing samples should be solved quickly because the interest to combine various databanks is strong. Such decisions should not be done by experts only. In the past, public discussion has helped in the decision of controversial ethical issues (11). Thus, public discussion should be encouraged in various countries before big decisions like wide banking of DNA from the population. How to do it in a way that it is based on understanding, is another question. For instance in Iceland, polls have shown support, but not understanding in connection with the deCODE project of banking DNA and combining the data with genealogical and health data (35).

In existing large-scale DNA banking projects both opt-in (people are invited to participate) and opt-out (all are included, but it is possible to ask one’s sample and data not to be included in the study) policies are practised. One problem with the opt-out system is that it requires much more activity from people’s side than opting in when asked. For opting out people need to become aware, for instance by following newspapers and TV, about the possibility and finding out what is the procedure. If it requires written forms, they need to request them. No matter how well the publication of information is organized, there are always people who are, for one reason or another, not reachable through regular mass media. This means that in some cases people would be included, who, if truly informed of the project, would actually want to opt-out.

**Informed consent**

There is no disagreement in international and national guidelines since the first documents in the 1930s about the importance of an informed consent in biomedical research on human subjects (11). The concept of informed consent is central in the Declaration of Helsinki formulated in 1964 with latest revision in 2000 (www.wma.net). It has been adopted in some countries in the legislation for research in human subjects, e.g. in Lithuania (38) and in Finland (Medical Research Act No. 488/1999, www.finlex.fi). It is recommended that informed consent includes information of the background of the study, the purpose of the study, methods and procedures, potential general benefits as well as benefits for the person in question and also potential harms. In addition, voluntarity, confidentiality and possibility to withdraw are included. Respectable scientific journals support these guidelines and the requirement for an informed consent in their publication policies (11).

What are the arguments for the requirement of informed consent? First, autonomy of the study subject to decide what his tissue and DNA is used for requires consent for a specific purpose. It is not self evident that all the causes held important by scientists, are such in the eyes of a lay person. Secondly, the principle of non-maleficence should be considered from more than just scientists point of view, the more so in genetic epidemiology where combinations of databases are pursued requiring retaining the identifiers in big studies. Thirdly, in the light of unsure benefits to people, they should be able to refrain from participation. Fourthly, to ask for an individual consent without information and explanation of the study seems rather useless. What would people in such cases consent to? In practise it would be not much more than a presumed consent, which equals no consent at all. An open consent, where outline of the study would be laid out, but specific measurements, e.g. genes to be studied, would be left for the future to direct, is problematic from the same point of view. Unexpected links between genetic traits and one gene associated with more than one susceptibility, like the APOE, which is associated with both cardiovascular disorders and Alzheimer’s disease (21) justify a periodic ethics review and new consent for new phases in long-term studies. Finally,

### Table II. National planned projects for banking and combining DNA/tissue samples and health data

<table>
<thead>
<tr>
<th>Country</th>
<th>Ownership</th>
<th>Policy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iceland</td>
<td>State but deCODE has exclusive license for 12 years</td>
<td>Encryption of data, Presumed consent with a possibility to opt out, Informed authorization proposed</td>
<td>17</td>
</tr>
<tr>
<td>UK</td>
<td>Public</td>
<td>Consent to ‘participate in UK Biobank’ covers any future study accepted by National Health Service multicenter research ethics committee</td>
<td>35</td>
</tr>
<tr>
<td>Estonia</td>
<td>Estonian Genome Project Foundation</td>
<td>Health questionnaire instead of medical records ethics review board decides of the need for an informed consent for controversial studies</td>
<td>17</td>
</tr>
<tr>
<td>Tonga</td>
<td>Autogen initiated the plan</td>
<td>Project terminated due to opposition</td>
<td>37</td>
</tr>
</tbody>
</table>

### Table III. Official recommendations and useful sites on the use of human biological material and consent practices

- **American Society of Human Genetics**: DNA banking and DNA analysis [www.faseb.org/genetics](https://www.faseb.org/genetics)
- **CIOMS**: International Ethical Guidelines For Biomedical Research Involving Human Subjects [www.cioms.ch/guidelines](https://www.cioms.ch/guidelines)
- **Human Genome Project**: NCHGR-DOE Guidance on Human Subjects issues in Large-Scale DNA sequencing [www.ornl.gov/techresources/Human_Genome/](https://www.ornl.gov/techresources/Human_Genome/)
- **National Bioethics Advisory Commission (NBAC, USA)**: Ethical and policy issues in research involving human participants [www.bioethics.gov](https://www.bioethics.gov)
- **UNESCO**: The Universal Declaration On the Human Genome and Human Rights—from theory to practice [www.unesdoc.unesco.org](https://www.unesdoc.unesco.org)

CIOMS, Council for International Organisations of Medical Sciences; NCHGR, National Center for Human Genome Research; DOE, Department of Energy.
most of the international guidelines and recommendations based on very thorough considerations by hundreds of experts through the years, stress the importance of informed consent. For instance, the CIOMS Guidelines (see Table III) recommend not only getting informed consent, but also periodically renewing the informed consent in long-term studies. According to these guidelines waiver of the informed consent should come from an ethics committee, and this should be an exception.

To make a consent truly informed in the spirit of the Declaration of Helsinki, requires full understanding, thorough discussions with the researcher and enough time to consider and consult with family and maybe other professionals (6). The first requirement is readability of the information given to study subjects. To ensure this, the Declaration of Helsinki recommends participation of lay people in the work of ethics committees. However, Paasche-Orlow and co-workers (39) have shown that committees may provide model texts that are below their own standards for good readability. This shows that ethics committees need more training and collaboration in communication skills.

It is easy for people to be intimidated in discussion with a professional. Good general background knowledge will help, and can be gained by education. It is the task of the school system and the mass media to keep the level of basic knowledge in science high enough to enable people to collaborate in scientific studies and not just act as ‘guinea pigs’. Deficiencies in understanding the research plan and the message of informed consent might and do occur (38). Even with knowledge, people need time to read the information at peace and think about it before discussing again with the researchers. A good test for whether the given information was understood has emerged from a long career as a teacher at the university: no questions means that the message did not go through. Also, if nobody refuses to take part in the study, the participation may not be truly voluntary. Recruitment may be too persuasive or the refusal has been made too difficult.

It has been suggested that if a study presents minimal harm, e.g., when studying a low-risk genotype like the known polymorphisms for carcinogen metabolism, the requirement of a consent could be waived even with identifiable samples (34,40). It should be considered, however, that a combination of low-risk genotypes may be much more predictive than a single one alone, and predict high risk. It is probable, that a genotypic pattern combining polymorphisms and mutations of carcinogen activating and inactivating genes with those of oncogenes, tumor suppressor genes and inflammation-related genes will reveal individual susceptibilities to at least some cancer types (for recent reviews see refs 14,41,42).

What has been said is self-evident in clinical research on drugs and clinical practises. There is actually an interesting duality in the current literature about the informed consent. In the evolving field of molecular epidemiology and the mega-scale genetic studies the ease to carry out research and potential (financial) benefits to the society may be running over autonomy and privacy. As discussed above, the discussion in molecular epidemiology of cancer includes even the question, whether an informed consent, or any kind of consent is needed. Considering the immense amount of work it would require to get an informed consent from individuals in big molecular epidemiological studies, and especially in studies using formerly collected samples, it is understandable that the need form of the consent is being discussed. Alternative procedures to the classical informed consent in connection with molecular epidemiology studies have been suggested (Table IV). In large-scale studies, like the national DNA banking projects, a two-level consent could be the best and fulfil the requirements for protection: a public consent after public scrutiny of the research and procedures, e.g., storage of samples and data. This would ensure that the information is understood by the society are listened to and taken on account. Individual autonomy would be served by an individual informed consent when the DNA sample is used for a certain study. An alternative procedure has been suggested in Iceland for the national database study (35). An informed authorization based on general knowledge of the purpose and practises of the study would be collected from people when the sample is donated. Separate studies would be decided then on the basis of the permission from the ethics committee.

### Ethics committees and molecular epidemiology studies

All ethics committees have to deal with the ethical aspects of the increasing volume and variation of studies, including the genetic molecular epidemiology studies (43,44). The committees face big challenges currently because in many cases there is no general agreement on the ethical aspects. New research tools, like oligonucleotide microarrays with a power to obtain an enormous amount of data in one measurement, complicate the ethical considerations exponentially (45). Decisions have to be made on an ad hoc basis, and in many cases based on insufficient details of the research and its implications and insufficient understanding of the basic background of the research field in question. The everyday work of the committees may be intimidating to the lay members, who are there (by law, for instance in Finland) exactly for that reason: to ask unpleasant questions on behalf of the public. Thus, there is the

<table>
<thead>
<tr>
<th>Consent</th>
<th>Characteristic</th>
<th>Source of samples and conditions</th>
<th>Reference for more information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>Individual written specific consent for a particular study</td>
<td>Any human study</td>
<td>Declaration of Helsinki <a href="http://www.wma.org">www.wma.org</a></td>
</tr>
<tr>
<td>Informed authorization</td>
<td>Individual written consent for participation in database studies based on general information</td>
<td>DNA banks</td>
<td>35</td>
</tr>
<tr>
<td>Presumed consent (no consent)</td>
<td>Presumed acceptance for a study presumed to cause no harm</td>
<td>Stored tissue samples when the study poses minimal harm</td>
<td>NBAC, 34</td>
</tr>
<tr>
<td>Open consent</td>
<td>Individual consent for future unspecified studies</td>
<td>Archived samples</td>
<td>23</td>
</tr>
<tr>
<td>Public consent/community consent</td>
<td>Consent from public, e.g. by polls</td>
<td>Large-scale DNA banks</td>
<td></td>
</tr>
</tbody>
</table>
need for the ethical committees to increase the effectiveness and organize education of lay and new members. In addition to these points, there is the need to carry out big multicenter studies. For equal treatment within one country and to speed up the evaluation process, Blunt and co-workers (43) propose the creation of multicenter ethics committees, and common standards for the multicenter and local committees. Local committees would make decisions of the local acceptability of the proposed study.

Considering the above-mentioned points it is no wonder that there are documented differences in the process and decisions of different committees within the same country (46,47). The beginning of the solution to the former would be an increase in the quality of the information given to the ethics committees by scientists. It is a matter of the clarity of language and the research plan, rather than the amount of information; too much information effectively hides the ethically important details. It should be understood that scientists are responsible to explain the importance of their research in the way that the lay members in the ethics committees have the possibility to understand the implications of research at hand. Furthermore, the scientists are also always responsible for the good ethical practice of their own research.

Full harmonization of the decisions may not even be beneficial for the ethics in the field, because it means that the discussion stops there. Considering the quick development of genetic knowledge and consequently new applications and implications for the ethics, it would be necessary to keep the general discussion going. In practise, the difficulty in the work of the ethics committees is the increasing workload not leaving enough time for thorough discussion, especially since the paperwork has limited handling time by law and by pressure, especially in studies related to commercial companies. A logical and just decision, which is the only ethically defensible practise, may not be reached in these circumstances.

**Education of ethics**

Because the results of genetic molecular epidemiology may have a strong impact on the lives of people, the ethical aspects have to be carefully considered before starting the studies. This is also the basic requirement in the legislation for biomedical research on humans in many countries. To meet this requirement scientists need to know how to deal with the ethical questions. They have to be able to recognize ethical aspects, to be able to reflect on the existing laws and literature, to write about ethics based on their considerations, for instance in applications for grants and ethics committees, and to make decisions that last beyond the current trends in science. It is a major undertaking for a laboratory scientist and requires training as much as any other aspect of the scientific work. It seems that a few courses here and there have not fulfilled this need, because too often still the question in the form for the ethics review board about ethical aspects of the study is answered ‘there are no ethical problems in the study’. Such an answer only shows total ignorance of the meaning of the phrase ‘ethical aspects’.

It would be important to realize that good knowledge in ethics is essential for the protection of both the public and the scientist. It is typical in life to react to catastrophes, but prevention of them could save lives and careers. Rather than regarding ethics committees as a nuisance, scientists should work together with the committee members, most of them their peers, for prevention of future difficulties. This is important also considering that the attitudes and practises of senior scientists are inherited by younger colleagues as a research tradition.

Thus, the education of professional ethics should be targeted both for doctoral students, staff scientists and group leaders alike. Since good science is inseparable from good scientific ethics, teaching of ethics should be integrated in all teaching of scientific practice.

**Money in molecular epidemiology**

One cannot discuss ethics of modern molecular epidemiology without touching the various financial aspects of the research. Because resources for independent research are decreasing, money is there from the beginning: outside funds are essential both in universities and research institutions to carry out the research. Currently, very few institutions are fully government supported, like the NIH in the USA, and thus financially independent. Since molecular epidemiology of cancer is expected to produce clinically useful preventive diagnostic and treatment-related methods, there is a lot of interest to invest in the research. This creates the danger of bending the purpose of the research to please the financing bodies. In many countries universities actually press such an alliance between the commercial world and universities. Such ties may, however, be problematic for expert work, e.g. in ethical committees (48). If financed by the industry, it is in their interest to be involved in the publication of the results as well, because publication affects the patenting process. This usually slows down or in some cases even hinders publication of results. Like in drug research, publication of negative studies on the clinical usefulness of a molecular marker may not be in the best interest for the company financing the development.

Ownership of samples, especially DNA banks with links to health data are regarded as ‘gold mines’ for future development of genetic tests and treatment options illustrated by the interest of commercial companies in biobanks (16,17). Another way to make use of sample banks is to sell characterized sample sets to other companies and scientists. This creates a special problem of privacy if identifiers are retained. Arnason (35) has warned about, in his words, ‘creative medical recording’ by doctors who worry about private medical information being misused. This is already an issue in countries with national projects to bank DNA samples (Table II) and combine them with health data (35).

Patentability of research results is stressed by governments, companies and universities alike. However, many scientists have insufficient knowledge of the related legislation and the realities of the financial world. No wonder that many small companies have gone bankrupt, sometimes with disastrous consequences for the scientist personally. The encouragement of scientists to do business should always be followed by financial training, as, fortunately, in some cases already happens. Another ethical aspect is the patentability of DNA. Human genes are part of human heritage (9) and as such the property of everybody. After thorough discussion the panel of the Nuffield Council of Bioethics (49) came to the conclusion that genes as such should not be patentable, only special applications using genetic data, to encourage new ideas and applications.

Finally, marketing tests and kits based on research in molecular epidemiology may involve ethically questionable

practises because the pressure for quick profit is great. These include marketing clinically unproven tests (50) and exaggerating the frequency or importance of a condition (51). Again, education of public and responsible reporting of scientific discoveries helps people to make rational decisions.

Conclusions and recommendations

The ultimate aim of the research in molecular epidemiology of cancer sounds good: it is certainly ethical to pursue prevention of cancer, which causes suffering to the individuals and families, and high health care costs to the society. However, how this is pursued is the ethically relevant question. Pursuing genetic testing for late disease in fetus or young child is ethically questionable; the more so, if there are no prevention measures or treatments for the disease. In the course of studies, when the value of the used marker is unclear and/or the possibility of misunderstanding. Giving people any information of unnecessary psychological stress and possibility of misunderstanding. Giving people any information of genetic analyses of possibilities to personal risk for diseases in any case should be linked to personal counseling.

General discussion about the possibilities and potential harm created by molecular epidemiology in cancer should be encouraged more. For that education is essential: for scientists consent from the society, for the purpose and plan of the study, and for scientists ethics of caring. At the movement of the scientist according to the ethics of caring. At the beginning of all possible harms to individuals support what official people and politicians to understand basic scientific facts. Consent for molecular epidemiology, especially a collection of large genetic sample and databanks with the aim of combining with health data is probably necessary at two levels, the public consent from the society, for the purpose and plan of the study, and an individual consent from those donating the samples and information. Especially in the case identification of the persons are retained, the novelty of the field, and general ignorance of all possible harms to individuals support what official guidelines and regulations already request: and individual informed consent according to the Declaration of Helsinki. Considering research subjects more as collaborators than subjects, and educating the public to understand scientific principles is the basis of good communication between scientists and the public. In addition, a detached application of ethical principles in medicine should be complemented by personal involvement of the scientist according to the ethics of caring. At the end the researcher could use the following most important question as a guide: “Would I allow my child to take part in the study or want to participate myself”?

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