

DNA Samples in Epidemiological Research

Working group on DNA and Epidemiology
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The Sub-Committee on Medical Research Ethics (TUKIJA) of the National Advisory Board on Health Care Ethics (ETENE)

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DNA Samples in Epidemiological Research

1. Introduction

Researching hereditary and other causes of diseases on a national level by means of epidemiological research creates a basis for the evaluation of both the significance of inheritance and the opportunities for disease control. Large-scale technical preconditions to study genes from DNA samples have not become available until during the last decade. These studies can also be conducted years from now, using stored samples that have been collected in association with population studies. In parallel with samples that have been stored for individual research studies, there have in the last few years been attempts to establish versatile tissue banks with samples collected from diverse sources.

This memorandum deals with the use and the conditions for use of DNA samples collected in relatively large population studies, with special attention given to actual scientific research conducted in universities and research institutions. Trials conducted for commercial purposes may involve other aspects, which are not discussed here. This memorandum and discussion based on it are meant to help create guidelines for ethics committees that would facilitate the handling of population-level DNA research. Ethical questions concerning DNA research will be discussed first, followed by epidemiological research and associated legal viewpoints.

The section on ethics focuses on the question of the potentially special nature of genetic information in comparison with other information about an individual's health, as well as the notion occasionally expressed that genetic research or its consequences are in some way against nature. The central question discussed in the legal section concerns what people actually want to protect when the use of DNA samples in epidemiological research is restricted in one way or another. The Medical Research Act (488/1999) requires that the research subject must give his/her consent to the research. The Personal Data Act (523/1999) allows even data of a sensitive nature to be used for research purposes without the research subject's express consent when the number of research subjects is large or acquiring the consent is difficult because of the age of the data, for example. Which category does epidemiological research with previously collected DNA samples belong to, and should separate conditions apply to the use of samples for later research purposes?

Questions that should be discussed in the future include changes that are made to the research protocol after the consent requested in association with the collection of samples has been received, and the effects of these changes on the legal protection of the research subject.

2. Ethical aspects associated with genetic research

2.1 Genetic information

Information about an individual's genes, i.e. genetic information, can nowadays be collected, stored, and used for many different purposes. This has given rise to many new ethical issues. Many – perhaps most – of these issues are based on the deeply rooted belief that genetic information, unlike other information about an individual's health, is unique from the viewpoint of morality and requires special protection. The details of the specific nature of genetic information vary depending on the viewpoint, and variation is also present in whether genetic information is considered to be specific in itself, or whether only some of its uses and targets are considered to be specific. These

opinions are called the strong and the weak interpretation respectively (Murray 1997). The strong interpretation is mainly built on the following statements:

Genetic information is more precise and more predictive than other information about an individual's health. This statement is correct only with regard to some rare genetic diseases with a single factor, such as Huntington's disease and cystic fibrosis, and even the precise and reliable prediction of these diseases by means of genetic testing is not entirely unproblematic. With regard to common multi-factorial diseases, such as mental disorders or hypertension, the prognostic value of the results of genetic testing is fundamentally poorer. Somewhere in between are certain diseases, such as hereditary cancers, the risk of which can be predicted by means of genetic testing with high probability, but not with certainty.

Genetic information concerns other people more than non-genetic medical information. This criterion does not make a qualitative distinction between genetic and non-genetic information either. Non-genetic information can also concern others in the sense that information on one person's state of health tells something about another person's state of health. For example, if an individual receives reliable positive results from a HIV test, this may tell something about the state of health of the individual's partner. A (not inherited) disease detected in a newborn infant may tell something about the mother's state of health. This feature is, however, almost invariably associated with genetic information.

Genetic information characterises the individual's essence and identity (what a person essentially is) and, in this sense, is more fundamental than other health information. Genetic information, as opposed to other health information, can be considered more fundamental or more closely connected to an individual's essence or identity only in a subjective sense, on the basis of an individual's personal thoughts and beliefs. Considered subjectively, any health information can be like this. For example, information about irreversible baldness or infertility caused by a disease may be a feature defining essence or identity for some persons. Genetic information is no more fundamental than other health information also in the sense that the attributes it reveals are not the only ones that are permanent and irreversible. For example, HIV or the herpes virus may be a permanent health attribute of the infected person (or a changing attribute, as medications progress) On the other hand, it is known that genetic factors that increase the risk of getting an illness can be increasingly influenced in the future.

According to the weak interpretation, some uses and applications of genetic information are exceptional and therefore call for special protection measures. The weak interpretation is expressed in the prohibition against using results of genetic testing in the context of insurance or employment, or the recruitment, for example. The argument that genetic information forms a particular problem in acquiring informed consent is more important from the perspective of clinical research in humans. Due to the complex nature of genetic research and the complexity and abundance of research-derived information, acquiring an informed consent has sometimes been considered impossible. In such cases, the problem has not been attributed to any defects in the knowledge or understanding of the research subjects or the inability of the investigators to explain matters intelligibly, but rather to the fact that viewpoints influencing the decision-making concerning participation in genetic research are often so various and so complex that understanding them fully is not possible when participation is being considered.

Claiming that acquiring a genuine informed consent in association with genetic research is impossible may be an exaggeration. However, it is clear that such a research protocol places special demands on acquiring a new consent. The research subject must be told exactly to what purpose the

genetic information is to be used, whether the results will be told to the research subject, who else will get the results, and where the DNA samples will be stored. Because of the complexity of genetic research, the subject's informed consent should be asked only for the purpose mentioned in the research protocol. Extending the research to new disease groups, for example, requires a new informed consent if the purpose of the research is fundamentally changed. Clear definition of research aims and the purpose to which the research data will be used have therefore central importance with regard to a new informed consent.

2.2 Is genetic research unnatural?

Genetic research is often considered to be a somehow unnatural type of research. Either the methods or the consequences of genetic research are thought to be somehow against nature. A common criticism is that humans should not defy the natural order by creating new species or combining existing species or trying to decide their own genotype (Räikkä & Rossi 2002).

When people speak about "unnaturalness" or "abnormality" in association with genetic research and its applications, these terms are often used in the sense that "nature knows best". According to this idea, nature in the form that we know it, is the result of extremely lengthy and well "tested" development (evolution). Modern genetic research would then be fumbling about in conditions that are only partly known. While the results of natural choices are reliable and compatible with nature, the results of man-made choices may be much more unpredictable and involve many more potential risk factors.

This interpretation of abnormality does not justify considering genetic research or its applications as unnatural. In addition, genetic research is often about accelerating the course of natural processes, in other words accomplishing the same things in less time. On the other hand, it should be noted that even nature does not always know the consequences of its own choices. Examples of this include many natural mutations (e.g. the genetic flaw that gives protection against lactose intolerance), "natural" extinction, and natural ecological disasters. Those who emphasise the aspect of abnormality may not always take into account the fact that fumbling and coincidence have had a central role in the development of species. But here as well, suspicions about abnormality return to the question of risk assessment and management. These ponderings and suspicions may be considered to be connected with gene manipulation and perhaps with gene therapy. It is, however, particularly difficult to see that such problems could be present in observation studies or population-level therapeutic trials. Indeed, population studies are conducted to gain information about the causes of a disease or possibilities to reduce the risk of the disease, and involve no genetic interference.

3. Epidemiological research and DNA samples in studies to be initiated

Epidemiological (i.e. population-level) health studies evaluate the frequency, distribution and causes of phenomena associated with health and illness in the population. (Morris 1975, Hernberg 1998). In population studies, research seeks to clarify the prospects for the early detection and prevention of diseases (Rose 1995). The common approach is to study a relatively large population sample and make an assessment simultaneously into the presence of several major diseases as well as their risk and protective factors. It is efficient and financially sound to study several target areas simultaneously. In general, the population samples in epidemiological studies are large (thousands or tens of thousands) or medium (hundreds, a thousand, or thousands). Similar epidemiological and statistical methods can be applied to rather small patient series, and during the last few decades, the

term "clinical epidemiology" has been used to refer to such situations (Fletcher et al. 1988). A more correct term would, however, be "clinical research".

When evaluating causes (in epidemiological studies), targets of research include diseases, accidents and injuries, functional limitations, and their determinants. These determinants include inherited and acquired characteristics, e.g. physiological factors, external exposing factors, and interaction between a person and his/her living conditions. Experimental research evaluates how changes in living conditions or habits, early diagnosis of diseases or early pharmacological or other treatment promote health or reduce the risk of disease. In connection with the data collection for these studies, it was previously (before current legislation) considered that the research subject gave a so-called silent consent to the study by participating in it. On this basis, data have been used for a variety of research purposes that has been possible with the research material. Official authorisations have also allowed, for example, the linkage of records from the national hospital discharge register or registers on treatment with medicines to the study material. Currently, an informed consent is required in population studies, and the research subjects are told about the purpose of use of the collected data as well as about any data that may be combined to it.

For the past 10 to 15 years, it has been possible to determine links between genes and diseases by researching DNA. During this time, researchers have learned to evaluate the relative significance of genotype and other factors much more precisely than before. Due to current genetic epidemiology (Khoury 1998), our knowledge of the aetiology of diseases and prevention options is increasing rapidly. At the same time, the opportunities are improving for targeting interventions (prevention and treatment) at the true risk groups and at the factors that can be changed. Most of the effects that genetic factors have on common public health problems in Finland are mediated through several genes, and several factors related to living conditions and habits contribute to the development of these diseases. Therefore, these diseases have multiple determinants, and even in the best case, DNA studies can only pinpoint an increased risk of the disease due to certain genotypic areas. Genetic factors are thus often comparable to other risk factors of multi-factorial diseases – with the difference that changing other factors may be possible, whereas genes cannot be altered or exchanged for better ones by current methods in large population groups.

Classical epidemiological causal research comprises either so-called case-control studies or follow-up studies (cohort studies) (Rothman and Greenland 1998). In the former type of research, patients with the disease and comparable controls are enrolled into the study and predisposing factors, i.e. suspected causes of the disease, are evaluated. In the latter type of research, a large number of suspected predisposing factors are measured, development of the disease is observed, and the links between the predisposing factors and the development of the disease are analysed. Follow-up studies are the most powerful study design. In general, a large patient population and a long follow-up period are needed. Particularly during a follow-up, the variety of suspected predisposing factors and the methods to determine those factors are likely to change as the research progresses. This being so, the most powerful research design is associated with the greatest difficulties to inform at the onset the research subjects about predisposing factors that are to be studied in detail and of the research methods.

There are both similarities and differences between epidemiological and clinical studies, and the border between them may also be flexible. Differences between epidemiological and clinical studies that may be significant in using data and acquiring consents are listed in Annex 1.

Typical designs when evaluating inheritance (as well as the interactions between genotype and other factors) include:

- 1) Cross-sectional study, which compares the genotypes (and other factors) of all patients and all healthy subjects of the population sample.
- 2) Case-control study, which compares the genotypes of patients and selected healthy control subjects.
- 3) Prospective (cohort) study, which compares the genotypes of patients with the genotypes of others. This type of research can also be carried out as a so-called nested case-control study by selecting 1 to 4 control subjects for every patient, which strengthens the design.
- 4) Studies with relatives, family members or twins, in which all the designs mentioned above can be used, but research subjects include the target individuals and his/her relatives, family members or twin. This enables the researchers to evaluate the role of the genotype as well as the role of early and current living conditions and habits in the development of the disease. In this connection, control groups are often also selected from the rest of the population.

Prospective or case-control studies nested into prospective studies are the most conclusive of observational epidemiological studies. Twin or family studies with a prospective design are also very strong. To fully utilise the potential of these studies and to gain enough power, all data and samples, often also DNA samples, need to be stored for a long time before analysis, and it is likely that new hypotheses and analysis methods will emerge during the follow-up period. When initiating the study, it is practically impossible to give the research subjects detailed information about anything else except the general aims and methods of the research.

The possibilities to conduct population studies by using original research data collected from research subjects as well as additional follow-up data concerning the development of the disease or the treatment are better than average in Finland because of the excellent health registers. Research concerning inheritance is supported by population registers including church registers that reach back to the distant past. Owing to its strong tradition of epidemiological research Finland also has several large data sets based on population studies. Associated to them both blood and DNA samples have been stored in recent decades. Moreover, Finland has an excellent twin cohort. Our genetic research is outstanding in international terms. Finns have exceptionally positive attitudes towards research and they readily participate in health studies. For this reason, the opportunities for researching the inheritance of public health problems and factors that predispose to them are probably better in Finland than anywhere else in the world. The fact that Finns form a rather homogenous population with regard to inherited characteristics is also positive from the perspective of genetic research. These possibilities should be used to full advantage in order to improve the health of both Finns and other populations of the world.

Researching a large population and conducting long-term follow-up is hard work that takes a great deal of time. By using previously collected data and follow-up, much unnecessary work can be avoided and, which is even more important, the research takes several (generally 5 to 10) years less. By using existing material, it is therefore possible to improve the prevention of public health problems years or decades earlier and at much lower costs than if the investigation of every hypothesis were started from scratch. The potential benefits are so great that comprehensive utilisation of existing data, samples and other possibilities, is necessary. In addition to the original purposes of use, approved operational procedures should be established to enable research based on new purposes.

In some cases, research subjects need to be contacted repeatedly after the baseline study for other reasons. Such new research events provide a natural opportunity for updating the purpose of use and acquiring a new consent. Unfortunately, we know from experience that only 70–80 % of earlier research subjects participate in a new, later organised phase of the research. Similarly not more than 70–80 % reply to inquiries by mail. The unwillingness to participate or reply is almost never due to unwillingness to allow the use of existing material for new purposes, but rather due to lack of time or interest, for example. If the only topic of a mail inquiry concerns informing the person about a new purpose of use for old data and asking for a new consent, it is extremely likely that not more than 50–60 % will reply. In some research designs, such a high non-response can badly distort the material and the findings. Since the population sample in epidemiological studies consists of thousands of people, a mail inquiry is however the only practical approach. This being the case, there is a risk of ruining the research material, not because the research subjects would necessarily have anything against the data being used for a new purpose, but because the research subjects may not even bother to reply to the inquiry. In addition, as the follow-up period increases, the proportion of dead or seriously ill research subjects increases. This being the case, acquiring new consents may be close to impossible in a considerable part of previously studied persons. A procedure is therefore needed whereby the original data can be utilized regardless of the loss during later phases. In Annex 1, there is also an assessment of how to minimise the harm caused by the increasing non-response with time, and we suggest a special permission from the authorities. Since the participants have already consented to a study once, it can be argued that the National Authority for Medicolegal Affairs or another authority could give an authorisation to complement a previously given consent when necessary.

4. Epidemiological studies and DNA samples in previously initiated studies

Epidemiological studies on public health problems have been conducted in Finland since the 1950s. In some of these studies, DNA samples have been collected from the 1980s onwards. Informed written consents were not always requested from research subjects at that time, but currently such consents have been requested from research subjects who have been repeatedly monitored. In studies prior to current legislation, research subjects have been considered to have given their consent to their data being used for research purposes by participating in the study. The linking of data has been dealt with by permissions granted by the authorities. If, according to the amendment of 2001 to the Act on the National Public Health Institute, a presumed consent is considered to apply to other than DNA samples, the presumed consent should be interpreted broadly for DNA samples as well, and the research subjects should be considered to have also agreed to the use of DNA samples for the purpose of researching inheritance. A new informed consent should however be acquired, if possible, during follow-up of the research subjects. More extensive use of previously collected data for a study with a changed fundamental purpose of use should, however, be determined by official permissions from authorities.

5. DNA samples in epidemiological studies – legal perspectives

If a medical research involving DNA samples or other genetic information includes a part that interferes with the integrity of humans, human embryos or foetuses, the Medical Research Act (488/1999) should be applied to research utilising genetic information in the same way that it would be applied to any other type of research. If the research uses samples that have been collected earlier for evaluation of treatment, diagnosis or cause of death, or for medical research purposes, the provision concerning changed purposes of use of samples, set forth in the Act on the Medical Use of Human Organs and Tissues (101/2001, § 20), applies primarily, and the Medical Research Act, secondarily. The Medical Research Act can be considered to determine in more detail the extent and

form of the consent the provision refers to if the new purpose of use concerns medical research (§ 6 and 30). There is no legislation that explicitly refers to DNA studies in large population groups or to the functions of DNA banks. Population studies have been taken into account in special legislation concerning national research institutes, e.g. the Act on the National Public Health Institute (828/1981, amendments 327/2001), and for some parts, legislation concerning the handling of personal data (Personal Data Act (523/1999), § 14).

The Medical Research Act requires a written informed consent before the research can be conducted (§ 6 subsection 1). Before the consent is given, the research subject must, according to law, be provided with sufficient information of his/her rights, the purpose and nature of the research, and the methods used in the research. The research subject must also be given sufficient information of possible risks and adverse effects. The information must be given in such a way that the research subject is aware of research-related issues that may influence his/her decision and is able to decide whether to give the consent or not on the basis of this information (§ 6 subsection 2). Expressions such as "sufficient information" and "research-related issues that influence decision-making" are used in the provision. Therefore, the provision does not require that studies be individualised by separate research protocols, even though in practice, the provision must be interpreted in this way, particularly in connection with clinical studies (directive 2001/20/EC, articles 3-6). However, is the situation similar when using previously collected samples? Does a consent required for changed purposes of use have to fulfil the same requirements of specificity that are needed in clinical research, e.g. trials with pharmaceuticals or other interventions? The Council of Europe Convention on Human Rights and Biomedicine (ETS 164) does not require such explicit consent in situations where samples of human origin are wished to be used in a way that differs from the original purpose, but refers to "appropriate information and consent procedures" (article 22). However, the Explanatory Report to the convention emphasises the necessity of an explicit consent if the samples can be connected to sensitive personal data (Explanatory Report, paragraph 137). In such situations, case-by-case evaluation and particularly the nature of the final purpose of use of the sample should also be taken into account.

Ultimately, answers to the question about changes in the purpose of use should be sought on the basis of fundamental civil rights. The difference between the two situations mentioned above is that clinical studies interfere in the research subject's physical integrity (The Constitution of Finland (731/1999) § 7) as well as gather information about his/her genes, i.e. interferes in his/her privacy (The Constitution of Finland § 10). When previously collected samples are used, only the research subject's privacy is touched. It is obvious that an interference of both of these fundamental rights requires the consent of the research subject. However, it is debatable whether there is a large enough difference between these two situations to lower the individualisation requirement when using previously collected samples. In order to find the answer, the consent requirement set forth in the Medical Research Act (§ 6) and the consent requirement set forth in the Personal Data Act (§ 12) should be compared.

5.1 Consent required by the Medical Research Act and the Act on the Medical Use of Human Organs and Tissues

The Medical Research Act provides that the consent be given in written form on the basis of sufficient information about the purpose, nature, methods, risks and adverse effects of the research. The adequacy of the information and the extent of factors affecting the decision-making of research subjects vary depending on the nature of the research. In clinical research that involves the research subject's physical integrity, the physical risks are greater and the information required for the consent is extensive. Since the risks associated with epidemiological population studies are

generally small or non-existent, and the possibilities to individualise the research participants are smaller, a broader interpretation of the provision is possible in principle according to the Medical Research Act. For example, the research subjects could give their consent not only to the actual study being conducted but also to future studies on the same disease group or groups. In such a case, the purpose, nature and methods of the study must generally remain unchanged, and the legal protection enjoyed by the research participants must not be compromised by the broader goals of the research.

The Act on the Medical Use of Human Organs and Tissues was not actually drafted to apply to research but rather to treatment. It does, however, regulate the research use of organs and tissue samples taken during treatment. The Act should be applied when a tissue sample that has already been collected from the subject is wished to be used in a way that deviates from the terms of the consent. The provision to be applied in such situations is § 20 of the Act on the Medical Use of Human Organs and Tissues, which requires the consent of the research subject or the permission of the National Authority for Medicolegal Affairs for a new purpose of use when the sample was originally collected for *treatment purposes* (§ 20 subsection 1). If the new purpose of use concerns research, and if the consent is requested from the donor of the sample, the consent must fulfil the provisions set forth in the Medical Research Act (§ 30). If the sample was originally collected for *research purposes*, the National Authority for Medicolegal Affairs is authorised to give the consent on behalf of the donor of the sample only after the research subject's death. Therefore, in most cases current legislation requires that the consent be given by the research subject himself/herself (§ 20 subsection 2).

Restricting the authority of the National Authority for Medicolegal Affairs to cover only samples collected for treatment purposes is seen problematic by researchers. Why would the National Authority for Medicolegal Affairs not also be able to give permission to change the purpose of use of the sample when it was originally collected for research purposes? After all, the change is bigger when the purpose of use changes from treatment to research than when only research-related details are modified. If the power of the authorities has been desired to be restricted because of the research subject's autonomy, why are these situations handled differently?

Although it can be concluded from the implementing provision of the Medical Research Act (§ 30) that the new consent referred to by the Act on the Medical Use of Human Organs and Tissues must fulfil the requirements of § 6 subsection 2 of the Medical Research Act, the Act on the Medical Use of Human Organs and Tissues does not give a more detailed definition of when a research is considered to deviate from the original research. In such a case, the central question is whether new biochemical or DNA analysis of certain samples, for example, can be considered mere technical changes to a previous research protocol that do not change the purpose of use of the sample or the nature of the research as such. It has been proposed that researching a disease that belongs to the same disease group or other genes predisposing to the disease, for example, would not represent a deviation from the original consent. However, no final statements have been made on this issue. Similarly, it has been proposed that an ethics committee or another authority, for example the National Authority for Medicolegal Affairs, could evaluate changes in the purpose of the research. However, the best solution would be if the legislator gave an explicit opinion on this question, which is a very important issue not only in epidemiological studies but also in establishing possible tissue or DNA biobanks.

5.2 Consent required by the Personal Data Act

According to the Personal Data Act (§ 12), exceptions to the prohibition against processing sensitive data include the express consent of the subject (§ 1) or processing data for purposes of historical, scientific or statistical research (§ 6). According to § 14 of the Act, personal data may be processed for purposes of historical or scientific research without explicit consent, if:

- 1) the research cannot be carried out without the data identifying the person and the consent of the subjects cannot be obtained owing to the large quantity of the data, their age or another comparable reason
- 2) the use of the personal data file is based on an appropriate research plan and a person or a group of persons responsible for the research have been designated.

If an express consent referred to by § 12 subsection 1, has been received for the use of personal data for research purposes, any deviation from this consent normally requires a new express consent, unless the age of the data, for example, necessitates application of the above exception of section 14 concerning scientific research. Since an express consent also for the use of personal data can be acquired in personal contact involved in collecting samples, the exception cannot be applied in such cases. If the purpose of use of the sample changes after the clinical phase of the research, the situation is different, but even then the special requirements of the exception may have to be evaluated. Even in such cases, the use of personal data for research purposes is restricted by the Council of Europe Committee of Ministers Recommendation No. R (83) 10, which prohibits the use of personal data for research purposes in a new research study, if the nature or purpose of the study is substantially different from that of the original research (Article 4.2 of the Annex).

Since there is no intervention in the research subject's physical integrity after the original tissue sample has been collected, one can only wonder why the provisions of the Medical Research Act instead of those of the Personal Data Act are applied to changes in the purpose of use of the tissue sample. When researching tissue samples, the interests to be protected are presumably similar to those in the Personal Data Act, i.e. the privacy of the research subject and data protection. Different requirements for provision presuppose that, for example, the genetic information in tissue samples is qualitatively special, which is debatable as shown above. Although the legislation concerning personal data primarily requires an express consent to register sensitive data, it also provides an opportunity to use the data for research purposes if the conditions for exemption are met (Lehtonen 2001). A compromise decision regarding changes in the purpose of use of research samples would be that the National Authority for Medicolegal Affairs could decide about it while making adjustments for exemption conditions set forth in the Personal Data Act.

6. Conclusions

In the above, we have discussed the use of DNA samples in epidemiological studies from three different viewpoints. In the following, we present some conclusions based on the viewpoints discussed above, and comment on certain specific questions that may have practical significance with regard to the decision-making of ethics committees.

According to the working group, the information derived from DNA samples does not of itself differ from other information produced by medical research. The specific ethical issues raised with DNA sampling have their roots in some purposes of use of genetic information. In epidemiological DNA studies, attention is given to the rights of the research subject and particularly on requesting the consent.

Legislation regulating research is meant to protect particular interests, which in clinical studies involve both physical integrity and the right to privacy. When researching samples of human origin, the need for the protection of physical integrity ceases to exist once the sample has been taken. However, the reason to protect privacy remains, and the interests to be protected are similar to those of questionnaires or register-based studies, for example. As a consequence, the consent required from the research subject should be similar to the examples in studies based on samples. In studies that interfere with the physical integrity of the research subject, the consent must be more detailed, as the degree of violation of the subject's integrity is correspondingly greater.

When researching causes of common chronic diseases, genetic information (DNA) can be considered equal to other information from questionnaires, interviews and laboratory tests that concerns the risk of the disease in question. When evaluating the ethics of research and the implementation of data protection, studies in which genetic data is collected should be considered the same as other clinical and population studies.

If the actual purpose of a research, say to determine the causes of a certain disease group X, remains unchanged, then making new tests from existing samples by new methods would not usually be considered a change in the purpose of use and would therefore not require a new consent. This also applies to provisions concerning genes. The above does not, however, apply to situations where a research purpose of use changes into a commercial one nor to the consent required in such a case. In the case that research subjects are repeatedly contacted during new phases of the research due to the nature of the project, they should be informed of the matter (by an addition to, or a new version of, the information sheet). Ultimately, the need for a new informed consent should be considered on a case-to-case basis.

In cases of mere handling and examination of already existing samples and/or utilisation of registered data, a broad interpretation of the existing informed consent could be justified. The starting point could be, for example, that a consent concerning a certain disease (e.g. diabetes or coronary heart disease) could also be considered to apply to other diseases of the same group or other closely associated diseases. In some cases, an even broader interpretation could be justified. In the absence of a legislative ground, evaluation should be made on a case-by-case basis. However, if it is concluded that there is a change in the purpose of use of the research, e.g. if a previous consent does not cover studies on the disease(s) in question, a new informed consent is required.

Acquiring a new informed consent is problematic in the sense that it can no longer be requested from dead or very seriously ill subjects. Even among other demographic groups, only 50–60 % reply to such inquiries. Since the validity of the results of population studies requires as extensive participation as possible, it is necessary to develop legislation in such a way as to allow the authorities to approve extensions to the purpose of use of the research when the number of research subjects is large and acquiring new consents is excessively difficult or expensive.

7. Further action:

The working group proposes that TUKIJA considers the memorandum and undertakes the following tasks:

1. delivers the memorandum for information to the ethics committees and to support the handling of research protocols;

2. Makes the Ministry of Social Affairs and Health a proposal on the revision of legislation concerning research on tissue samples In principle, the need for revision applies to all clinical and epidemiological research and is not restricted to genetic studies discussed in this memorandum. The essential need for changes includes the following areas:
- defining similar and new purposes of use for already collected samples and research data, and the need for a new consent
 - enabling the use of already collected samples and research data for new purposes of use by official authorisations, also on the part of living research subjects if acquiring a new consent is not possible under the conditions set in section 20 of the Act on the Medical Use of Human Organs and Tissues
 - defining the borderline between commercial studies and scientific studies as well as any differences in provisions.

Annex 1. Comparison of epidemiological and clinical studies

- A large population sample (E) – A rather small patient group (C)
- Based on healthy persons or a large number of patients (E) – Based on patients (C)
- Often have multiple uses (E) – Usually concerns one issue or hypothesis (C)
- There is little time to collect data and acquire consents, often no more than one research visit (E) – Several research visits are often arranged (C)
- Personal follow-up is infrequent (E) – Follow-up usually frequent for therapeutic reasons (C)
- Only research data is collected, and the methods are risk-free for the research subject (E) – Extensive research data is collected, medical records are used, research methods may involve risks (C)
- Data on individual persons are purely statistical observation units (E) – Above and beyond statistical units, they are patients familiar to the treatment centre (C)
- The follow-up is conducted by the use of registers, questionnaires and sometimes by repeating studies (E) – The follow-up is typically conducted by recurrent clinical investigations (C)
- The value of the research increases or is achieved only during long-term follow-up (E) – The value of the research is achieved soon after collection of the research data (C)
- Data and samples are stored for a long time (E) – Data and samples are stored for a long time (C)
- Applies both to the living and the dead (E) – The main focus is on the living, although there are exceptions (C)

In epidemiological research, the protection of privacy of individual persons is excellent due to the large number of research subjects. The protection of privacy is good in clinical research also, but research subjects can be identified more easily in small patient groups. In epidemiological studies, the consent is needed mostly for the use of data collected during the study or other data combined to it, whereas in clinical studies, the consent is needed for research and treatment procedures as well as for the use of research data. The loss occurring during follow-up is often greater in epidemiological studies than in clinical studies, since there is no doctor-patient relationship. For an epidemiological study to succeed, the follow-up must be as extensive as possible. However, because of the large number of examinees, it is more difficult to carry out than clinical research. Moreover, in epidemiological research, receiving information about research subjects who have died as well as about those who are in a poor condition and those who cannot be contacted is essential during follow-up. This is not to say that some clinical studies do not require similar follow-up. At the very least, the use of data and samples that have been previously collected from such persons (with their consent) must be allowed in the research.

In epidemiological research, the data with regard to missing and dead research subjects includes: (1) data from interviews and questionnaires, which the research subject has already given for research use (2) samples (DNA, serum, etc.) which the research subject has given for research use (3) clinical data approved for research use by the research subject (4) register data approved for research use by the research subject. The discussion about the possibility of using such data at a later stage therefore concerns maintaining a (sufficiently) similar purpose of use and the purpose of the earlier consent. It also touches on fundamental questions such as a person's need and right to decide about his/her samples and research data, independent on whether he/she can be contacted or not.

Currently researchers have a research subject's informed consent for the use of data and samples in the medical research, and the research project is more strictly or more widely defined from the start. Data is usually processed in a way that the research subject's identity is not revealed during the

process, although personal data is needed for linking of data from several sources in connection with the research itself or in other research studies. When the target of the research is extended or changed, new data on the disease or predisposing factors are combined with the material, or new biochemical or genetic tests are made. After linking of data, the link to the personal data can again be dissociated, which means that there is no such link during the statistical analysis. In practice, then, the only change is the addition of new data to the research material, and during data handling, this data no longer has features that would require protection of privacy. In such cases, does the research subject need to know and agree to the data and samples collected from him/her being used for a research purpose different from the original? If so, how different would the new use have to be in order to be considered a new purpose of use? It is obvious that drawing a line to differentiate between new and original purposes of use often requires consideration on a case-by-case basis.

In principle, the solution to the problem could be acquiring a new consent whenever the new purpose of use is "too different" from the previous one. In long-term follow-up of the population, losses, serious illnesses and deaths are inevitable, which often makes acquiring a new consent impossible even if the person concerned does not or did not have anything against the data being used for a new purpose. If serious or fatal diseases are left out of the material, the results of the research are biased. The validity of the results is also impaired because of losses due to other reasons. Therefore, operating procedures need to be found in order to enable the use of previously collected data in later studies. Permissions granted by the authorities represent the best option.

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