THE DANISH COUNCIL OF ETHICS

Genome testing

Ethical dilemmas in diagnosis, in research and direct-to-consumer

Background report

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Indhold

Boxes and figures

Summary - The Danish Council of Ethics' recommendations

Genome testing should be used with caution, as it can compromise the examinee's right not to know, to self-determination and to privacy. The authorities should not prevent citizens from buying genome tests from private providers, regardless of the fact that their health value can be dubious, but conversely should ensure adequate regulation

Where genome testing is used in research, trial subjects should not be offered feedback on findings relating to genetic risk factors

If genome testing is used in diagnosis, patients' wishes concerning feedback on incidental findings should be agreed before testing is initiated. The scope of such feedback should be agreed between patient and doctor jointly

Whether under public or private auspices, genome testing should be accompanied by comprehensive and impartial advice, counselling and information

Information, counselling, referrals and follow-ups to genome testing should always be conducted by professionals with adequate skills. Nowadays general practitioners (GPs) are not equipped for these tasks. Citizens and physicians etc. should have access to a website with professionally well-founded and up-to-date information that can support them in their decisions about genome testing

Citizens who have become concerned on the basis of genome testing done by private providers should have access to counselling and information in the public health services. The health services should be aware that this development may lead to an undue strain on health budgets, e.g. owing to over-diagnosis and over-treatment


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Summary of Chapters 1-3 of the background report

Chapter 1: Introduction

- Genome testing can generate great volumes of information about possible genetic risk factors. In some people's opinion that creates promising possibilities for prevention, while others point out that the information will represent a strain, first and foremost, for some. Some will want the information, others will not. This gives rise to a dilemma with regard to how to respect some people's right to know and others' right not to know. To this can be added questions including how the public health services are being equipped for a possible future in which citizens have far easier access to personal genetic information. The Danish Council of Ethics has focused on four questions:
  - Justification for genome testing?
  - The examinee's self-determination?
  - New requirements for genetic counselling?
  - Consequences for the public health services?
- In the space of a few years, technological development has made it far cheaper and faster to generate genetic data, but interpreting those data is challenging
- Genome testing is already being widely used in research, being offered via private providers and in the process of being taken into service in Denmark's hospitals. Genome tests can be relevant for something approaching half the patients currently being referred for genetic investigation
- Genome testing can also produce reliable knowledge about serious hereditary disease. However, The Danish Council of Ethics' work has focused on the large body of uncertain information.

Chapter 2: Importance and relevance of genome testing for health

- Genome tests can produce large volumes of unreliable information about the examinee's possible risks for disease – risk factors that can be of varying relevance to health. This uncertainty applies not least to the prediction of common major diseases like type-2 diabetes, cancer and cardiovascular disorders, and it is uncertain whether this will change notably with more research, since the development of these diseases is conditioned largely by environment rather than heredity
- Patients and trial subjects must be informed of findings which are clearly of essential relevance to health. Through their records, patients have access to all health-relevant information produced about them, including any information they may have declined to be told about. Trial subjects do not have the right to information about individual results but are often offered some information as a kind of quid pro quo for taking part

- The majority of genome information falls within a grey zone between what can be regarded as clearly essential and clearly unessential in health terms. Such information will often be of interest to researchers but not sufficiently reliable for what has traditionally been regarded as a suitable basis for making health-related decisions. Hospitals normally have a narrow focus on the patient's diagnosis, but when the entire genome is examined the likelihood of incidental findings increases
- As a result of genome testing, most people who have a genome test done will presumably be able to obtain reliable new knowledge about at least one disease to which they are significantly more disposed than the average
- The relevance of genome information for the individual depends on specific aspects of both the finding and the examinee. For many people, attaining the level of understanding required for genuine self-determination will be demanding
- As a basis for making up one's mind, the legislation emphasizes information rather than counselling. In practice, however, some importance is attached to counselling, but there are only a handful of clinical geneticists in Denmark
- Fundamentally, genetic counselling must be non-directive, but in real life this is not possible, and neither do many patients wish for it. As a result, the doctor's facilitation of genetic risk information is instrumental to some extent in indirectly defining whether the knowledge of one's own genes is good or bad
- Existing evidence about examinees' interpretation and handling of genome information can neither confirm nor refute that genome testing creates concern, or that such information motivates them to live a healthier life.

Chapter 3:
Genome testing - ethical deliberations

- Generating information about possible risk factors by genome testing gives rise to a number of ethical dilemmas
- For the doctor or researcher the dilemmas arise particularly in relation to whether they should respect the patient's or the trial subject's autonomy by supplying them with as much as possible of the information generated by the sequencing, or whether they should respect the person's right not to know about this uncertain information. This dilemma can be handled by involving the patient or subject beforehand in the decision as to which information the person in question wishes to receive
- Since generating a lot of uncertain knowledge gives rise to the dilemmas mentioned, however, there is much to advocate careful consideration of whether the use of genome tests is appropriate, and to utilizing them conservatively. There is also reason to exercise reticence about generating large volumes of surplus, unreliable information if the value created is limited
- However, in relation to both patients and subjects wishing for extensive knowledge—even about uncertain information—as well as individuals who have genome testing done through private providers at their own initiative, there is an additional dilemma. For while such information can presumably enable the person to prevent disease in a timely manner in some cases, in many other instances the information will be so vague that the person tested will feel the urge to consult his or her own doctor and, where appropriate, demand referrals to specialists on an inadequate basis. Other things being equal, this will pose a strain on the public health system, since resources will be deployed on this to the detriment of other areas

Box 1
What is a genome test, and what is it used for?

Genome tests are examinations which simultaneously generate data on large parts of the examinee's gene pool, the genome. So far hospitals have only examined a single gene or a few genes at a time.

The genome is our hereditary material or genetic make-up, organized into 46 chromosomes, each of which consists of one long DNA molecule. The DNA molecule is structured like a spiral made up of four different so-called nucleotides (A, C, G and T), the sequence of which is important for the way the body's cells work, particularly those parts—a total of 1-2% of our DNA—that make up our genes. In some cases reading these "letters" can determine whether the examinee is suffering from, or will suffer from, a hereditary disease, because a gene contains a deviation – a mutation – in these letters.

Diagnosis

Hospitals often use genetic examinations to investigate whether an individual has a disease gene - that is to say a gene containing a mutation that causes disease – which can explain the heredity of a disease in a family. In many instances it can be crucial to know the precise composition of the disease gene. This is why recent years have seen the start of work at hospitals to sequence genes, i.e. to map the precise structure of DNA 'letters' in the genes frequently implicated in the patient's possible hereditary disease. In cases where no mutation can be found to account for the hereditary disease, it may be relevant to perform an extended diagnostic examination in which less commonly known gene variants are sequenced one by one. This is estimated to be true of at least half of patients. Instead, it may soon become cheaper and simpler to sequence the entire genome rather than individual genes, and several Danish hospitals are on the threshold of starting to carry out genomic sequencing.

Research

Researchers, for example, use genome testing to examine the genetic and non-genetic causes of disease. In many respects, however, our knowledge of the interaction between genetic and non-genetic causes of disease is still limited. Danish researchers are working away to examine "Danish gene variants" more specifically, and eventually the hope is that such examinations can be based on genomic sequencing of many thousands of Danes' genomes.

Genome testing direct-to-consumer

Private providers offer a large number of different products that generate personal genetic information, ranging from more narrow examinations of specific genes to genome testing of something in the order of 20 to 50 diseases. Although such examinations are less extensive than genomic sequencings, they will be included here under the term "genome test".

Some providers offer lifestyle-related examinations of e.g. muscle structure or metabolic type. To date the most popular and cheapest offers of genome testing have been based on relatively uncertain methods, but this may gradually change as technology and analytical facilities become better and cheaper. In 2010 it was estimated that the company 23andme had 35,000 customers, most of them American citizens presumably.

Box 2
Timeline - from traditional gene tests to genomic sequencing

- The first genetic tests saw the light of day in the mid-1980s. Many more have since made an appearance. Genetic chips ("microarrays") consist of many individual tests for hundreds of thousands of gene variations. These "traditional" gene tests and genetic chips will presumably continue to play an important role for some years to come.

- The first human genome was mapped in 2004 with the Human Genome Project. The price ended up at three billion US dollars.

- In 2010 it was gauged that the total volume of DNA that had been sequenced globally as of 2004 was now being sequenced every 16 minutes, thanks to new second-generation techniques.

- The technology has since accelerated further, and in 2012 a third generation of techniques was trialled. It is expected to bring the price of genomic sequencing down to less than USD 1,000 and the sequencing time for an entire genome down to a quarter of an hour. Several companies are vying to bring out the most usable technology. Among other things, one of the methods uses a device the size of a matchbox, which can be slotted into the USB port on a laptop computer. It cannot sequence a complete genome, however.

- The price of more superficial genome testing, which is often used by private providers, has fallen over the past five years from approx. USD 1,000 to USD 100. In 2011 the company *23andme* launched an offer for partial genomic sequencing at a cost of USD 1,000 for existing members.

Oxford Nanopore are now manufacturing this disposable DNA sequenator (or sequencer), the minION™, which is fitted with a USB for plugging straight into e.g. a laptop. The sample is dripped down into the hole in the middle. Source: Oxford Nanopore


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Chapter 1
Introduction

Current years are witnessing rapid developments in techniques that make it possible to study the genetic material from living organisms. The immediate consequence is that many people now have access to extensive information about their congenital dispositions to disease, because it has become cheap and simple to scan our entire set of genes - our genome.

For many years now hospitals have performed genetic examinations to test for one or a few genes at a time and on that basis have been able to pronounce with great certainty in some cases that the examinee is at high risk of becoming seriously ill later on in life.

Most disease genes are unknown, however, and it is rare for disease to be due to mutations in any single gene. There are few diseases that can be diagnosed with traditional gene tests, therefore. Genome testing makes it possible, at one time, to achieve insight into many of the examinee's genes and thus diagnose more patients with signs of hereditary disease.

However, genome testing is increasingly being used to investigate healthy people's risk for future disease too. In principle, genetic risk factors can be computed for any given disease on the basis of the data generated by a genome test. Unlike traditional gene testing, then, genome testing largely addresses healthy individuals, e.g. with a view to prevention. In many cases, however, the information is far more unreliable than what could be generated by traditional gene tests. This is due to the genes usually playing a limited role in the development of disease, and the interaction between the various genes involved and environmental factors being highly complex. So although a great deal of information can be generated with genome testing, the ability to predict disease in the examinee on that basis is a rare occurrence.

There is broad consensus that genome testing represents a very promising tool in research and diagnosis. The tool will provide hitherto unseen possibilities for generating precise and reliable genetic information and thus help ever more families with hereditary disease. And researchers have been given a powerful new tool for mapping the fundamental links between genetic and non-genetic causes of disease.

However, the bulk of the information from a genome test will not be usable for diagnostic purposes, since it will only indicate more or less uncertain risks for future disease; but nor can it always be written off as irrelevant in advance. This is a new situation.

An ethical dilemma thus arises: On the one hand this information can be viewed as relevant for health, and it may therefore be understandable that some people wish to have it, e.g. with the wish to prevent future disease; on the other hand there is a danger that the

information will be a burden, a cause for worry, above all, to some people. The question of how to respect some people's right to know and others' right not to know thus raises its head with renewed vigour. In addition, there is the question of when it is even appropriate to take genome testing into service, and how to equip public health services for a possible future in which citizens have far easier access to personal genetic information.

Unreliable information for everyone?

Traditionally, only few people have had access to genetic information. The health services normally only offer a patient a genetic examination when there is sufficiently firm suspicion of serious hereditary disease[1]. The use of genome testing in both diagnosis and research can potentially make genetic risk information about more widely accessible (see Box 1). With the advent of private providers of genome tests, anyone can gain insight into a huge array of dispositions to disease for as little as USD 100. The information is characterized by far greater uncertainty than has traditionally been the case in the context of genetic examinations.

The uncertainty surrounding genome testing is due, firstly, to the fact that the bulk of the information generated gives a fuzzy picture of whether the examinee, in later life, will develop the disease to which the information relates. The risks involved are far more moderate than those in which doctors have traditionally taken an interest, e.g. in the order of a 10-20% lifetime risk. This is especially due to the key role in developing disease being played by non-genetic factors. These include e.g. the stresses and strains to which we are exposed through e.g. diet, work, infections or environmental stressors during the fetal state.

Secondly, the reliability of any evaluation of the role played by the genes will typically be relatively uncertain, owing to our knowledge of the link between disease and genes still being in its infancy in many cases. New studies suggest that we are all walking around with 100 or so defective genes; but as yet we have only a limited understanding of the meaning of these[2].

1 Danish Council of Ethics (2000). Genetic Investigation of Healthy Subjects - Report on Presymptomatic Gene Diagnosis (in Danish only). Copenhagen: Council of Ethics. (See: http://etiskraad.dk)

2 Burgess, Darren J. (2012). "Genomics: How pervasive are defective genes?" Nature Reviews Genetics. Vol. 13.

Figure 1
Genetic and non-genetic factors in developing disease

Non-genetic factors

Stresses and strains during the fetal state

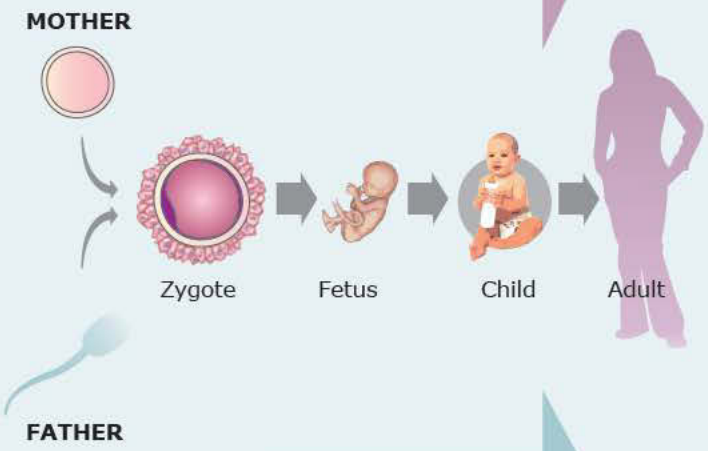
During pregnancy the fetus is largely subjected to the influences the mother is exposed to, e.g. diet, disease and pollution, which can alter the child's later susceptibility to disease. Although the DNA is not necessarily altered, the activity of the genes can be influenced by non-genetic factors through what is known as epigenetic modification.

Post-natal stresses and strains

Throughout life we are constantly being exposed to stressors that affect which diseases we are afflicted by. Some people, for instance, are exposed to hard physical labour, solvents and so on, which can render them more susceptible to particular disorders like respiratory disease or degenerative arthritis. Sedentary work, on the other hand, can lead to problems with the locomotory apparatus or cardiovascular disease.

Interaction between genetics and surroundings

Some diseases are primarily due to defects in the genetic material we get from our parents. The diseases we usually fall ill with are the result of complex interactions between genetic and non-genetic factors. The genes influence the body, but their activity is itself influenced by the body and hence by e.g. the external influences the body is subjected to.



Genetic factors

Genetic heredity

Children inherit a mixture of their parents' genes and hence also a mixture of their biological variation and genetic defects, which has a bearing on developing disease. However, new mutations with a bearing on disease can also arise spontaneously.

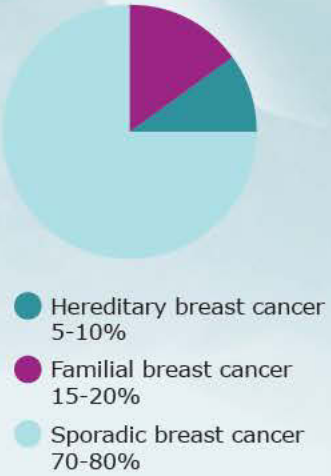
Genetic influences

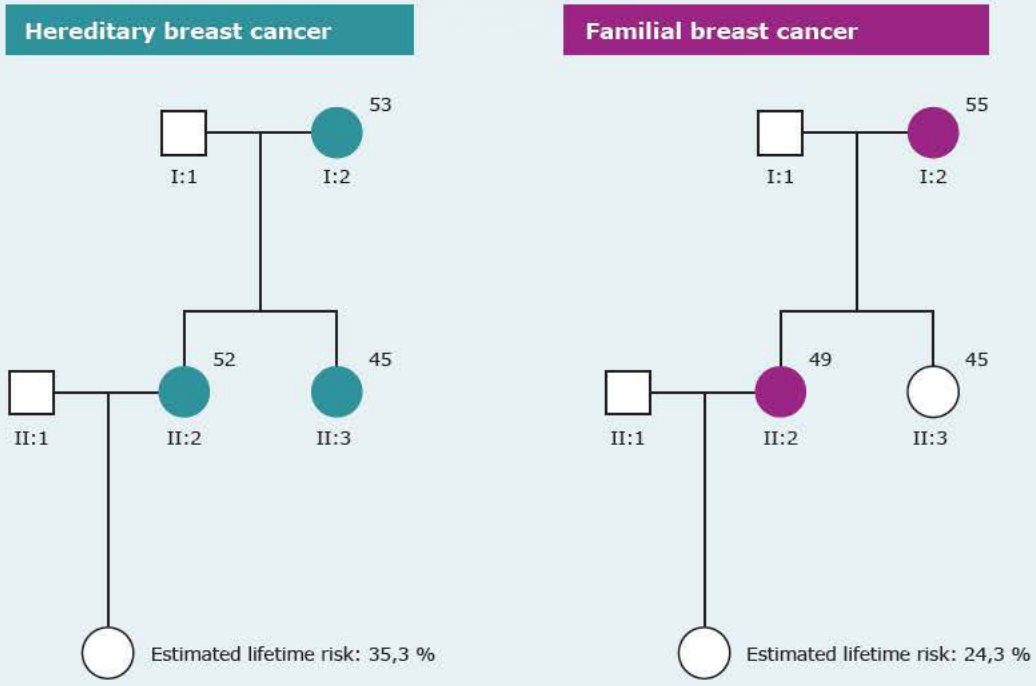
Local genetic changes during childhood and adult life can impact on later development of disease. Such changes can be a result of external influences, e.g. radiation or pollution, disease, diet, smoking etc., but can also be due to spontaneous mutations, and can be more frequent as a result of weaknesses in those genes that repair faults in the genes.

Figure 2
Disease and heredity

In the pie chart it is seen

- that only 5-10 percent of all breast cancer cases are attributable to a **disease gene**. These can already be diagnosed today.
- 15-20 percent are **familial cases**, i.e. the accumulation of disease in the family has not been able to be identified using traditional gene tests. A number of these are expected to be more readily diagnosable with the aid of genome testing.
- the remaining 70-80 percent of breast cancer cases are **sporadic cases**, i.e. the genes here presumably play a limited role. Therefore, genome tests will typically only be able to provide unreliable knowledge about the individual's risk of disease.





In some families many are affected by the same disease and often at a young age. That is a sign that the disease in the family is due to a disease gene that is inherited. How frequently members of the family are affected by disease, however, depends on the disease gene in question, and typically also on other genes and external influences. Some disease genes often or always lead to disease, following a clear-cut pattern or hereditary succession; these are called monogenic diseases. In other families the hereditary succession is more diffuse, because several genes interact with one another and with external influences. The risk of a healthy family member being affected by disease can be estimated on the basis of information about occurrence in the family and about the disease gene(s). (Empty sphere = healthy woman. Figures alongside sick women represent their age at outbreak of the disease.)

Source: Professor Anne-Marie Gerdes, Head of Department of Clinical Genetics at Rigshospitalet

Some people envisage genome information being able to be used for prevention more generally, as it can alert us to dispositions to disease and sensitivities, and thus enable us to modify our way of living. For example, the examinee can avoid activities which the information shows to be particularly risky for that particular person, or make sure they consult a doctor quickly if symptoms arise. Thus, having once been a tool typically used to diagnose sick people, genetic examinations are increasingly becoming a tool that addresses healthy people. The hope is that fewer people will fall ill and require treatment if more people act on a knowledge of their congenital dispositions to disease and sensitivities. That way, the advocates emphasize, more widespread use of genome testing can benefit the individual and society alike. Some even envisage a future in which we are all genome-tested at birth, and in which genome data can help us continuously and throughout life to live as healthily as possible[3]. Certain examinations indicate that users of genome testing via private providers can handle the uncertainty associated with the information and do not become particularly concerned, but the picture is not altogether clear.

Others are more sceptical as to whether it makes sense for healthy people to seek insight into possible dispositions to disease. It is stressed that the uncertainty of the information questions the health value of the information on the one hand, and the examinee's chances of grasping the significance of the information on the other. The consequence can be false security - or false alarm.

One may also ask whether information about possible future conditions even makes people's lives better at all. Some may become concerned without good reason and lead a lesser life than they would otherwise have done. For some it can be difficult to interpret and handle unreliable information and make up their minds whether they want access to it at all[4].

Moreover, there is little help to be had in interpreting and handling genetic information by looking for help from GPs. A study shows that only 10% of US doctors feel suitably equipped to help patients in relation to using genetic tests[5]. Another study shows that doctors who nevertheless take the initiative for follow-up measures generally make inappropriate decisions[6]. This raises further doubt about the prospects of the individual benefiting from genome testing, particularly when it takes place outside of the established system. The value of genome testing for the examinee can thus be very modest, if not out-and-out negative. If many people seek access to such information, and especially if patients require referral for additional examinations, the consequence may also be that counselling and follow-up provided to concerned patients become a strain on the health services.

The question of the genetic information's relevance to the examinee is not just about its significance for health and the uncertainty connected with evaluating it professionally, it is

3 See e.g. a summary of attitudes for and against genome tests in Borry, P. et al. (2012). "Legislation on direct to-consumer genetic testing in seven European countries." European Journal of Human Genetics advance. One prominent and relatively optimistic debater in a Danish context is the science journalist Lone Frank, who wrote the book *Mit Smukke Genom* [English title: My Beautiful Genome] (2010), on her reflections in conjunction with being genome-tested.

4 See e.g. Council of Ethics (2009). The Future of Prenatal Diagnosis (in Danish only). Copenhagen: Danish Council of Ethics. (See: http://etiskraad.dk)

5 Quoted In: Bloss, C.S., N.J. Schork & E.J. Topol (2011). "Effect of direct-to-consumer genomewide profiling to assess disease risk." N Engl J Med. Vol. 364, no. 6.

6 Plon, S.E. et al. (2011). "Genetic testing and cancer risk management recommendations by physicians for at-risk relatives." Genet Med. Vol. 13, no. 2.

also about the individual's specific situation and opinion. Some people prefer to receive feedback on even the most unreliable information, whereas others decline to receive even the most reliable information. To a large extent the wish for knowledge must be assumed to be individual and depend on specific circumstances. The question is whether—and if so, how—the doctor or researcher can and should take these individual wishes into consideration.

The legislation stipulates both a right to know and a right not to know. In practice, in a diagnostic and research setting, this is resolved by clarifying the examinee's wishes prior to the examination, wherever possible. But that does not solve all problems. As a patient, deciding whether one wishes to have access to unreliable information can, for example, be just as challenging before the examination is initiated as after.

An essential question in a diagnostic context is what the health-care staff do in those situations where entirely unforeseen findings are made, on which the examinee has therefore not specifically been able to take a stance. The use of genome testing is expected to increase the frequency of such "incidental findings". In research projects too incidental findings can be made.

The question here is to what extent this genome information should be passed on to relatives who, in the process—and possibly involuntarily, may learn about their hereditary dispositions to disease. When being tested, in other words, it is not merely oneself but partly also one's closest family that is being tested.

Finally, genome testing of children poses a special challenge. If children are genome-tested, they are saddled very early on with knowledge which there is no way of knowing whether they will eventually find onerous.

A number of the challenges mentioned are well-known, but the dilemmas take on renewed relevance as a result of the potentially large amount of unreliable information generated by the new possibilities for genome testing.

Four ethical questions

Genome testing makes possible highly precise and reliable information, in many instances more precise information than alternative methods, of potentially great relevance to the examinee. In this context, however, the Council is focusing on the potentially extensive information whose relevance to health can neither be taken for granted nor dismissed out of hand. The information can be said to pertain to risk factors rather than disease in the traditional sense. The Council considers that the generation of risk factors is first and foremost what raises new or intensified ethical dilemmas.

The report will therefore have only a limited focus on the classic hereditary diseases[7].

7 In 2000 The Danish Council of Ethics published a report with a more sharply defined focus on genetic testing of family members of a person with hereditary disease: Council of Ethics (2000). Genetic Investigation of Healthy Subjects - Report on Presymptomatic Gene Diagnosis (in Danish only). The focus in this report, however, is on hospitals' screening for gene variants with an obvious relevance to health. In 2009 the Council published a report on the future of prenatal diagnosis, raising a number of the ethical questions examined in the present report, though with the focal point largely on the issue of which diseases can form a basis for aborting foetuses: Danish Council of Ethics (2009). The Future of Prenatal Diagnosis (only in Danish)

In this project The Danish Council of Ethics has chosen to focus on the following four ethical questions:

- **Justification for genome testing**
  When is the use of genome testing justified? And under what circumstances should the use of genome testing be promoted at all?
- **The examinee's self-determination**
  How is the examinee's self-determination respected with regard to feedback of information from genome testing?
- **Counselling and information**
  Does the prospect of feeding back risk information from genome testing, which may be of variously unclear relevance to health, make special requirements of genetic counselling and information – and, if so, how?
- **Consequences for the public health services**
  What responsibility should the public health system assume in a possible future situation where many consumers express a demand for genome information, and consequently seek follow-up counselling, diagnosis or treatment?

The four questions are dealt with in the following chapters, with Chapter 2 introducing the factual background and Chapter 3 examining central ethical aspects. Finally, the Council offers its reply to the questions in the form of recommendations in Chapter 4.

The focus has been on elucidating ethical dilemmas linked to the use of genome testing in diagnosis, in research and direct-to-consumer via private providers. Within each of these three sectors, the questions mentioned are raised, albeit with varying emphasis.

Different guidelines, routines and practices have been introduced in these three sectors with a view to ensuring to a reasonable extent that citizens—whether as patients in the health services, as subjects in research projects or as consumers of genetic examinations via private providers—are not granted insight, unprepared, into information deemed not to be of benefit to them and their families. The Council has focused particularly on informed consent, feedback and counselling procedures and, in the context of private providers, the conditions for marketing in vitro diagnostic equipment in Denmark.

In selecting the focus mentioned, the Council has opted out of going into other topics in depth, though these are not necessarily any less topical and pertinent. Not least, this applies to questions related to storing and accessing genome data, disclosing information to relatives, particular issues relating to fetal diagnosis[8] or police investigation[9], genetic examinations with an eye to personalized treatment, paternity tests and tests for normal traits ("lifestyle examinations") as well as classic hereditary diseases.

Several of the topics are touched upon superficially, however. This applies particularly to the question of how storage of genome data can challenge the respect for the examinee's privacy. This question is briefly dealt with in Chapter 2, Box 6, as the Council touches on it in the recommendations.

8 See Council of Ethics (2009). The Future of Prenatal Diagnosis (in Danish only).

9 See Council of Ethics (2006). *Et DNA profil-register, som omfatter alle borgere i Danmark?* [A DNA profile register that includes all citizens in Denmark?] (in Danish only). Copenhagen: Danish Council of Ethics. (See: http://www.dketik.dk/da-DK/Udgivelser/BookPage.aspx?bookID=%7b36ECA29A-CD9F- 4AF3-A08E-4C6B0A5A7D44%7d)

Box 3
Examples of genome information

The information which genome testing is potentially able to generate can be divided into two categories of health-relevant information, reflecting differences with regard to the degree of uncertainty: Disease genes containing vehemently pathogenic mutations, and risk factors where the importance of the genes for developing disease is more limited. The borderline separating them is fluid, however, and partly arbitrary. In many instances it will be controversial to define whether a particular finding belongs to one category or the other, since the delineation concerns the relationship between normality and disease.

Disease genes
A gene is a disease gene if pathogenic mutations occur in it. All genes are potentially disease genes, therefore. In families where such mutations are passed down, there will be a greater number of people with the same hereditary diseases, and they are often affected at an early age. Disease genes often refer to monogenic hereditary diseases, that is to say that they are due to a mutation in one gene.

Examples of relatively frequent disease genes are:

- BRCA1 or BRCA2: Breast/ovarian cancer, lifetime risk 50-90% / 10-60% (background risk 12-13%/1-2%); incidence estimated at up to 1% of the Danish population
- LDL receptor gene: Hereditary tendency to artherosclerosis, >50% of men and 15% of women with a defective gene die before the age of 60; incidence approx. 0.2% of the Danish population.

In families where there is a suspicion of hereditary disease, genetic investigation is offered at hospitals, but some hereditary diseases can “hide”, e.g. by skipping generations, thus leaving the family unaware of the presence of the disease gene. Genome testing that generates data about the entire genome can in some cases identify such disease genes and thus potentially benefit the examinee and his or her family.

Overall, WHO estimates that there are something like 10,000 rare hereditary diseases, so even though each one individually is rare, a great many people are affected, taken as a whole. Many of these individuals will be aware of the hereditary disease beforehand and will therefore be offered genetic investigation even as things stand now.

For many of the diseases, however, it is true to say that there is as yet no complete clarity as to their incidence, or the importance of particular gene variants for developing disease. In a number of cases, therefore, it can be difficult to provide a clear assessment of what finding a particular disease gene—or absence of the same—actually means for the examinee. A precise interpretation requires specialist knowledge, which only very few doctors in Denmark provisionally have.

Risk factors
More often than not, the diseases we suffer from are a result of many different factors, both genetic and non-genetic, and are therefore called multifactorial or complex diseases.

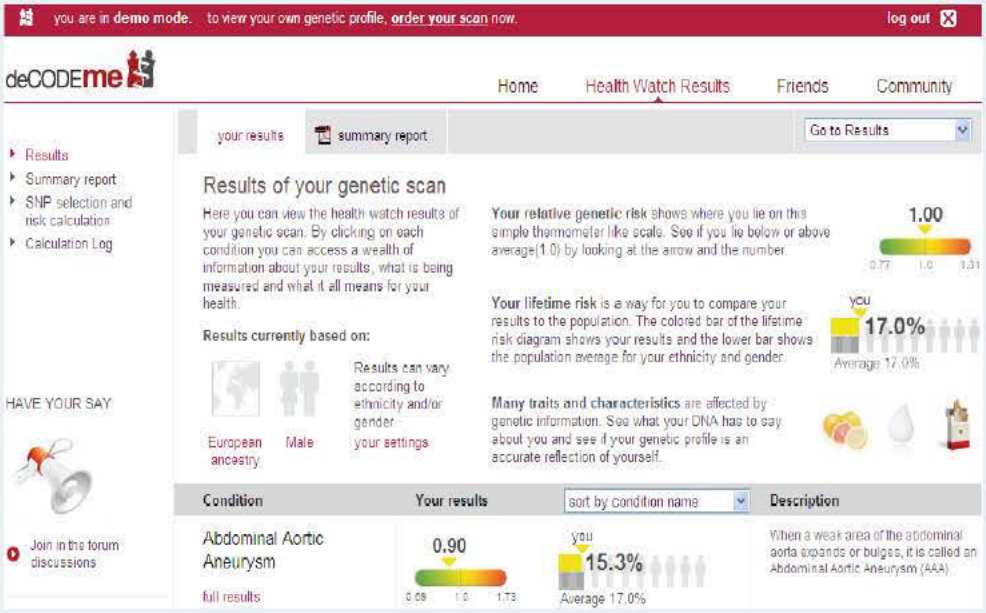
In some 95% of cases of type-2 diabetes, forms of cancer and cardiovascular disease, the heritability of the disorder is modest.

Here the congenital disposition to disease is a result of complex interactions between many genes, each of which individually perhaps plays only a modest role, and the surroundings. By examining many of these more or less "normal" genes simultaneously, however, it is hoped to be able to provide a picture of the examinee's genetic risk factors.

Viewed as predictors of disease, these evaluations are typically far more unreliable and the risks far more moderate than those based on findings of disease genes.

Risk factors are examined partly by comparing variations in the gene stock statistically with the occurrence of disease and with non-genetic factors such as diet, exercise and grow-ing-up conditions.

Risk factors are frequently analyzed for research purposes, but the results are seldom re-garded as reliable enough to say anything meaningful about the individual person's risk of disease. The examinations used by many private providers are typically used to identify risk factors rather than disease genes.



Displaying genetic risk factors from a genome test (demo version from "DecodeMe"). The examinee's risk factors are displayed relative to the average and as a lifetime risk for 48 disorders and imperfections, e.g. bald-ness, obesity, cardiac arrest, Alzheimer's and cancer of the bladder. Under each disease there are links, among other things, to relevant scientific literature. *23andme* is another large private provider of genome testing, but a great number of providers exist besides, offering different products.


TCCGGAATTALZHEIMERCCGGA
ADIABETESCCGGAATTAPOLU
ICCGGAATTALZHEIMERCCG
NCCGGAATTAEDUCATIONC
ATTADIABETESCCGGAAT
CCGGAATTABREASTCA
ATTADIABETESCCGGA
TCC

Chapter 2
Importance and relevance to health of genome testing

Genome testing generates data about large parts of the examinee's genome, and potentially therefore information about many dispositions to disease not previously known to the examinee[10].

When the relevance of genetic information for the examinee is assessed, its importance for health plays a pivotal role. In most instances assessing the importance of genome information for health is more unreliable than we have been accustomed to in genetic diagnosis by hospitals.

What relevance the genetic information has for the examinee also depends on other factors which doctors routinely factor into their evaluation. This applies not least to the specific patient's situation and wishes.

This chapter describes the special challenges raised by genome information with regard to the unreliability and relevance of the information. On this basis the chapter continues by looking at the role played by information and counselling in connection with the stance taken by those examined.

10 The exception is when the examination is used purely to diagnose serious heritable disease in families with heritable disease without generating information about other conditions. These cases, as mentioned in Chapter 1, are not dealt with in this report.

Box 4
Genes and disease

The human genome is made up of DNA, organized into 46 chromosomes, 23 of which we receive from each of our parents. DNA is shaped like a double helix, or a twisted ladder; the steps consist of four different “letters” (A, G, C and T), also called nucleotides or bases, whose sequence determines the function of the genes. DNA can generally be divided into two types based on its biological function (see Figure 3):

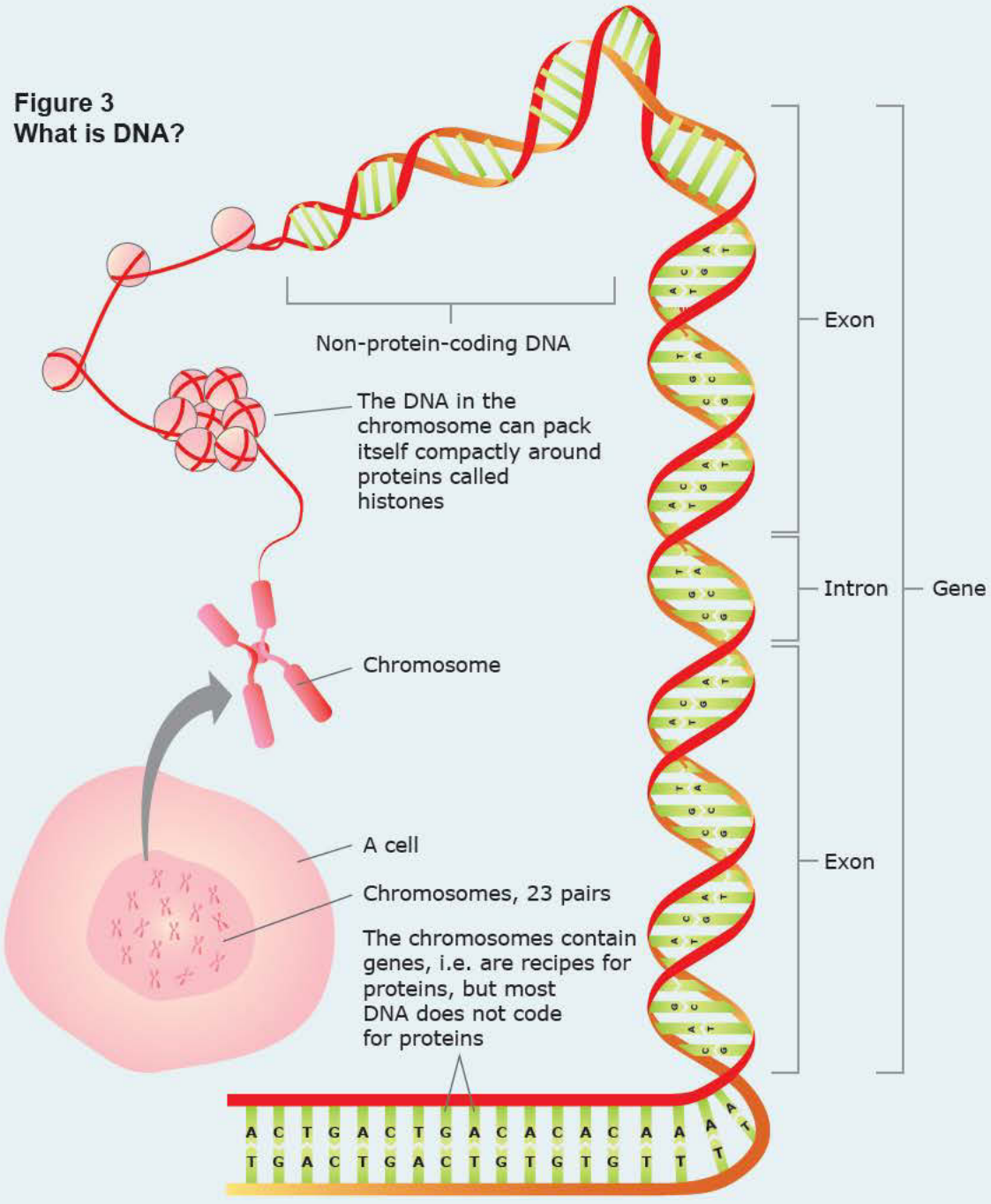
- **The genes** are the basic hereditary unit. Many genes act as a “recipe” for a particular protein, such as an enzyme. Proteins are fundamental to cells’ properties, and hence to the function of living beings, and can be crucial to whether cells behave like liver cells or nerve cells, say. The genes make up only about 1-2% of our DNA.

- **Non-protein-coding DNA.** In the infancy of gene mapping the other DNA was called junk DNA, because it was thought to be of no significance to the function of the organism. However, the research of the past decade has shown that DNA can have important biological functions, even though it does not code for protein, e.g. for regulating how active different genes are to be. Therefore, mutations in non-protein-coding DNA can also play a role for the development of disease.

Every gene typically exists in many different variants in different individuals—in many instances far more than a hundred—since every gene can vary for each of the individual bases. Some of these gene variants can inhibit the function of the protein for which the gene codes. This may mean that the person becomes ill or succumbs to illness more easily. The variations arise on account of random mutations in the DNA, that is to say substitutions of the “letters” the DNA consists of. Among other things, mutations can occur under the effect of high-energy radiation, such as the sun’s ultraviolet light; but in order to be hereditary, the mutations must occur in the sex cells or gametes.

Since genomes contain vast volumes of information, the greatest challenge consists in finding the significant variations in the “haystack”. Bioinformatics software is an aid to sorting; it can search for well-known gene variants or specific forms of mutation. Mutations are divided into different types, some being more prone to modify or entirely destroy the gene function. E.g. so-called nonsense mutations (“stop mutations”) typically entail defective genes. If the researcher prompts the computer to view all nonsense mutations, from experience the result will be a list of some 100 genes, thereby making the task of pinpointing the mutation or mutations that cause disease more manageable. But at the same time, the investigator may also gain insight into other serious dispositions to disease, i.e. make incidental findings. The investigator can try to avoid this by limiting the number of genes displayed by technical means, but in so doing will also limit the possibilities for diagnosing the patient’s disease in many instances.

Figure 3
What is DNA?



Patients' and trial subjects' access to health-relevant information[11]

Individual genetic risk factors for any given disease can be evaluated on the basis of genomic data. In other words, based on genomic data, copious amounts of information about the examinee's congenital dispositions to disease can be generated.

11 In this review of the examinee's access to information, the similarities between practice and legislation with regard to the user of genome tests in therapeutic and research settings, respectively, may appear more similar than they actually are, and the representation does not necessarily allow for all conceivable situations. Trial subjects, for example, can simultaneously be patients, involving extended duties and rights.

In a diagnostic context the focus will centre basically only on those disease genes that most frequently cause hereditary disease, thereby making it possible to weed out the most superfluous and unreliable information at an early stage (see Box 4). However, it is not unusual for frequent disease genes not to be identified in the patient, so that in order to be able to make a diagnosis, it may be necessary to perform an extended diagnostic examination, in which the doctor delves more broadly into the patient's DNA. But delving broadly into the patient's mutations increases the likelihood of making incidental findings, which is to say findings of congenital dispositions to diseases other than the one the patient is specifically being checked for. Such random findings, if deemed to be health-relevant, must be logged in the patient's records.

Patients have a right to unrestricted access to their records. Consequently, they also have the possibility of seeing information the doctor has not considered it important to actively inform them about.

Trial subjects essentially have no such equivalent right to such information, as no records are kept in this case. The researcher, however, is free to offer the subject certain pieces of information. In a research context, there exists a certain tradition of offering those being examined some feedback as a kind of consideration for taking part. However, the extent to which this takes place will probably be a matter of resources in many instances.

At the same time, patients' and trial subjects' right not to know must be respected; this can be done partly by clarifying their wishes for information regarding incidental findings prior to the examination. There is currently no legislative requirement for this to happen, however.

[Read more in: *Det menneskelige genom - retlig regulering i klinisk og forskningsmæssig sammenhæng*] ["The human genome - legal regulation in clinical and research settings" (in Danish only)]]

Box 5
Example: Incidental findings and the right not to know

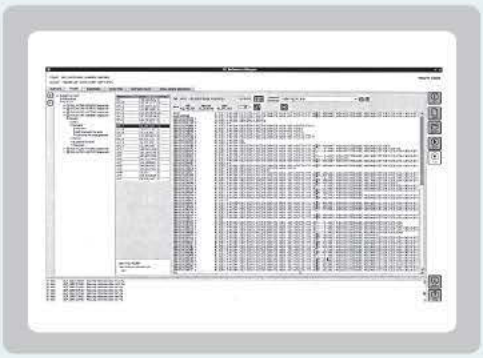
Certain mutations in the breast cancer gene BRCA2 also predispose people to prostate cancer in male family members who have inherited the mutation, albeit the risks are significantly more moderate than for breast cancer. So it is not certain that the patient or subject will wish for this knowledge. Prior to the examination the doctor can ask the patient or subject whose sample is being analyzed for hereditary breast cancer whether he or she wishes to receive feedback in the event of information on prostate cancer being generated.

However, totally unexpected findings can also be made. Maybe the researcher will make a finding indicating a predisposition to disease that is altogether unrelated to the point of the research project; or the doctor may accidentally discover that a patient being examined for a heart complaint is disposed to dementia hereditarily. Because the finding has occurred unexpectedly, the doctor will not have been able to ask the patient to decide on a position about feedback for that specific finding. However, if the doctor approaches the patient here to enquire about his or her wishes, there is a risk that the patient's right not to know will be violated, as the doctor must necessarily give the patient some information as a basis for that decision. Furthermore, in this situation, it can be difficult for the patient to decline information which he or she must presume to be of some relevance.

Figure 4
Incidental findings during genome testing at a hospital

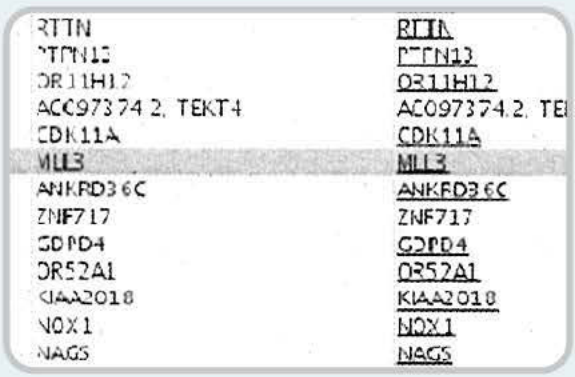
1

A patient with breast cancer is referred for genetic investigation owing to multiple cases in the family. The patient supplies a blood sample containing the genetic material, from which only a few selected genes most frequently involved in hereditary disease are sequenced.



2

Molecular biologists and bioinformaticians analyze and interpret the information by looking for mutations to explain the presence of this accumulation of the disease in the family. Conversely, if the examination shows a normal result, it may be due to a less well-known disease gene being the cause of heritability. The patient can now be offered an extended diagnostic examination, in which the doctors look across a broader spectrum of the patient's gene stock to find a cause. This can be done by mapping the whole of the person's genome.



3

The analysis process is repeated, only now it focuses on the whole of the patient's genome. The analysis can generate information about mutations in genes involved in diseases other than the one the patient is being examined for, so-called incidental findings, and the doctor must then judge whether the finding is so significant that it is relevant to inform the patient. However, the computer can also be prompted to show only mutations of relevance to e.g. cancer.

4

The patient is advised on the basis of the results and invited to discuss further action, involvement of the family and so on.

Source: Lars Jønson, Centre for Genomic Medicine, Rigshospitalet

However, patients declining information about incidental findings still have access to their records and hence to the information they have declined. With the introduction of electronic records (e-records), in which doctors record all health-relevant data, it has become possible for patients themselves to access entries in their records via the Danish Internet portal sundhed.dk (health.dk). As a result of this, 2009 saw the elimination of doctors' possibility of restricting patients' right to access their own records for inspection. At that time the Danish Council of Ethics stated that "new technology can provide such a profound insight into the person's future state of health that consideration must be given to which forms of information are relevant and appropriate for patients to have." Owing to patients' free access to their records, the Council felt that "it is of extremely great importance that this type of information not be generated at all and thus not make it into the records". Here it was foreseen that situations might arise in which it is appropriate to limit the amount of information offered to the patient, which should therefore not be generated. As mentioned, however, such information can be difficult to avoid altogether if genome testing is conducted as part of an extended diagnosis, say.

Genetic records have always been managed differently from hospital records in general. This is primarily due to the fact that, as part of his reasoning for diagnosing hereditary diseases, the doctor draws on sensitive personal data about the patient's family members and their disorders not readily accessible to other doctors. The introduction of electronic patients' records has made it necessary to screen genetic records, which means that only the department itself can see the notes. The genetic records cannot be accessed by the patient via sundhed.dk either. However, such screening can also be useful in situations where the patient declines information about incidental findings—information which may be useful, for instance, in connection with subsequent treatment pathways.

Duty to feed back on health-relevant information

In both a diagnostic and a research context, doctors must actively inform patients and subjects about all findings of essential relevance to health. Here, then, both patients and subjects have an unqualified right to information. With the generation of much information by means of genome testing, it is going to be a great challenge to decide when a particular finding can be said to be essential. Clearly, some findings will foreseeably be essential, whereas others will not. Many items of genome information will be located in a grey zone, however, somewhere between these poles, for which reason it can be relevant to look at the legislative principles on which the doctor's judgement is based.

Obvious relevance to health

If, in a diagnostic context, guidelines are to be posited for when genetic findings can clearly be said to have an essential relevance for health, partial recourse can be had to the deliberations made under the explanatory notes on the Danish Health Act when weighing up *the duty of confidentiality* to the patient and *regard for family members*. The doctor is not normally at liberty to disclose health information about the patient to others, including the doctor of the patient's family members, without the patient's consent. But precisely because the genetic information can also have very considerable implications for family members who—just like the patient—may have inherited a disease gene, it has been deemed that in certain situations the information can be of such essential relevance to health that regard for the relatives weighs more heavily than regard for the duty of confidentiality, and that information can therefore be disclosed without consent[12].

12 The rules referred to regulate the disclosure of information by the patient's doctor to one of the family members' doctor.

Translating these principles to establish an information requirement implies that the doctor will have a *duty* to inform patients whenever:

- a serious disorder is involved,
- there is a reasonable degree of likelihood of a genetic disposition being present,
- there is a reliably documented link between genetic disposition and developing the disease,
- the tests used to establish genetic disposition are reliable,
- the disease is very largely preventable or treatable.

To what extent these conditions have been met is a medical judgement call.

A corresponding set of criteria for evaluating health-science research projects involving genomic sequencing from a research-ethical perspective has been published in 2012. [Read more in: *Det menneskelige genom - retlig regulering i klinisk og forskningsmæssig sammenhæng*] ["The human genome - legal regulation in clinical and research settings" (in Danish only)]]

One example of a finding most doctors would presumably consider to meet the criteria are specific variants of the BRCA1 and BRCA2 genes, though there is less than full clarity concerning the meaning of the different variants in individuals from healthy families and hence incidental findings[13]. In what follows, this type of information is called *information of obvious relevance to health*.

Although the relevance of some information to health is taken for granted, there will potentially be situations where the information is not wanted. Feedback here will result in a violation of the examinee's right not to know. In such instances there is no ruling out that the duty to inform may also apply, *even* if the examinee has previously declined information. Such a duty to furnish information presupposes that the information is of concrete and self-evident life-saving importance, and that the examinee has not expressly said no to receiving information about that specific finding. If these prerequisites have not been satisfied, the examinee's right not to know must be respected.

Unclear relevance to health
Implicit in the requirements mentioned is the fact that assessing whether the examinee should be informed—and whether he or she wishes to be so—gets harder, the less severe the disease, the more unreliable the information and the smaller the possibility of preventing or treating it.

In some cases the doctor will presumably have to inform the examinee. The duty to do this is assumed to depend on a case-by-case judgement of whether feedback is appropriate. In what follows, such information is called *information of unclear relevance to health*. Different reasons can be imagined, each of which, taken in isolation or in combination, mean that the relevance of the information cannot be taken as given.

- the information's ability to predict development of disease is poor or uncertain,
- the treatment or prevention options at the time of examination are poor,
- the complaint involved is more minor,

13 The doctor will be unable to comment with the same degree of certainty on the importance of a given mutation present in a healthy person as if it were present in a person with symptoms, because the link between mutations and disease has primarily been studied in families with heritable disease. Incidental findings will typically be those relating to asymptomatic disorders, i.e. a person healthy in that context.

- the examinee is a healthy genetic carrier, and the risk of having sick children is modest unless both parents are carriers.

Again, the precise evaluation reflects a medical judgement.

Although the duty to inform is more or less identical in diagnosis and research, the patient in a diagnostic setting will presumably expect to be informed more widely than in a research setting. That means that the chief investigator in a research setting is not considered to be obliged to notify findings in quite the same way if these are not deemed to be of a clearly essential health nature, and thus satisfy the criteria for such. It is not inconceivable, however, that feedback will be required in certain cases, insofar as doctors and other health professionals have to judge, also in the context of research, what information satisfies the principle enshrined in law regarding due diligence and conscientiousness. One example of a finding that would presumably be deemed to come under the duty to furnish information in a diagnostic context, but not necessarily in a research context, might be the finding of a mutation that will lead with great certainty to Alzheimer's, as this disease is difficult to prevent or treat.

At the present point in time, information of unclear relevance is a more frequent result of genome tests than information of obvious relevance to health. The reason is that, in principle, it includes all risk factors, unlike the classic hereditary diseases, which are rarer. It will, however, presumably be possible to identify one or more special risk factors in everyone who is genome-tested (more about this later).

The vast majority of information that can be generated via genome testing is clearly of insignificant relevance to health, in as much as it indicates very modest and uncertain risks, and will not be discussed further[14].

Genome information and uncertainty

As mentioned in Box 3, the possibilities for predicting the development of disease with the aid of genetic information are generally limited as far as commonly occurring diseases like type-2 diabetes, cardiovascular disease and cancer are concerned. It is still uncertain whether this will change markedly with future research, as contracting these diseases depends mostly on the particular lifestyle led in the majority of cases.

For example, 48 sites in the genome have provisionally been identified where gene variation has a bearing on the development of type-2 diabetes; each individually contributes 3-35% increase in the risk of developing diabetes. But even assessing all the genes as a whole, the test's ability to predict who will become ill is little better than pure guesswork. Traditional evaluations based on knowledge of the patient's conventional risk markers like body mass index (BMI), occurrence of diabetes in the family, sex and age etc. typically provide better scope for predicting whether the disease will be developed than genetic information[15].

14 Berg, J.S., M.J. Khoury & J.P. Evans (2011). "Deploying whole genomic sequencing in clinical practice and public health: meeting the challenge one bin at a time." Genet Med. Vol. 13, no. 6; McGuire, A.L. & W. Burke (2008). "An unwelcome side effect of direct-to-consumer personal genome testing: raiding the medical commons." JAMA. Vol. 300, no. 22.

15 For type-2 diabetes the precision (AUC) describing how good a test is at predicting who in a given group actually becomes a patient is, on the basis of the 48 loci, 0.65 (statistically, 0.50 indicates a pure guess). In order to be regarded as relevant for prediction, AUC must be at least 0.8 (Oluf Borbye Pedersen, personal communication). It should be mentioned that specialist expertise distinguishes between overweight (BMI>25) and obesity (BMI>30).

With the increasing number of obese people and the correlation between overweight and a number of high-incidence diseases, investigations into the hereditary component of obesity have attracted a good deal of interest. Our present-day knowledge of the correlation between genetic variation and overweight implies that even in a person with high-risk genes the finding “only” entails a risk of becoming overweight that is a good twice the average. This means that if the population were screened for these genes with the ambition of identifying 80% of them who would actually become overweight, 70% of those who would not become overweight would simultaneously be misdiagnosed[16]. It must therefore be assumed that a finding of such obesity genes in a genome test would constitute a relatively unreliable marker for the examinee, who on that basis might make inappropriate choices.

The uncertainty attaching to the use of genome information as a basis for predicting and preventing disease can be divided into two different kinds of uncertainty[17]:

- *Unpredictability – uncertainty as to whether the examinee will actually contract the disease*
  Genome information will typically indicate a relatively modest increase in the risk of disease, e.g. 5-10% higher lifetime risk than the standard population. In many cases, whether the disease is actually developed will largely be down to the life led by the examinee. At the same time, it can be hard to fathom how serious the risk is in relation to all the other risks we are exposed to throughout life. A lifetime risk of 50%, for example, need not mean that half of those who have a particular gene variant will die of the disease; the same person can thus have several risks of 50% but will normally only be affected by one or a few of the diseases.

- *Unreliability - uncertainty about the evaluation*
  It is a relatively simple and cheap business to produce more or less “qualified guesses” as to what risks of disease the examinee has, but there is a big difference between the reliability of different examinations. Consequently, an evaluation of e.g. 20% lifetime risk for a particular disease can be more or less reliable. The reliability of results is highly dependent on how good the available background knowledge is. This widely fluctuating reliability is seen e.g. in the fact that evaluations of the risk of disease fluctuate massively in some cases, as and when fresh knowledge is generated. A study has shown that the same person obtains very different results by sending his or her sample to two different private genome test providers. This is presumably due to the use of different methods and background knowledge[18]. One of the deciding factors is that the knowledge about the relationship between genes and disease underlying an evaluation of the particular examinee’s risk factors is based on examinations of genetically comparable individuals. Often, too, there will be a big difference in the technical quality of the examinations, which may entail actual errors, including substitution errors.

16 Sandholt, C.H. et al. (2010). ”Combined analyses of 20 common obesity susceptibility variants.” Diabetes. Vol. 59, no. 7.

17 As mentioned in Chapter 1, there are exceptions from the uncertainty described in as far as findings are made of well described disease genes that result with great certainty in disease.

18 Nuffield Council on Bioethics (2010). Medical profiling and online medicine: the ethics of ’personalised healthcare’ in a consumer age. UK, Nuffield Council. (See: http://www.nuffieldbioethics.org/personalised- healthcare-0)

It can be difficult to establish whether a particular gene variant is or can become the cause of disease, since it can be what is known as a variant of unknown significance (VUS). However, health-care staff are continually updating their knowledge via scientific literature and professional communities.

Also crucial to the reliability of the evaluation is whether the knowledge of a finding's importance is based on adequate knowledge about the relationship between genes and disease. For instance, knowing whether the gene has been the cause of disease in other family members can be crucial to the evaluation. The same gene singled out as a cause of disease in some families or specific individuals will not necessarily provoke disease in other families or individuals. This can be due to some families or individuals having other genes that have a protective effect; it can also be due to differences in childhood, adolescence and lifestyle that can affect the genes' activity. In many instances, however, the importance of disease genes is primarily known about in families in which hereditary disease occurs. We are only slowly working out the importance of finding the exact same gene variants in healthy families, and thus of incidental findings; what is known, however, is that the prognosis is often better in healthy families than in sick families.

The constant change in our understanding of the genes' importance for disease is further exemplified by the interaction between our genes and our surroundings. It is now known that the role of the genes is not just given at birth, but their activity can be influenced by the way we live. E.g. there is research into the way our DNA is characterized by so-called epigenetic modification during pregnancy and childhood. This, for instance, is suspected of being one of the possible explanations for children who are underweight at birth and thereafter gain weight quickly, finding it hard to lose weight as adults, and to boot perhaps, passing on such acquired characteristics - in the form of modified DNA – to their children. Children, in other words, can have the same genes – and hence the same results from a genome test - but develop differently - and even pass on such acquired characteristics to their children – since the activity of their genes may have been altered more or less permanently as a result of their adolescent years.

The value of genome tests for healthy people

Access to genome information is regarded by some as a promising tool in a preventive context, i.e. for use with healthy subjects who, based on the incidence of disease in the family, have no prior tangible suspicion that they are at risk. It is this fact that makes genetic examinations potentially relevant for all, rather than just for families with hereditary disease.

The question is, however, what is the probability of information being generated about previously unknown conditions of relevance to health when a healthy person has a genome test done? Provisionally, there seems to be a good deal of uncertainty as to the answer.

Disease genes

As mentioned, it has been discovered that all individuals are likely to be walking around with 100 defective genes. Less is known about the significance of this. Many of the defective genes are presumably only of importance for those with children by someone who has the same genetic defect; in most cases this is not particularly likely, because the population frequency of the defective gene is very small. The probability of identifying a disease gene of obvious relevance to health in a random healthy subject via a genome

test, or as an incidental finding in a patient, is basically considered modest[19]. More recent results, however, indicate that one percent or more of those tested genomically can obtain potentially life-saving information about a disease gene[20].

Risk factors
In a study, researchers calculated the predictive power of information from genomic sequencing of healthy subjects, i.e. individuals with no known hereditary disease, in respect of 24 different severe diseases with a modest genetic component[21]. The researchers concluded that:

- on average, examinees obtain negative results for the 23 diseases but a negative result typically does not alter the evaluation of people's risk of getting the disease that much anyway. Negative results are false, therefore, in as far as they cannot be taken as indicative that, based on the result, the examinee can expect to avoid the disease to any considerably greater degree.
- 90% of examinees obtain relatively reliable knowledge about a risk factor that is at least twice the size of the background risk in the population and equivalent to at least a 10% lifetime risk; in many instances the risk is more than double that of the average.

To sum up, it can be said that genome testing is expected to lead relatively rarely to unexpected findings of disease genes of clear relevance to health in a healthy person, but it can happen.

However, genomic sequencings do appear to be able to provide most people with reliable knowledge about one risk factor at least, i.e. a disease to which they are somewhat more predisposed than the average. How many have prior cognizance of this risk, however, is not known. Whether the information is regarded as relevant to the individual is another matter still, and one which depends on many specific considerations.

The relevance of genetic information

Although the individual is seldom able to obtain reliable information about dispositions to those diseases he or she is most likely to die of, the uncertainty can gradually lessen in some cases. The fact that the information involved is reliable is, however, not necessarily synonymous with those who are examined wishing to have insight into them.

Some of the factors that probably play a part in helping most people to make up their minds are shown in the chart on the next page.

19 Berg, J.S. et al. (2011). Deploying whole genomic sequencing in clinical practice and public health: meeting the challenge one bin at a time. p. 501.

20 Johnston, J.J. et al. (2012). "Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes." Am J Hum Genet. Vol. 91, no. 1.

21 Roberts, N.J. et al. (2012). "The predictive capacity of personal genomic sequencing." Sci Transl Med. Vol. 4, no. 133.

Figure 5
Different factors of possible importance to whether a genome examinee wishes for feedback on examination results

Penetrance	In all likelihood will become ill due to genes (hereditary disease)	Significance of genes for disease moderate (risk factors)	Significance of genes for disease modest (risk factors)
Scope for action	Disease preventable or curable	Disease e.g. partly preventable or treatable	Symptoms can be relieved at best
Consequences of the disease	Disease is fatal	Disease is incapacitating	Disease can be lived with
Time of outbreak	Disease breaks out during childhood	Disease breaks out during adulthood	Disease breaks out in old age
Heredity	There is a 25-50% risk of children inheriting the disease	There is a moderate risk of the disease being passed down	There is a low risk of the disease being passed down
Reliability	In all probability diagnosis is correct	Diagnosis is probably correct	Correctness of diagnosis uncertain

The individual diseases and characteristics tested for will be spread differently across all these factors, and essentially many people are bound to find it more relevant to receive information about findings figuring on the lefthand side of the diagram, whereas findings seen on the righthand side of the diagram are less relevant.

There may be other aspects of information generation that can have a bearing on the examinee's desire to be genome-tested. This applies e.g. to the fear that information about personal risk factors will fall into the wrong hands [see Box 6].

The same information which some may regard as useful may be perceived as burdensome for others.

Some will see genetic risk information as a chance to plan and live their life better. Studies show that some people find information from genome testing valuable as one of several sources of knowledge about their health. They may be fully aware of the uncertainties that beset such information and use the information as a basis for the choices they make, without overestimating the value of such information for health. Some studies indicate that users of private providers in many instances look for genetic information out of sheer curiosity or for the sake of entertainment (read more about "Citizens' interpretation and handling of risk information from genome tests" (in Danish only))[22].

22 See e.g. Nordgren, A. (2012). "Neither as harmful as feared by critics nor as empowering as promised by providers: risk information offered direct to consumer by personal genomics companies." J Community Genet.

Others may become unduly concerned. One can imagine, for example, the finding of sensitivity to a particular heart disease causing the examinee to opt out of activities - e.g. travel abroad or sporting activities – on his or her own initiative, merely out of a fear of possible heart disease. That can have negative health, social and psychological consequences.

On the one hand the uncertainty surrounding the importance of the results can act as an extenuating circumstance, which should make the examinee less worried about a genome test, in that the risk of any danger really being afoot is generally low. On the other hand it is unclear whether those seeking out genome information do actually also take the information in such a suitably relaxed manner. Conversely, then, if examinees do overinterpret the genome information, they can end up as "concerned healthy subjects" or "unconcerned sick subjects".

Consent and information

The prerequisite for being able to decide on the relevance of genome information is that the examinee is in a position to understand the implications of being genome-tested. As has been made plain, the mere question of the importance of the results in health terms can be exceedingly complicated. To this can be added other issues relating e.g. to the importance of sharing such information with one's family.

In both diagnostic and research contexts Danish legislation stipulates that informed consent be obtained before initiating a genome test[23]. As mentioned, the examinee's wishes for feedback of information about incidental findings can also be clarified to some extent before the examination is set in motion. The purpose of the informed consent is that the patient's or trial subject's choice will have been made of their own free will and on the basis of comprehensive information.

In a research context the self-determination requirements have been weighed up against regard for progress of the research. However, criticism has been levelled at the current practice, which in the critics' opinion serves neither the interests of those being tested nor those of research to a sufficient extent. The private providers' consent procedures also come in for criticism.

In the scientific journal Nature, for instance, it is reported that when the private provider *23andme* announced their first patent in May 2012—for a gene associated with Parkinson's disease—it was not long before a customer publicly expressed scepticism about whether she had given consent for this. She had, but on the basis of a declaration of consent of the type that most people click their way through as a matter of routine. According to the author the case points to a wider problem with informed consent that has become particularly pressing in connection with large research projects of the type that increasingly includes genome research:

"(...) Protections for participants (…) are proving even more problematic in the 'big data' era, in which biomedical scientists are gathering more information about more individuals than ever before. (…) Many people argue that participants should have more control over how their data are used, and efforts are afoot to give them that control. Researchers,

23 See more about this in: "Citizens' interpretation and handling of risk information from genome tests" (in Danish only), though research projects in which only completely deidentified samples are used will not normally be subject to registration. However, see Box 6 on limits for deidentification in genome research projects.

meanwhile, often bristle at the added layers of bureaucracy wrought by the protections, which sometimes provide no real benefits to the participants." [24]

The legislation, as mentioned, has emphasized voluntariness and comprehensive information. Information is no guarantee of comprehension, however, if this is understood to mean that the examinee has a reasonable basis for making his or her decision—in part because it goes without saying that there will be a big difference as to how much information different individuals wish for or feel capable of studying, and in part because it can be challenging for the individual to place this information in relation to his or her own life situation. In many instances the examinees presumably base their consent on trust in the doctor or the researchers to a greater extent than their own study of the technical details.

Counselling

The concept of genetic counselling attributes importance largely to the examinees' understanding of the situation they find themselves in and to support in dealing with it. The National Society of Genetic Counselors (NSGC), a US-based organization, defines genetic counselling as "the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease."

No regulations on genetic counselling are in evidence in Danish legislation other than in connection with fetal diagnosis. The Bioethics Convention, which Denmark has signed and ratified, stipulates that "tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling"[25].

Genetic counselling can be time-consuming. Recent studies indicate a need for 5-6 hours' counselling in connection with both informed consent and feedback to the examinee on the results of genome testing[26]. Studies further point to many doctors lacking the skills to advise on the basis of genetic information[27].

An American study based on six group discussions between interdisciplinary groups of specialists also showed that, in crucial respects, genome testing engenders a lack of clarity about existing information and counselling procedures, e.g. how much information the examinee should and can relate to during the preliminary counselling. The process to date of developing guidelines to support doctors, e.g. on the reliability of genome results, is too slow in light of the rate at which new tests are arising. From 1999 to 2011 the number of registered genetic tests rose from 700 to 2,300.

24 Hayden, Erika Check (2012). "Informed consent: A broken contract." *Nature*. Vol. 486.

25 The Council of Europe (1997). Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo 4, IV 1997. (See: http://conventions.coe.int/Treaty/en/Treaties/html/164.htm)

26 Berg, J.S., M.J. Khoury & J.P. Evans (2011). "Deploying whole genomic sequencing in clinical practice and public health: meeting the challenge one bin at a time." Genet Med. Vol. 13, no. 6.

27 Plon, S.E., H.P. Cooper, B. Parks, S.U. Dhar, P.A. Kelly, A.D. Weinberg and S. Hilsenbeck (2011). "Genetic testing and cancer risk management recommendations by physicians for at-risk relatives." Genet Med. Vol. 13, no. 2.

Even specialists have a hard time keeping up with this rapid development and lack the skills to interpret the highly diverse test results from e.g. private providers[28].

In conjunction with hospital-based genetic examinations for hereditary disease in patients or their families, great weight is attached in practice to genetic counselling before, during and after the examination. Genetic counselling is performed by clinical geneticists and described as a process of communication that involves both information and support, routinely bringing in psychologists. The dialogue with the patient and his or her family is not just a one-way process, where the doctor informs patients about the implications of the test. It can involve family consultations, in which the doctor has an opportunity to gain insight into the family's history of disease. This can be of great importance for the doctor's interpretation of any genetic findings made. Genetic counselling also creates space for individual family members to make different choices[29].

In the context of approval for research projects through the scientific-ethical committee system, the emphasis can also be on counselling. No cases yet exist in which the need for counselling has been discussed specifically in connection with genome tests, but in cases about feedback on hereditary disease the emphasis has been on counselling[30].

No counselling requirements are normally imposed on genome testing when provided by private companies, nor are there any stipulations that a doctor or geneticist has to be involved. Danish law, however, does allow for the possibility of imposing certain requirements: the Minister of Health can lay down a requirement that medical kits may only be issued by a doctor or through a pharmacy, as a certain degree of counselling at the time of issue can help safeguard against erroneous use with e.g. increased risk of infection as a result.

Some private providers of genome testing have established different forms of counselling services at their own initiative, in some cases as an add-on purchase to the actual examination. However, studies suggest that many customers are not aware of the relevance of counselling[31]. Danish law sets out some requirements regarding adequate product information.

[Read more about the legal aspects of consent, information and counselling in diagnosis, research and direct-to-consumer - Appendix 2 and Appendix 3 (in Danish only)]

Risk communication

A characteristic trait of genome information is that it will rarely provide certainty concerning future disease but will merely describe a number of risk factors. For the examinee, however, the central question will be precisely whether they themselves are going to be stricken by the disease, or whether the probability of this is so great that they should take some action to prevent the disease.

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28 Uhlmann, W.R. & R.R. Sharp (2012). "Genetic testing integration panels (GTIPs): a novel approach for considering integration of direct-to-consumer and other new genetic tests into patient care." J Genet Couns. Vol. 21, no. 3.

29 Professor Anne-Marie Gerdes, Head of Department of Clinical Genetics at Rigshospitalet, personal communication. See also the Danish Medical Association's description of genetic counselling: http://www.laeger.dk/portal/page/portal/LAEGERDK/Laegerdk/R%C3%A5dgivning/ETIK/GENETISK _RAADGIVNING_OG_UDREDNING, and the Danish Health and Medicines Authority (2007): Arvelig nonpolypøs tyk- og endetarmskræft i Danmark – en medicinsk teknologivurdering. Copenhagen: The Danish Health and Medicines Authority.

30 See e.g. the National Committee on Health Research Ethics, lack-of-consensus case: Prostatakræft og BRCAness (http://www.dnvk.dk/omDNVK/komiteensafgoerelser/2011.aspx

31 Levin, E. et al. (2012). "Genetic counseling for personal genomic testing: optimizing client uptake of post-test telephonic counseling services." J Genet Couns. Vol. 21, no. 3. pp. 462-468.

Doctors constitute the interpretative link between statistical statements and patient. Compared to the more paternalistic doctor-patient relations of bygone ages, a change has taken place, with the doctor seeking by merely acting in an advisory capacity to respect the patient's self-determination. The Danish Health and Medicines Authority's description of genetic counselling as a professional medical speciality shows that genetic counselling must be fundamentally non-directive, that is to say that the doctor must not sway the patient to make a particular decision[32]. Some researchers, however, do point out that in practice counselling cannot be neutral:

"(...) knowledge about risk [is entrenched] in specific understandings of what is relevant to know, and what has to be done in the light of that concrete knowledge. With knowledge about risk, values are communicated about what constitutes the good, normal life, just as questions of guilt and responsibility in relation to health are part of the communication process. Risk communication is thus a form of control that chalks out implicit standards for interpreting the body and how people need to act in order to lead a healthy life."[33]

From this perspective, communication of statistical risk information is not a conveying of naked facts but ties in with specific understandings of what it is relevant to know, and what knowledge is for. In order to be able to create meaningful knowledge, the doctor more or less consciously expresses his own or the system's values and notions of what will be a good life for the patient. In a preventive context, particular values are prevalent according to this interpretation:

"Risk communication in relation to health promotion and prevention contributes to an ever growing focus on health as an ultimate value of a person's existence. In so doing, risk communication can potentially detract attention from other areas of human existence such as mental wellbeing and functional social relations. By virtue of the increased focus on risk and risk evaluations, health has become a metaphor for self-control, self-discipline, self-denial and willpower. Risk communication is thus instrumental in redefining what the good life includes. In broad outline there is a movement away from life enjoyment and development towards discipline and constant vigilance in terms of how people live their lives. At the same time, the focus is being shifted from the importance of external factors for health towards the individual—health has become an individual matter and an individual responsibility. It is our judgement that risk communication supports an idea that the individual can choose between health and disease through lifestyle choices and that individuals themselves are to blame if they fall ill."[34]

The fact that doctors try to hold patients accountable in this way by interpreting the statistical figures and advising on follow-up measures must be seen in the light of many patients actually wishing for the doctor to adopt a position for them. This may be only natural, given that the doctor is typically expected to be better able to evaluate the importance of such information for health; but also because, for the patient, it can be very difficult to gauge what relevance particular items of information have for him or her.

The doctor need not be interested in being directive, as he can thus be held accountable for making a choice the patient regrets. In other words, it may be the patient rather than the doctor who wishes the doctor to determine what the correct choice is. Ultimately, how-

32 Danish Health and Medicines Authority (2007). Rapport for specialet: Klinisk genetik.

33 Hansen, Marie Brandhøj & Mette Nordahl Svendsen (2005). Risikokommunikation i relation til sundhedsfremme og forebyggelse. The Danish Health and Medicines Authority. P. 27.

34 Ibid.

ever, the upshot of the doctor being unable to act in a value-free fashion, and a possible desire on the part of both doctor and patient to have the doctor be the arbiter of what is the correct decision, may be that certain narrow conceptions of the good life may eventually crowd out the patient's own notions and wishes.

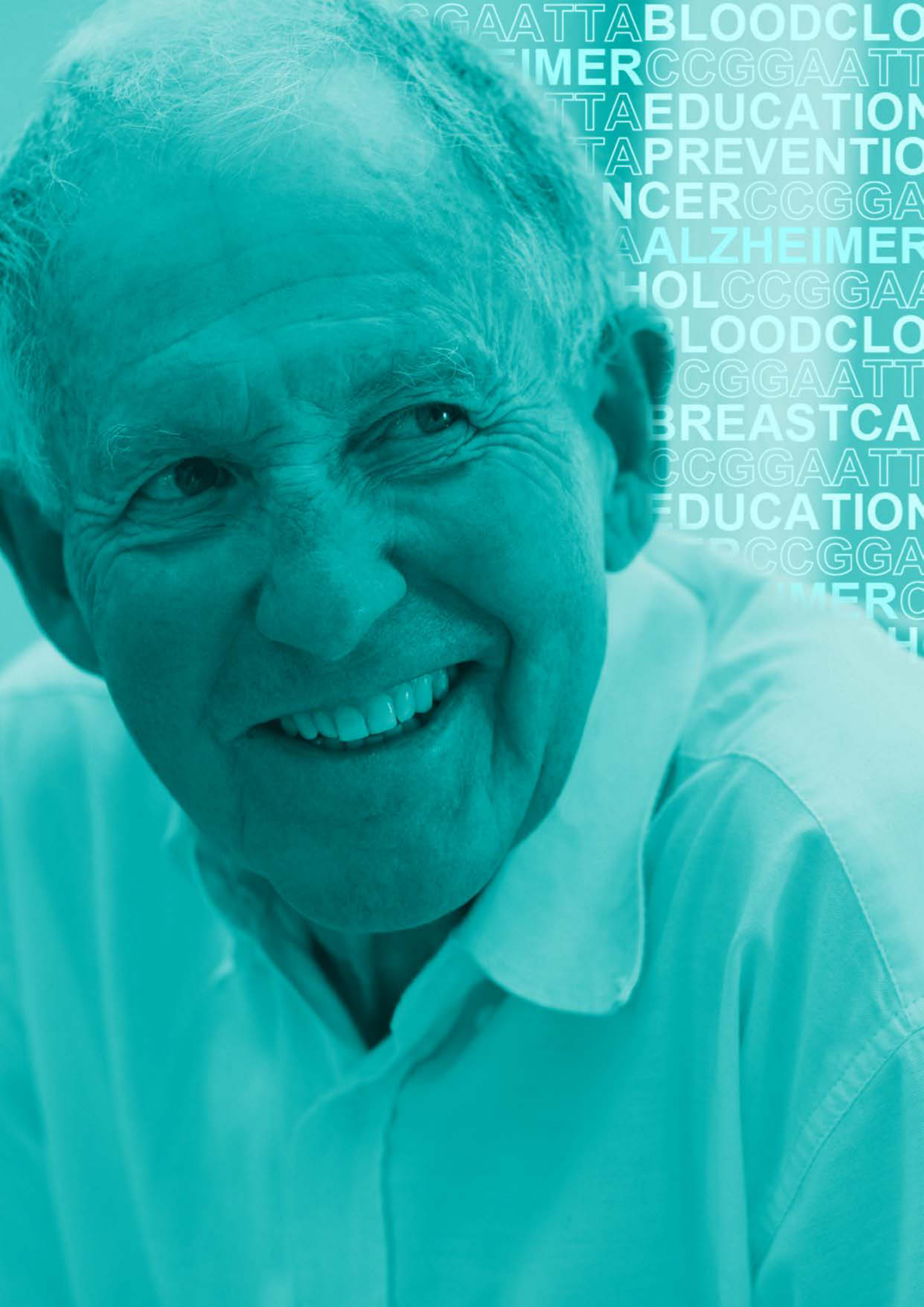
Box 6
Genome testing and privacy

The question as to how genome testing can challenge respect for the examinee's privacy is relevant in a diagnostic context. This is due to genome testing's ability to generate huge volumes of personal sensitive data and information, which is stored, even though only a modest proportion may ever be used. Genome testing thus challenges a principle of transparency in its administration, which dictates that patients should have the same access as health-care staff to the personal sensitive information stored about them.

In a research context, too, the question is relevant, because studies highlight the difficulty in some cases of maintaining the examinee's anonymity if genome data can enable deidentified subjects to be re-identified.[35]

In both a diagnostic, research and private setting there is a risk of e.g. insurance companies and employers gaining access to stored, personal sensitive health information. For the sake of good order it should be mentioned that, legally, insurance companies are not allowed to ask customers about the results of genetic examinations.

35 PHG Foundation (2011). Next steps in the sequence - The implications of whole genomic sequencing for health in the UK. UK, The PHG Foundation.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Chapter 3
Genome testing – ethical deliberations

Developments in genetic testing, as described, have progressed apace since the first tests emerged in the 1980s, moving rapidly both with regard to knowledge about the genes and with regard to the possibility of examining for predisposition to a large number of diseases.

But while the new genome tests are generating far more data than the early tests, it has become clear that interpreting these data is far more complex than then assumed. The correlation between genetic variation and disease turns out, for nearly all instances of the more frequent diseases, to be far less direct, as the genes enter into complicated interactions with one another and with the environment.

So although researchers' knowledge about the genes has expanded a great deal during the period, that increased knowledge has provided insight into how complex the links between genes and diseases are. It has also become clear how much knowledge we still lack in order to be able to understand these links, and that in many cases they are so complex that even greater knowledge will not make it possible to say for certain whether a gene variation will lead to developing a disease. In a few instances genome testing can provide scope for more precise diagnosis, but for the majority of diseases the test results will take the form of probabilities rather than knowing whether the patient is going to develop the disease.

The focus here is on which ethical dilemmas arise in the process in terms of use, respect for the patient's self-determination, information and counselling, and for priory-setting of the health services' resources.

When is genome testing justified?
The point of genome testing is to obtain knowledge: the purpose for health-care staff and for the examinee is to procure access to knowledge able to form the basis for actions that can prevent or treat a genetically conditioned disease. The purpose for the researchers is to source more knowledge about the correlations between genes and diseases. The purpose for those private individuals buying gene tests is generally to gain knowledge about their dispositions to disease and normal traits that may possibly call for prevention or treatment.

A central question in therapeutic contexts will thus be: whether and when the knowledge to which a genome test provides access is suitable as a basis for diagnosis, treatment or prevention of different diseases. Whether this is the case depends on a series of factors associated with the disease being examined for, and on the options currently available for preventing or treating it.

As mentioned in Chapter 2, other things being equal, the greatest value will lie in testing for diseases set to occur with certainty, which can be prevented or cured, which are serious, and which break out early on or relatively early on in life. That type of knowledge can form a basis for relevant health decisions if the test can say something definite about the onset of the disease; but for the time being geneticists understand the importance of only a fraction of the gene mutations, and they know even fewer well enough to consider our knowledge about them sufficiently reliable to make health decisions. Finally, the tests' ability to provide relevant knowledge is conditional on their being undertaken by people with sufficient specialist knowledge to be able to interpret the tests. Or—if the test is not performed by specialists—that the examinee has access to specialists who can interpret the results and give a relevant response. It is worth recalling here that, in the case of the vast majority of gene mutations, interpreting their relevance calls for a degree of specialist knowledge; as a result, only few people in Denmark will be in a position to prescribe relevant treatment or relevant follow-up examinations. As mentioned in Chapter 1, studies show that most non-geneticists by far who refer patients for supplementary examinations on the basis of genetic tests make inappropriate decisions in relation to which follow-up examinations are relevant.

In the case of most diseases the results of genome testing are associated with uncertainty: In part the knowledge is often lacking to be able to make reliable interpretations of the data generated; and in part, the results are often of the nature of probabilities rather than certainty about the onset of the disease. Uncertainty surrounding the link between the examination results that can be measured and interpreted on the basis of our present knowledge and the onset of diseases is a condition of medical science. Complex correlations are often the order of the day, and researchers' knowledge of them will presumably never be complete. "Wide" analyses, in which the entire genome is examined in detail, have only been possible for a few years, and there is still uncertainty about their implications, therefore.

That raises an overarching question of whether it is always a good idea to use genome testing, and more particularly it raises a question of whether and to what extent the examinee should have access to his or her genetic information.

The fact that genome testing generates so many unexpected and unreliable findings may be felt to represent an argument for using such examinations for diagnostic purposes in the Danish health services only in odd cases. In the future, however, more and more situations will presumably arise where the doctor considers genome testing to be the best method of diagnosis. Here a dilemma can arise when surplus information of an unreliable kind simultaneously emerges, unintendedly, about pathogenic mutations or risk factors other than those being examined for. Some patients will not wish to be told about these data and will not wish for them to be stored in their records. Others may want just that: access to the information, and on the basis of that information, to make lifestyle adjustments.

So opinions may be divided as to whether genome testing should even be used for diagnostic and research purposes. Recognizing the necessity of using them in some cases, it raises the further question of whether a doctor or researcher should also disclose the unreliable information emerging in the process. We shall be discussing these topics below.

Respecting the examinee's privacy

Another consideration that may be compromised by genome testing has to do with respect for the examinee's privacy. Genetic information is regarded as sensitive personal

information, for which reason it is normally endeavoured to deny unauthorized parties access to it. In general, the person from whom the information stems has a right to exercise control over the information, e.g. whether or when it may be stored. Experience shows that there can be different views of when that person's privacy is not being respected. For example, there are divergent opinions about how secure such data storage has to be, and who should have access to the information. Moreover, there are examples of out-and-out security breaches. As a basic premiss, therefore, every effort is taken to ensure that sensitive personal information is stored only with the patient's consent and for well-founded and clearly defined purposes like, say, specific diagnosis and treatment. A genome test, as mentioned, will generate large volumes of data and information which has no clear or specifically health-related purpose, unless it involves extended diagnosis. Storing large volumes of information basically entails a risk of unauthorized access to sensitive personal information.

The examinee's self-determination

Respect for autonomy and informed consent
Central to the tradition of medical ethics is the principle of respecting the citizen's or the patient's autonomy. Respect must be accorded the citizen and the patient as an individual with their own goals and plans for life, values and views. This respect is expressed in the requirement to obtain informed consent prior to commencing a medical procedure. According to the informed consent requirement, health professionals such as doctors and researchers have a duty to give patients and subjects comprehensive information about the procedure they want to subject the patient to, and a duty not to influence the patient improperly in his or her deliberations on whether consent can be granted. Against the backdrop of the information given, patients can choose to grant consent to receive a particular treatment or opt for inclusion in a research project.

Historically, the principle of informed consent came about following criticism of so-called medical paternalism, where the doctor took all decisions regarding treatment based on his medical assessment of what was in the patient's best interest[36]. One argument for letting patients make an informed choice instead was that they may well have different, conflicting interests at the same time (e.g. an interest in living as long as possible, but at the same time an interest in living their life without anxiety and concern), and that the interest appearing most important from a narrow medical assessment is not necessarily the one which the person themselves will weight heaviest.

A particular problem arising in connection with genome testing is linked to the health professional's and the patient's negotiation of informed consent.

In principle, then, the idea is that negotiating informed consent should also include negotiating the nature of the feedback which the patient will subsequently receive. The patient will reasonably be offered feedback about the health-relevant aspects of any given intervention or procedure.

In addition, health professionals like doctors and researchers are bound by a duty to inform, which means they are obliged to inform the patient about unexpected findings of a materially health-related nature.

36 Paternalism here is defined as the doctor making decisions for the patient with a view to benefiting the latter but without his or her consent or knowledge.

Genome testing generates large volumes of data of possible relevance to the health of a particular patient. The informed consent requirement calls for negotiation as to which information the patient will receive feedback on. The duty to inform dictates that the patient must have information about unexpected findings of material relevance to health. The question, however, is whether, on the face of it, this is a reasonable requirement, given the potentially large quantity of information and not least the nature of this information. Different points of view by way of a response to these questions will be elaborated on below.

Promoting autonomy vs paternalism

Having to handle and mediate the large volumes of information generated during genome testing in and of itself raises a problem for health services and patients alike. The problem for the Danish health services will be dealt with in a later section. The problem for the patient is linked to the concept of autonomy. As mentioned, a central component of medical practice is protecting and promoting the patient's possibilities for pursuing their own goals and plans, values and views. Large volumes of information about possible dispositions to disease can be difficult for a patient to relate to their life situation and understanding of life. Grasping these implications will require a great deal of effort in dialogue with the carer or practitioner. On the face of it, therefore, a requirement for the practitioner to provide all information of relevance to health will create difficulties for patient and health services alike.

The problem is intensified when the nature of the information generated during genome testing is taken into consideration. A certain amount of this information will be reliable and based on extensive scientific studies, but a large part will be unreliable or uncertain in the sense that insufficient reliable evidence is available of the correlation between a particular mutation and a disorder or other complaint. This information can therefore be of very unclear relevance to health.

In terms of protecting and promoting the patient's autonomy—i.e. the patient's possibility of pursuing their own goals and plans, values and views—two different points of view can be held at any rate.

The most far-reaching view will be that only the individual him/herself should decide what information to receive, and how he or she wishes to act on it. The fact that such information is uncertain and unreliable in some cases merely forms part of the decision-making basis it should be left to the individual to relate to. Given ample information, the patient will have full sovereignty in terms of planning his or her life and taking precautionary steps in relation to possible risks identified by means of genome testing. In a nutshell, there will be no protecting and promoting the patient's autonomy if personal information of relevance to health is withheld from him or her.

A less far-reaching point of view will be that the individual should have influence over the health-relevant information he or she is given access to in connection with genome testing. The patient must be ensured the opportunity to receive information that is reliable and of obvious relevance to health. This information puts the patient in a better position in terms of controlling and planning his or her life and taking precautionary steps in relation to possible risks identified by genome testing. Uncertain and unreliable information does not put the patient in a better position in terms of pursuing personal goals and plans—it will only form a poor basis for making decisions. In a nutshell, there will be no protecting and promoting the patient's autonomy if all personal information, regardless of its reliability and uncertainty, is shared with the patient.

Both points of view can be said to involve protecting the patient's autonomy.

It is clear, however, that the weak point of view opens the way for paternalism in a weak form—because who is to determine what is reliable information of relevance to health?

Here it could be argued that the doctor should be the one to play an essential role in terms of selecting the information that can be considered sufficiently reliable and certain for the patient to be able to influence whether he or she wants this information. Advocates of this emphasize that the relationship between a patient and a doctor is basically an unequal and asymmetrical relationship, in which the doctor and the health professional command specialist knowledge and experience which the patient does not have. At the same time, a patient is in a vulnerable situation and may therefore risk making decisions that are not in his or her best interests, e.g. because they lack insight into the medical aspects.

In support of the doctor playing a part in selecting information, it can also be stated that information about more or less uncertain dispositions to disease will cause some patients concern or cause them to focus unduly and exaggeratedly on disease, which can impair their quality of life.

However, it is inconsistent with protecting the patient's autonomy to leave it to the doctor or other health professional alone to decide the scope of such information based on the doctor's notions of what constitutes particularly burdensome information.

Furthermore, having to sift through this information on behalf of the patient or trial subject is not necessarily without its costs for the doctor, laying himself open to subsequent reproach by the former if he misjudges in relation to the person in question's wish to receive information.

Knowing, not knowing or ignorance

In relation to the discussion about what information should be exchanged between practitioner and patient in connection with genome testing, it must be stressed that respect for the individual also applies to the person's scope to opt out of receiving such information. Article 10 of the Council of Europe's Convention of 4 April 1997 on Human Rights & Biomedicine thus says in Section 2 that "Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed."

In some situations the patient will certainly be the one who wishes to leave it to the doctor to interpret and relate to the information emerging from genome testing. This may apply particularly in relation to uncertain data, which it can be difficult to relate to as a non-professional, i.e. the type of data generated by genome testing. The patient may feel incapable of working out what is the right thing to do in the overall scheme of things and ask the doctor to gauge what information he or she should have. To the extent that it is the patient's choice to entrust that decision to the doctor, it can be viewed as the patient exercising his or her self-determination by delegating it to the doctor, and this may be in due accordance with the principle of autonomy and the right not to know, as laid down in the Bioethics Convention.

In terms of respecting the patient's right not to know, a special problem must be highlighted: when enquiring whether or not a patient wishes to know his or her genome, the

timing is altogether crucial, as are the categories of information on which the patient is asked to take a position.

If an enquiry about knowing the result of a genome test is addressed to a patient after the examination has been conducted, the doctor will be placed in a dilemma, respect for the right not to know having already been challenged when the examinee is contacted to address the question of whether that person wishes to be informed about the findings made in connection with the genome test. For even at this point the person may have received more knowledge than he wished for in the form of knowledge that there is 'something' to know about his state of health. And when it comes to genome testing, this may involve many forms of unexpected findings of varying relevance. Even if the person invokes his or her right not to receive more detailed particulars of the information, a concern may have been planted as to whether the information opted out of pertained to serious findings perhaps.

A distinction must namely be made between not-knowing and ignorance, where ignorance cannot be kept up if one is aware that information has been generated about the state of one's health. On the one hand it can be argued that there are situations where ignorance is preferable to both knowledge and not-knowing. That will apply e.g. to instances where a genome test has generated knowledge about a low risk of developing a less severe disease, and where the scope for action is modest in terms of avoiding developing it. This, then, involves knowledge which, at best, is unusable and, at worst, leads to futile worrying. On the other hand it can also be argued that there are situations where ignorance is a problem. E.g. if one is not told that one has a very definite disposition to developing a severe disease that can be cured if detected in time.

Figure 6
Knowing, not-knowing and ignorance

	Knowing	Not-knowing	Ignorance
Positive			
Negative			

A distinction must be made between not-knowing and ignorance, where just being offered knowledge generated about oneself makes it impossible to remain ignorant, which in some cases is preferable.

At any rate the way the convention is phrased can be seen as acknowledging that people differ in their wishes whether or not to know about their dispositions to disease. Some people will wish to receive knowledge about even non-definite dispositions so that in some areas they can choose to arrange their life accordingly. Others will not wish to be advised of such non-definite dispositions. For them, merely having to relate to the possibility of developing disease will create great concern and an unfortunate focus on the body, leaving fewer resources over for other things. Apart from differences in temperament between people, there are also differences in patients' wherewithal for being able to make use of uncertain health information. Some of those examined may themselves be doctors or geneticists, or for other reasons be well qualified to understand the implications of the genetic information and the associated uncertainties.

For others it will be very difficult to relate to such information and assess whether there is cause to be concerned about it, and whether changing lifestyle in order to prevent disease is a relevant option. This difference can also give rise to a difference in the desire to know the result of a genome test.

In the preceding, the premiss on which deliberations have been based is that an enquiry about learning the result of a genome test is directed to a patient after the examination has been performed. As described, that can give rise to the patient relinquishing "important knowledge", but—whether or not important knowledge is involved—can also lead to the patient relinquishing information but worrying about the knowledge a doctor now has which might be about serious matters.

These deliberations indicate that there may be reason to direct the enquiry about whether the patient wishes to know the result of a genome test to the person in question before carrying out the examination, and that the enquiry gives the patient some general categories of information to relate to.

Information about genome testing results – a model
The deliberations above on informed consent, autonomy and paternalism, and especially knowledge, not-knowing and ignorance, all indicate that there may be a need to operate with a number of categories of information laid down on the basis of factors that may be expected to be of relevance to the examinee.

In the model proposed below it is assumed that only dispositions to diseases of a certain severity are to be offered. In addition to the seriousness of the disease, the therapeutic or preventive options available and the reliability of the emerging knowledge also have a bearing—whether pathogenic mutations that are highly likely to lead to the disease erupting or whether risk factors where the link between test result and disease is less certain.

The idea is that, when negotiating informed consent prior to starting the genome examination, the patient or subject should decide whether he or she subsequently wishes to be informed of findings within the following categories:

- **Pathogenic mutations that can lead to severe disease which can be prevented or treated**
  That is to say findings which indicate a high risk of developing such a disease—these can be e.g. gene variants that present a high probability of developing hereditary breast cancer or intestinal cancer

- **Risk factors for severe disease which can be prevented or treated**
  That is to say findings which indicate a slightly raised or uncertain risk of developing such a disease – these can be e.g. results suggesting a slightly increased risk of developing a blood clot or diabetes

- **Risk factors for severe disease which cannot be prevented or treated**
  That is to say findings which indicate a slightly raised or uncertain risk of developing such diseases – these can involve e.g. certain forms of dementia. They could also include being a carrier of severe diseases which can lead to severe disease in the carrier's children, if the person in question's partner is also a carrier of the gene

- **Pathogenic mutations that can lead to severe disease which cannot be prevented or treated**
  That is to say findings which indicate a high risk of developing such a disease – these may involve e.g. genes for Alzheimer's disease or other forms of dementia. [37]

However, it must be mentioned that such a model will not necessarily solve all problems, as it is not necessarily clear-cut where in the diagram to place a particular disease. Here the information which the doctor or researcher should pass on to the patient still has to be gauged.

As regards the first category, special considerations apply. Here, then, a finding has unexpectedly been made of pathogenic mutations, giving a very certain disposition to developing severe diseases which, if detected early on, will be preventable or curable. Knowledge of this disposition can therefore be a question of life or death for the patient. It is presumably relatively rare that this will happen, but to the degree it does happen it gives rise to deliberations about whether, legally speaking, there is a duty to inform a person about it if such mutations exist as a side-effect of a sequencing.

It can be argued that, other things being equal, the doctor or researcher has a moral duty to disclose life-saving information to a patient or subject, and here a duty to inform will normally exist too (see Chapter 2). At the same time, though, there is a duty to respect the patient's preceding choice, if any, not to receive information. What is important here, however, is that the patient has made his choice on an adequately informed basis, and that at the very least that must entail the patient having to have been informed about the nature of the specific disease and its preventive or therapeutic options. Arguably, choices not made on an adequately informed basis should not be respected if the consequences of doing so can be fatal for the patient—the point being that the choice cannot always be an informed one if the finding is made randomly. Based on this reasoning, patients or subjects should not be asked in non-specific terms about their wish to receive information of this nature.

Yet the situation described is atypical compared with the findings usually thrown up by genome testing, i.e. information which is uncertain both as regards the correlation between mutation and disease, and as regards the probability of the disease breaking out. As mentioned, the main focus here is on the potentially many items of information whose relevance to health can basically neither be said to be clearly great or small. These are the situations, in particular, which may call to secure the patient's stance as to what information he or she wishes to receive in advance.

It should also be mentioned that it is implicit in the model that the doctor is not to inform anyone about the type of findings to which the new genome testing can give comprehensive access: that is, unreliable knowledge about less severe diseases or sensitivities - e.g. allergies or flat feet. Some, of course, might also wish for access to such information, and the question is then whether the patient should have a chance to be given this type of information too. Here again a dilemma arises, for rights do not exist in a vacuum; they are associated with duties and with responsibilities, so it is relevant to discuss whether a right to genetic information can actually harm others in some situations, and must therefore be restricted. Moreover, it raises a number of questions as to how patients' self-determination or autonomy should be weighed against other relevant regards, e.g. for the common

37 Professor Anne-Marie Gerdes, Head of Department of Clinical Genetics at Rigshospitalet, personal communication.

health system. We shall be returning to that, but first some deliberations on counselling in connection with genome testing.

Counselling

The preceding deliberations deal particularly with the doctor informing the examinee about the unexpected findings genome testing can generate; but as mentioned in Chapter 2, informing is no guarantee of understanding. There are many factors at work in communicating complex information in a way in which the recipient both understands its implications and can act on it. The emphasis in the concept of counselling, therefore, is largely on the doctor having to base it on the examinee's understanding of the situation the person is in, and helping to handle it.

Counselling takes being neutral or non-directive as an ideal, and as such offers a possibility for the examinee to make his or her own autonomous choices in accordance with his or her values. The question, of course, is whether neutral counselling is possible; as mentioned in Chapter 2, some researchers think that, in his counselling, the doctor will implicitly express his own or the system's values and notions as to what will be a good life for the patient. At the same time, many patients and research subjects will actually wish for the doctor to undertake to counsel more directly on the correct choice to make in relation to the risk factors a genome test can generate.

But regardless of the problems involved in providing entirely neutral counselling, it is clear that the need for interpretation and counselling is hard to overestimate, in relation to the results of both genome testing and other types of gene tests used on the commercial market. With the vast bulk of genetic variations, as stated, interpreting their relevance requires a degree of specialist knowledge, meaning that only few people in Denmark are in a position to prescribe relevant treatment or relevant follow-up examinations. It is worrying, therefore, if private providers of gene tests do not offer relevant counselling to those tested. Without counselling it is difficult to see that those examined receive sufficient relevant knowledge and support to be able to choose how they wish to act on the test results. In reality, many will contact their own GP and ask for referrals for follow-up examinations with specialists, which raises the question of the repercussions for the public health system.

Repercussions for the public health system

Working from a principle of respect for autonomy, therefore, it is possible to arrive at different conclusions in relation to how much of the knowledge that genomic sequencing can generate should be given to patients or subjects. Some, as mentioned, will think that respect for people's autonomy dictates that we have a right to all knowledge about our genetic dispositions. There can be different degrees of rights involved, however.

Some will feel that people must have the right to access all the information that is generated during genomic sequencings performed for therapeutic and research purposes. Such a right would entail the doctor or researcher being obliged to make all information available, including information that does not relate to the concrete diagnosis or research project in hand. It might possibly also involve the patient or subject being entitled to have a clinical geneticist undertake an analysis of the results, since only very few will be in a position to understand the results without genetic counselling. Entitlement to the latter might also pose a great strain on the health services' resources.

A somewhat less sweeping view might be that we have a negative right to not have others prevent us from gaining access to our genetic information at our own initiative. Such a right would militate against the government introducing restrictions in relation to private providers of genome testing.

Yet, other things being equal, even if there can be said to be either a positive or a negative right to access knowledge about one's genetic dispositions, nevertheless it is not the case that these rights can be absolute. As mentioned, they are associated with duties and with responsibilities, making it relevant to discuss whether a right to genetic information can actually harm others and should therefore be restricted in some situations.

Individuals' right to know about their genetic dispositions must be weighed against other interests. E.g. even a negative right to have the government not interfere in citizens' right to themselves pay to have a genome test done with a private provider may risk clashing with society's priority-setting requirements, because genome testing will always reveal a raft of more or less increased dispositions to disease that may give rise to concern on the part of the person being tested. Users of commercial tests in particular may feel unsure as to how to take all this information in the event of the genetic counselling accompanying the tests proving to be inadequate.

Studies have indicated that a large part of those tested voice a desire to consult their own GP to get counselling and, if necessary, be referred for supplementary examinations. This will lay claim to resources in a health system already under pressure to prioritize its resources. In this connection some people have voiced concern that we may thus be approaching a user-controlled health service, where it is the patients' demand for examinations and pressure for treatments rather than the professionals' materiality considerations that determine how to prioritize the health services' limited funds. Priority-setting choices are ethical choices, because the implication of spending the health services' limited means in one area will, in a situation without unlimited funding being available, necessarily lead to other patient groups having their priority downgraded. Consideration should therefore be given to whether the risk of straining the Danish health services may advocate placing restrictions on the provision of commercial genome testing.

It is imperative that patients do not start to see the health system as a kind of market where the motto is "You pays your money and you takes your choice", where the doctor becomes a kind of "cooperative store manager", blindly writing off for all the examinations the patient asks for. The doctor needs to use his expert knowledge to judge which examinations are medically relevant and which are not, as the doctor also has a responsibility to safeguard the interests of the community, e.g. to prioritize limited health resources as best possible. This may be particularly relevant in cases where a person has had a commercial genome test done and then wishes to have additional examinations financed by the public purse.

In the latter type of situation the doctor can opt to dismiss the patient's wish for additional examinations because he deems them to be unnecessary and costly. In practice, however, more often than not it will be difficult for the doctor to dismiss the patient's wishes, and some thought might be given to the desirability of introducing guidelines that seek to prevent the public sector having to make examinations available purely on the basis of poorly validated results of genome tests from private providers. But even the drain on public health services represented by private test providers' customers consulting their own GP about such tests needs to be factored in too. It might therefore be relevant to officially

direct private providers to attach advisers whom examinees can consult as part of the service they are purchasing, so as not to strain the public health services.

It must be added that it is perfectly possible and fair to think that people fundamentally have the right to have their autonomy promoted while still recognizing the need to weigh up which rights should take precedence in any given situation. E.g. any right that individuals may have to access information about their genes will be weighed against society's right to prioritize limited health resources for deployment where they are most beneficial. So the regard for those who need treatment elsewhere in the Danish health services must be weighed against all citizens' right to have sequencing and analysis of their genome carried out.


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TAPREVEN
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OHOLCCG
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RCCGGA
AEDUCA
NCERCC
ALZHEIM
TATTGAL

Chapter 4
The Danish Council of Ethics' recommendations concerning the use of genome tests in diagnosis, in research and direct-to-consumer

In this chapter The Danish Council of Ethics presents its recommendations on the use of genome testing in research, diagnosis and through private providers. Genome tests are tests that at one time generate data about large parts of the examinee's gene pool or genome.

The purpose of The Danish Council of Ethics' work has been to map out the ethical dilemmas attaching to the use of genome testing with regard to advising politicians, administrators and practitioners as well as contributing to public debate.

As described in Chapter 1, the Council has elected to focus on four ethical questions. In what follows, the Council's replies to these questions are presented in the form of recommendations. To recap, The Danish Council of Ethics recommends that:

- **Genome tests should be used with caution,** as they can compromise the examinee's right not to know, to self-determination and to privacy. The authorities should not prevent citizens from buying genome tests from private providers, regardless of the fact that the health value of the test can be dubious, but should additionally ensure adequate regulation
- If genome examinations are used in **research**, trial subjects should not be offered **feedback** on findings of genetic risk factors
- If genome tests are used in **diagnosis**, patients' wishes regarding **feedback** about incidental findings should be agreed *before* testing is initiated. The extent of such feedback should be agreed between patient and doctor jointly
- Under both public and private auspices, genome examinations should be accompanied by **comprehensive and impartial advice, counselling and information**
- Information, counselling, referrals and follow-ups to genome testing should always be performed by professionals with adequate skill-sets. GPs are not currently equipped for these tasks. Citizens, physicians and so on should have access to a **website with professionally well-founded and updated information that can support them in decisions about genome testing**

- Citizens who, on the basis of genome examinations supplied by private providers, have been given cause for concern should have **access to counselling and information in the public health services**. The health services should be sensitive to the fact that this development may lead to **undue strain on health budgets**, e.g. owing to over-diagnosis and over-treatment.

Genome testing for everyone
In 2000 The Danish Council of Ethics published a report on presymptomatic genetic testing, which is to say genetic testing of healthy people who are in a risk group for serious hereditary disease due e.g. to the over-frequency of a specific disease in the family. With genome testing, on the other hand, the importance of the genes can be studied in all diseases, not only those traditionally considered as hereditary diseases. Consequently, genetic examinations are increasingly appealing to healthy individuals too.

Genome information is often uncertain
One particular feature of genome testing, however, is that the relevance to health of the wealth of genetic information that can be generated is often uncertain. For most people the result of genome testing will consist of gaining insight into more or less reliable information about congenital personal risk factors for disease, including the "common diseases" like type-2 diabetes, cardiovascular disorders and cancer (see Chapter 2).

Having said that, genome testing can also be a highly valuable tool in the search for disease genes, that is to say genes containing strongly pathogenic mutations, and in such cases generate reliable information on conditions whose relevance to health is obvious, but this has not been focused on in the Council's work. Admittedly, genome testing at hospitals does aim to diagnose severe disease, but it also generates large volumes of surplus data. It is foreseen that this will lead more frequently to making incidental findings whose significance for health may be characterized by the uncertainty referred to.

Genome testing in prevention?
The Danish Council of Ethics notes that a prevailing argument in the debate on genome testing is that the information generated will be of benefit to the individual and society alike, in that it can contribute to preventing disease. Others question the health value of genome information and point out that the information can be outright life-impairing, e.g. as a result of making inappropriate choices based on unreliable information (see Chapter 1).

Right to know and not-knowing
Examinees - or their relatives – can interpret and handle genetic risk information in different ways. In so doing there can also be a difference in whether the information as a whole is perceived as useful or burdensome. The ethical dilemma that thus arises is often formulated in terms of respect for the right to know versus respect for the right not to know. The legislation recognizes both rights, but it is unclear how best to respect them, particularly when unreliable information is at issue (see Chapters 2 and 3).

Unclear legal status
On balance, the Council considers that the appropriate use of genome testing makes it relevant to review the existing legislation for both diagnosis/treatment, research and private providers of genome testing.

In the context of discussions on the use of genome testing, The Danish Council of Ethics

has discussed the advisability of introducing a special act regulating the use of genetic examinations within the human field, as is the case in a number of other countries. The discussions connected to genome testing illustrate how bio- and genetic engineering frequently raise a battery of particular issues that are currently regulated through provisions in a number of general-purpose laws and regulations. This report mentions e.g. the Danish Health Act, the Committees Act, the Personal Data Act, the Healthcare Authorization Act, the Danish Product Safety Act and the Executive Order on Medical Devices for In Vitro Diagnosis. In complex interaction these laws and regulations regulate e.g. procedures for informed consent, record-keeping, the duty and right to furnish information, and regard for individuals' right to privacy. This distribution can make it difficult for practitioners, patients and many others to fathom which rules apply to which activities, and hence which duties and rights apply when. Added to this, when general laws are to be applied in specified fields, it can make for interpretative unreliability and hence the emergence of divergent practice at the individual sites where genome testing is used. Overall, the Council's view is that there is a lack of a common set of guidelines in this particular field to ensure the transparency of legal status for both doctors and patients. The recommendations below will provide examples of areas where, in the Council's view, there is a need for guidelines or for clarification as to how to interpret such general laws and regulations.

Regulating private providers is challenging

The Danish Council of Ethics is aware of the practical problems in managing regulation that pertains to private providers of genome testing who operate from countries outside the EU. Although the Council is aware of two Danish companies that have begun to provide genome testing within the past two years, companies headquartered outside of the EU still dominate. The Danish Council of Ethics supports efforts to introduce a national and international certification scheme. However, it should be endeavoured to ensure that such a scheme cannot be used as an official recommendation to make use of privately offered genome testing. Moreover, the Council hopes that the recommendations can be of use to consumers and be instrumental in supporting efforts to establish accountability within the sector, as well as contributing to the development of a Danish view of in the field.

Box 7
Additional ethical dilemmas

While working on genome testing, the Danish Council of Ethics has discussed a number of problematic issues along the way. In the Council's estimation these are highly topical but, for reasons of time, the Council has not been able to explore them in depth. Examples of these are:

- **Storage, right of disposal and access to genome data**
  Genome testing raises new or heightened questions relating among other things to access to genome information for e.g. insurance companies and employers, ownership of private genome databases and DNA theft. Furthermore, it is unclear whether the present structure for publicly financed biobanks ensures sufficient prioritization of the resource made up by biobanks. This raises ethical question about fair prioritization, self-determination, respect for the right not to know and respect for the right to privacy.

- **Dispensation from consent to take part in genome research**
  When using information and tissues from established/older biobanks, researchers may be obliged to advise subjects about findings of disease genes even though the trial subjects cannot have known about genetics or about the implications of feedback on hereditary disease when consenting to participate, and possibly to feedback. The respect for trial subjects' and their relatives' right not to know can thus be violated.

- **Data research**
  Research based solely on health data, such as genetic data, is exempt from application for scientific-ethical approval despite such data being able to reveal hereditary disease in subjects. In some cases such information must be fed back out of consideration for the trial subject's right to insight into potentially life-saving information. The need for this is normally appraised in connection with scientific-ethical consideration.

- **Research on anonymous material**
  For reasons of efficiency, research on anonymous material was exempted from scientific-ethical approval in 2011. However, studies suggest that developments in genomic sequencing are increasing the risk of said anonymity being able to be disregarded. Anonymity is traditionally seen as a fundamental right for subjects, intended to safeguard respect for their right to privacy.

The Council urges the relevant politicians and authorities concerned to be alert to the ethical dilemmas following from this.

1. Justification for genome testing

When is the utilization of genome testing justified and under what circumstances should the use of genome testing even be promoted?

Advantages and drawbacks of genome testing
Genome testing represents a promising new tool in diagnosis and research, but also brings with it a raft of possible disadvantages by dint of generating large volumes of personal sensitive data and information on risk factors. This can place the examinee in precarious quandaries as regards feedback on results and compromise the person's right to privacy owing to the large volumes of data and information being stored.

Recommendation 1.1
Genome testing should be used with caution

Diagnosis
The Danish Council of Ethics believes that genome testing for diagnostic purposes should basically be used only if the method is expected to entail significant, concrete health benefits for the examinee as compared with other methods. Genome tests should not be used as a matter of routine e.g. for reasons of efficiency.

Research
The Danish Council of Ethics basically considers it inappropriate to limit researchers' scope for using genome testing as a research tool. Such use must, of course, take place in full awareness of the specific drawbacks that may possibly result for subjects, and put in place suitable protection, in accordance with the following recommendations.

Direct-to-consumer
The Council does not think obstacles should be placed in the way of those wishing to source information about genetic risk factors, who may be altogether conscious of the constraints on such information. Similarly, in some cases, it cannot be ruled out that genome testing can lead to the identification of hereditary disease, also in individuals who previously had no suspicion of this and had therefore not necessarily been investigated under the public health system [see Box 3: Examples of genome information].

Conversely, by debating with politicians, practitioners and the population as a whole, the Council wishes to raise awareness and conduct discussions about the advantages and constraints of genome testing, and the conditions that should be imposed in order for the technology to benefit the individual and society as much as possible.

The Council recommends that the relevant authorities monitor the area closely and continuously evaluate the need to stipulate additional requirements for private providers, e.g. with regard to comprehensive information and counselling (see recommendation 3.1) and skill-sets (see recommendation 4.1).

Finally, the Council recommends that the possible social and psychological drawbacks connected with genome testing should, in principle, be able to be incorporated in evaluating which requirements to impose, through regulation, on genome testing by private providers. First and foremost the present rules aim at protecting the consumer from physical perils that have arisen e.g. as a result of wrong use of the equipment, and at ensuring that the equipment can deliver what the manufacturer promises.

Recommendation 1.2

Genome testing of children and young people

Position 1: Children should only be genome-tested by way of exception
Some members of The Danish Council of Ethics (Anne-Marie Mai, Christina Wilson, Edith Mark, Ester Larsen, Gunna Christiansen, Jacob Birkler, Lotte Hvas, Niels Jørgen Cappelørn, Søren Peter Hansen, Thomas Ploug) recommend that genome testing for health purposes only be used on children and young people when the method is deemed, in practice, to represent the only option for diagnosing severe disease in themselves or close relatives. That applies irrespective of whether a genome test is offered under the **public health system** or sought out directly by the consumer via **private providers.**

The members have misgivings about the ease of access to genome testing children and young people which citizens now have through private providers; but they do note that Danish and European legislation can be difficult to enforce vis-à-vis companies operating via the Internet from countries outside of the EU.

Genome testing of children and young people should only be used in research when the method is deemed to entail significant and concrete health benefits with regard to diagnosing hereditary disease in comparison with alternative methods.

Children and young people under 18 cannot be expected to be independently capable of adopting a position on the prospects of being genome-tested. It is the parents who must take up a position on diagnosis on behalf of the child when the child is under 15. An 18-year limit applies to research. Information about risk factors can create undue concern in the child's parents and in the child when, at a later juncture, the child can gain access to this information under freedom of information legislation.

Position 2: Children/young people should not be treated differently to adults
Other members (Christian Borrisholt Steen, Jørgen Carlsen, Jørgen E. Olesen, Lillian Bondo, Mickey Gjerris, Rikke Bagger Jørgensen) do not think that the rules applicable to children and young people should differ from those applicable to adults. It should be the parents' rather than society's responsibility to determine whether it is appropriate to genome-test children and young people. The members see no relevant differences between decisions about genome testing and many other decisions parents are already handling on behalf of children and young people at the moment. If, via genome testing, children and young people gain insight into information they find burdensome, they should, as in the normal course of events, be offered counselling through the public health services.

2. The examinee's self-determination

How to respect the examinee's self-determination with regard to feedback of information from genome testing?

The meaning of "relevant information" is up for discussion
Doctors have a better chance of evaluating what genetic information is relevant for the citizen's health choices than citizens, in as much as they have sound specialist knowledge. Conversely, citizens know best what relevance the information will have to their lives.

Only in rare cases can the doctor take the relevance of genetic information for granted. The health services have a duty to respect citizens' right to self-determination, but what that means is not clear when applied to patients' access to unreliable information on, e.g., genetic risk factors.

In other words, the question arises of what influence citizens should have over their access to information about possible dispositions to disease in their genome. Central to this discussion is the question of how to balance respect for the right to know and the right not to know. Such rights basically vary, depending whether the examinee is a patient in the health services, a subject in a research project or a consumer.

Recommendation 2.1

Feedback from genome testing

Access to information about risk factors should be regulated in such a way as to respect the right not to know, wherever possible. It should be one of the authorities' responsibilities to put in place joint guidelines to support doctors' and researchers' estimation of the need for feedback.

Research: Feedback should be limited
In a research context, feedback about personal risk factors should be limited. Access to information about e.g. congenital predisposition to lifestyle diseases can play an unfortunate part by way of an incentive to participate, even if the value of the information is dubious. Here it should be kept in mind that the purpose of taking part is not diagnosis but research.

The National Committee on Health Research Ethics should see to it that those involved in genome research projects are reticent about offering subjects information on genetic risk factors.

Diagnosis: Feedback requests should be agreed before the start of testing
In the context of genome testing, patients' wishes regarding feedback on incidental findings should always be clarified at the time of informed consent, before starting testing.

To the greatest extent possible the procedure should ensure that once the results are available, no doubt arises as to the examinee's wishes concerning feedback. Offering the examinee feedback about personal results when the results are already available constitutes an undue compromising of respect for the person's right not to know. The patient must be told about facilities for seeking insight into the information he or she is opting out of (cf. recommendation 2.2).

Wherever possible, surplus information about risk factors should essentially be avoided, since resources should be concentrated on treating and preventing hereditary disease in the traditional sense.

If a patient has declined particular types of information about incidental findings, it should be endeavoured to ensure that such data are not generated, partly to limit the volume of information known to the doctor, but not the patient, and partly because storing large volumes of personal information can compromise the examinee's right to privacy.

However, the Council does acknowledge that for diagnostic reasons there may frequently be weighty reasons for carrying out extended diagnostic examination. Such examinations generate a wealth of genetic data and entail a greater probability of incidental findings, including some that may be entirely unrelated to the disease/condition for which the patient is being tested—regardless of the fact that the patient may have already requested not to have information about incidental findings. Here, then, generating surplus information to which the doctor, but not the patient, becomes privy may not necessarily be avoidable.

The Council also acknowledges that the question of where to draw the line between relevant and irrelevant information should be seen partly as an individual affair. The Council therefore feels that interested patients should have a reasonable degree of influence over the extent of feedback if it is foreseen that the information will inevitably be generated.

Many different features of the incidental findings that may possibly come to light can, in different combinations, be of vital significance to the patient's perception of whether he or she wants feedback - e.g. severity, onset, penetrance, therapeutic options and so on (see page 38). In practice, therefore, it will be difficult to ask patients to take a stance on every conceivable finding. One solution might be that, in dialogue with the doctor, the patient takes a stance on broader categories of findings (see proposal on page 51).

The Council thinks that in this connection a "triviality threshold" should be introduced, so that doctors do not spend extra time and resources analyzing and reporting back information unless, as a minimum, the information involved is reasonably reliable and concerns serious illness. However, in conjunction with the consent procedure, it should be ensured that the patient is made aware of the clinic's feedback policy, including which types of information of possible relevance to health the clinic does not generate or make accessible to the patient.

The decision about feedback should be made jointly between the doctor and the patient, taking into account a number of specific considerations and weighing up interests. Every effort should be made to ensure that in attempting to respect the patient's autonomy, some patients' need for more directive counselling is not ignored.

Recommendation 2.2

Patients' right not to know and self-determination should be respected in the context of logging information opted out of

The Danish Council of Ethics recommends that the authorities put in place common guidelines safeguarding regard for genome-tested patients' right not to know and self-determination in balance with other considerations. The Council wishes to point out that, in relation to the patient's access to genetic information, genome testing creates or amplifies some ethical dilemmas, but does not wish to recommend any one particular solution over others.

Doctors must enter all health-relevant findings in the patient's records. With digitization (e-records), records nowadays are very easy to access, both for other doctors and for the patients themselves via sundhed.dk (health.dk). The introduction of genome testing, however, raises a question of whether it is always appropriate for the patient to enjoy easy access to data on record. Thus the Council does not think that the patient's right not to know and self-determination is respected if a patient who does not wish for insight into incidental findings of unclear relevance to health can inadvertently stumble across the information, as the case would be if they were released in e-records, say, via health.dk.

Ideally, information which the patient does not want should not be generated or get into the records at all. In the case of extended diagnostic examinations, however, the premiss may be precisely that such information has of necessity to be generated. The rules for record-keeping state that all health-relevant data about the patient coming into the doctor's possession must be noted down in the records. Such information might assume importance, for example, in later therapeutic pathways. In other words, with the present rules, patients are likely to stumble relatively easily across information they do not wish to know about.

Current practice in genetic departments is already to screen information, but for other reasons (see page 32). In such cases the rules of the Danish Health Act about the patient's right to information recorded about the patient still apply, but the patient's access is through the GP. Patients' scope for gaining insight into the information collected about him or her represents an important initiative in creating trust.

Such screening could, however, also serve to protect the patient's right not to know. However, it can be argued that screening genome information, even if requested by the patient, creates an asymmetry with regard to knowledge, and hence responsibility, not wished for by the GP.

3. Counselling and information

Does the prospect of feeding back risk information from genome testing of potentially unclear relevance to health in different ways make special demands of genetic counselling and information – and, if so, how?

Need for focus on counselling and information
A central pillar of the endeavours to safeguard citizens' autonomy is informed consent. Comprehensive information is a prerequisite, but not sufficient, to ensure autonomy. Information, for example, can be insufficient in terms of discussing the existential questions and life choices that may arise for the examinee both before and after a genome test. For some people, one condition for exercising autonomy in connection with genome testing can be support and dialogue with a qualified counsellor. The Council would therefore seriously question the focus of existing legislation on information without corresponding requirements for and specifications of the need for genetic counselling.

The Council (minus one member) notes that it is difficult to enforce Danish and European legislation vis-à-vis companies operating via the Internet from countries outside of the EU, and hence ensure the same level of information and counselling as those that can be stipulated vis-à-vis companies operating from an EU country or in connection with public research and diagnosis/treatment.

For the reasons mentioned at the start of the chapter, however, the Council has decided, despite everything, to put forward recommendations. The Council further wishes to create attention around measures which can presumably limit the possible inappropriate consequences that may follow on from inadequate counselling and information.

Recommendation 3.1

Legislative requirements concerning impartial and comprehensive genetic counselling and information
Genome testing should be accompanied by impartial and comprehensive counselling before and after the examination. This should be a requirement in conjunction with genome testing, whether performed under public or private auspices.

The only exception should be research that does not involve feedback of the genetic information (cf. recommendation 2.1).

Genetic counsellors should be aware of and work on the significant challenges that many patients, subjects and consumers must be expected to have in interpreting and managing information about risk factors.

Diagnosis and research
The health authorities should lay down guidelines for the criteria to be satisfied by good counselling in diagnosis and research of which genome testing forms part. For children and young people under 18, information and counselling should be given in the presence of parents or others with parental responsibility.

Private providers
Private providers should be ordered to provide comprehensive and qualified counselling and information to customers who have chosen to have themselves tested so as to give them a basis for making appropriate decisions.

Whenever possible, the providers should ensure that consumers do not order a genome test unprepared, e.g. without being clear as to the kind of information they will thus be gaining access to, and its possible implications. They should satisfy themselves that, before purchasing the test, consumers are aware of the most basic premisses for genome testing. Where possible, the relevant authorities should resort to instruments that can safeguard consumers against misrepresentation.

The health authorities should draw up guidelines regarding the required information, such as:

- what importance to health can be attributed to the results
- the uncertainty of the results with regard to predicting disease and the reliability of the results, respectively
- interpreting the information's significance for health often requires specialist know-how
- whether some of the conditions are non-treatable or non-preventable (e.g. Alzheimer's)
- special ethical considerations are associated with genome testing of children and young people under 18
- challenges associated with sharing the results with relatives.

Private providers should present the information required in a way that offers reasonable certainty of users reading and understanding it.

The health authorities should further ensure that consumers have a reasonable degree of access to impartial information about what a genome test involves, e.g. via a public website which is continually updated (see recommendation 4.2).

4. Consequences for the public health services

What responsibility should the public health system assume in a possible future situation where many consumers will be demanding genome information and the resultant quest for follow-up counselling, diagnosis or treatment?

Risk of unfair prioritization in the health services
Follow-up counselling, diagnosis and treatment of unduly concerned citizens can become a great burden on the public health services. This may be reasonable and make financial sense in as far as such a trend concurrently leads to better prevention of disease. To the Council, however, it seems unlikely that such an impact can provisionally be realized as a result of generating information about risk factors. The possibilities for predicting the most widespread diseases on the basis of genetic information are poor, because the importance of the genes here is generally limited. At the same time, these are the diseases that make up the greatest burden on the national economy by far.

Many of the patients making use of genome testing from private providers are likely to seek counselling from their doctor. Very few doctors today are qualified to handle such approaches. It is unacceptable to have genome testing and the results from such requested, performed or interpreted by professionals who do not command sufficient skills.

Recommendation 4.1

Need for competence building and a public website

It should be ensured that doctors are always the ones requesting genome testing and advising patients on the basis of this, and referring patients to specialists. In addition, it should be ensured that such doctors possess the requisite skill-sets. If GPs are expected to have to carry out such tasks, it is recommended giving them access to upskilling and to impartial, updated and professionally well-qualified information.

The authorities should take the initiative to set up a homepage where relevant specialists can present updated information about the importance of genetic variants for health, examination methods, false results, legislation etc. The webpage should be available for use by both GPs and other health professionals who are not clinical geneticists, and by patients and others who are considering having genetic tests conducted.

Recommendation 4.2

Need for guidelines on the public health services' responsibility for following up genome testing

The Danish Council of Ethics recommends that in cases **where patients have gained insight into results from genome testing that provide evidence of a great risk for serious hereditary disease**, patients should always have access to follow-up measures under a qualified doctor in the public health services.

In cases **where patients have gained insight into results from genome testing whose importance for health is deemed to be unclear**—and there is no specialist medical

evidence for referring the patient for follow-up measures—the patient should be able to be referred for impartial and professionally well-founded information (see recommendation 4.1). However, all citizens should have access under the public health system to counselling on the importance for health of the genetic risk information they have procured e.g. via a private provider.

In support of doctors, researchers, citizens and private providers alike, it should be made clear where the public health services' responsibility starts and ends, wherever possible. One component might perhaps be a positive list of genetic findings that always qualify people for follow-up in the public health services, compiled and regularly updated in collaboration with relevant specialist environments and other relevant parties. It should be possible to list the findings for which doctors are obliged to refer, including findings of strongly predisposing pathogenic mutations that can be prevented or treated. Fast-paced development in the field and individual patient situations can make it difficult to draw up a complete list, and the doctor's judgement will still be decisive, therefore, so it is important that doctors can consult the webpage mentioned in recommendation 4.1 compiled by specialists in the field.

In organizing procedures for informing and counselling Danish customers, private providers of genome testing should strive to ensure that consumers are familiar with the Danish health services' practice as regards follow-up initiatives, so that whenever possible they only have resort to the public health services if the findings made can reasonably be said to be relevant healthwise.

The health authorities should take the initiative to ensure that relevant consumers are made aware that they cannot expect follow-up under the public health services in all situations, e.g. through patient folders, public information campaigns, contact with GPs or other channels.

By contrast, The Danish Council of Ethics believes that banning genome testing through private providers would reflect a lack of respect, if only with reference to the health services' limited resources. As mentioned, there is no dismissing the fact that there are some instances where examinations through private providers will be able to generate vital information.

In a possible future where many people search for insight into their genetic dispositions to disease, the consequence can be a spate of over-diagnosis and over-treatment, and hence a drain on resources as a result of resources in the health services being deployed on uncertain risk states rather than more serious disorders. This would be tantamount to an unfair redistribution of the health services' limited resources, in which case patients' demands for follow-up diagnosis might need to be countered with more stringent requirements in terms of which indications entitle them to such examinations.

Special position
- addition to the overall set of recommendations
One member (Lene Kattrup) finds that:

- there should be a change in the law, to introduce a ban on genome-testing healthy children and young people under the age of 18 in testing, diagnostic and research milieux
- requirements should be stipulated for the quality of counselling before and after the genome test, and to the effect that those who are allowed to provide this direct person-

al counselling must be doctors with such further training in statistics, risk assessment, risk communication and genetics as must be regarded as relevant in relation to the examination, diagnosis and counselling currently on offer. These stipulations should apply under both public and private auspices, whenever information and counselling is being provided to individuals

- The IVD Directive (general IVD), with performance evaluation and CE-marking of tests carried out by the manufacturers themselves, does not provide adequate consumer protection. There should be authority-based quality assurance of the products, including an evaluation of the tests' positive predictive value for individuals, which will no doubt involve these tests having to be categorized differently—possibly even as medicinal products. By the same token the laboratories should be quality-assured and a stipulation imposed that companies operating in Denmark have a physician specializing in genetics as their chief investigator.


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