Clinical genetics in practice

The whole truth and nothing but the truth, but what is the truth?

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Abstract

The moral aspects of genetic counselling are explored in situations where the outcome of a DNA test does not lead to certain knowledge. The most frequent type of interaction between counsellor and counsellee is when factual information is given, but sometimes "factual" information is difficult to obtain. How do counsellors deal with "uncertain" knowledge in genetics? Arguments and assumptions are presented and the finding of a 27 CAG repeat in the Huntington gene is used as an example. However, the questions "how far does the duty to inform reach?" and "to what extent is the doctor responsible?" are important in the whole field of genetics, and will be even more important in the future. The aims of science and clinical practice are discussed; we conclude that counsellors run the risk of taking on an infinite responsibility.

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For several years Huntington's disease (HD) (MIM 143100) has served as a paradigm for presymptomatic testing for hereditary diseases. Genetic testing for HD by direct analysis of the size of the CAG repeat has been possible since 1993.[1] In contrast to the earlier linkage test, testing the repeat lengths seemed to allow definitive diagnoses, enabling a yes or no answer: allele sizes of ⩾40 CAG repeats lead to HD, all sizes <40 do not. For a short time all seemed crystal clear, but a more complex situation soon emerged. Allele sizes of 36-39 CAG repeats were sometimes also associated with HD. However, the HD phenotype is not always penetrant in subjects with HD alleles in this size range. There are indeed unaffected subjects aged >70 years with alleles of 36-39 CAG repeats. Empirical penetrance risks for the HD phenotype in subjects with these numbers of CAG repeats are unknown. Accordingly, subjects with these sizes of repeats cannot have predictive certainty about their HD status from their test outcome. Furthermore, it appears that allele sizes sometimes show mutability; an allele with CAG repeats <36 could indeed change into an HD allele in the next generation. For some time the "safe" limit seemed to be 30 CAG repeats, and the danger range for mutability 30-35. Then, in 1995, McGlennan *et al*[2] reported an allele of 27 CAG repeats which was found in the father of an HD affected subject with 38 repeats, indicating the apparent instability of a CAG repeat of 27.[2] This led to a redefinition and after 1995 the "safe" area was defined as below 27 repeats. The likelihood of an allele in the 30-35 repeat range being transmitted as a full HD allele is unknown. Potential factors include the repeat size, the sex of the transmitting parent, and whether it is identified in a (new mutation) family or in the general population.[3] It is even more unclear how great the risk is in the 27-29 repeat range.

The aim of genetics

The aim of genetics is, like every branch of science, to gather "true knowledge". Geneticists hope that knowledge about genes and mutations may help to explain causes of diseases and that understanding the cause can be used to assist in treatment. Unfortunately, nature often behaves like Hydra, the many headed monster: when science cuts a head from this monster, two other heads appear. Otherwise formulated: every new solution to an old problem creates two new problems. In science, "true" is what "has been proven", but scientists often have to live with ambiguous and limited knowledge. Scientific progress does not only mean "gaining certainty". In a way, the uncontrollable field does not become smaller. Geneticists are also confronted with this paradox. They attempt to make our world more understandable, they want to explain reality and try "to handle" it. The discovery of the nature of the Huntington gene mutation with its CAG repeat mechanism initially created more certainty, enabling "reliable" presymptomatic testing. However, the reverse became true also: the dynamic nature of the mutation brought more and new uncertainties. For example, we do not know what a safe margin is in the case of mutable CAG repeats. We do not know if, when, how, or why an allele becomes unstable. Opinions about this subject have changed and will probably change again in the future, but in spite of this geneticists want to try to draw "safe

borders". The German philosopher Leibniz had already written in 1703 to his friend Bernoulli: "Scientists are able to discover patterns in nature. Those patterns are caused by occurrences which repeat themselves, but that repetition is not perfect".[4] This is the reason that these newly discovered patterns create new uncertainties. How will the repetition be? Will there be any repetition and when will it next occur? Or will it be a single event that will never happen again? Genetics is, like all other scientific fields, a field of trial and error. This fact leads in clinical genetics, where counsellors use scientific discoveries, to questions concerning good clinical practice.

The aim of clinical genetics

Genetic counselling is defined as "a communication process which deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family".[5] Among other things, this process involves an attempt to help the person or the family "to comprehend the medical facts, including the diagnosis, the probable course of the disorder and the available management".[5] Providing factual information is a very central interaction between counsellor and counsellee. That part of the counselling process is meant to help a person "choose the course of action which seems appropriate to him and act in accordance with that decision".[5] However, respecting the patient's autonomy does not only mean "informing", but also "sharing responsibility". We know it is important that counsellees get full support from their counsellors in the decision making process. So, respect also involves "treating persons to enable them to act autonomously",[6] requiring values such as empathy and compassion.

In the light of these values, what exactly does "factual information" mean? Patients have a right to be informed and the doctor has a corresponding duty. But how far does that duty to inform reach, how far does the doctor's responsibility reach, and, most of all, what is in the best interest of the counsellees? We have to consider these questions again and again, because genetics constantly changes and possibilities grow. Genetic technology is less like a knife, which, in the hands of man, can be used or abused, but rather more comparable to a car or a plane: the advantages and the disadvantages go together, they develop simultaneously. Desired, foreseen, undesired, and unforeseen consequences go hand in hand.

The duty to inform

Factual information should at least consist of true statements. A true statement is: "the absence of HD pathology has not been documented in any individual with an HD allele size of $\geq$40 CAG repeats who died, disease free, after living up to or past the normal life expectancy".[7] This means for those tested, a yes answer is possible, in contrast to the group of people with 36-39 CAG repeats. In that group, a yes or no answer is not possible, as was shown above. The number of CAG repeats is a fact, but how this fact has to be interpreted is sometimes ambiguous. A true statement is also: "allele sizes of $\leq$26 CAG repeats have never been associated with an HD phenotype",[7] so a no answer seems possible too, but in fact these statements are only true for the time being. What has not been proven is not necessarily "untrue". That also goes for the statement: "allele sizes of $\leq$26 CAG repeats have not been demonstrated to show mutability". Scientists admit that "truth" in this area has always had a "for the time being" element. In the *Laboratory guidelines for Huntington disease genetic testing* it is stated: "Although no examples of mutable alleles of this size have been reported, it has not been shown that allele sizes of $\leq$26 repeats cannot be mutable".[7] To detect HD appears to be easier than to exclude it. There is a difference between "true for us" and "really true".

What does this mean for the golden rule in clinical genetics that a counsellor must provide medical information in order to give counsellees the opportunity to choose between alternatives? How should the rule be applied when a test shows a CAG repeat of 27 or 28? In that specific situation, what is the relevance of the factual information? To what extent can or should a doctor inform? It is obvious that the theory (30 CAG repeats is a safe limit) has been falsified, but should the detection of one mutable 27 CAG repeat change the content of the information?

Some categories of patients with repeats between 27 and 30 can be discerned, for example, predictive and diagnostic test applicants, relatives of a newly identified mutation carrier, test applicants who have inherited 27-30 repeats from the unaffected parent, and partners of carriers who are tested as controls because of prenatal diagnosis. Is there a difference between the different categories? Should all or some counsellees be informed about a repeat length between 27 and 30 and what should the message be? Is it justified or perhaps obligatory to always offer prenatal testing to exclude the unknown risk of repeat expansion in the fetus?

The pros and cons

Physicians who feel obliged to inform a person about a repeat length of less than 30 repeats give different arguments for doing so. (1) The risk is small, but it is real. (2) There is something to offer, namely prenatal diagnosis. (3) One must give all the available information concerning HD. (4) If a person asks for information about a genetic disease, then he/she wants information not only about him/herself but also about his/her offspring. (5) When a doctor does not provide this kind of information, it could be that future parents are wrongly reassured.

Others formulate arguments against. (1) It is impossible to inform a couple precisely, because it is unclear how great the risk is and no one knows when and why mutability occurs. (2) Prenatal diagnosis is a "solution" for this problem one would rather not have. (3) The repeat size will probably remain stable and not change at all in the next generations. (4) Cou-

ples might change and adjust their reproductive decisions unnecessarily and on the wrong grounds. (5) When a doctor provides this kind of information, future parents might suffer unjustified fear.

It is clear that counsellors face a moral dilemma. How should a counsellor go about respecting the patient's freedom and at the same time do no harm? Freedom of choice only means that one is free to choose[8] but not necessarily that one knows what the right choice is. Both doctors and patients seek arguments to defend their choices. However, most of the time arguments are used to defend an already chosen opinion. This is because people often suppose they know in which direction the "right" answer must be found. Many doctors are inclined to give counsellees "all available information" and defend the decision to inform about a 27 CAG repeat. They are at least of the opinion that they should explore the counsellee's wish to know such an intermediate allele test result.[3] It is therefore sensible to take a closer look and consider the assumptions that lie behind these decisions, decisions which tend towards doing rather than towards refraining. In discussions with clinical geneticists of several departments in The Netherlands the following assumptions have been put forward.

Assumptions

(1) ONE OUGHT TO AVOID FUTURE REGRET

In general, people regret more what they did not do or what they have forgotten to do than what they did, even when it went wrong. Similarly, doctors appear better at providing arguments justifying a wrong action than when they omit something. Fear of future regret directs a counsellor towards informing and a counsellee towards doing something with the information because they both experience the same "anticipated decision regret".[9] However, the moment a counsellor explores a counsellee's wish to know a certain test result, the counsellee's right not to know is in a way violated. More precisely, is it necessary to explore whether there is a wish to be informed if a CAG repeat of 27 is found in an unaffected parent or in the partner of a carrier? "Do you want" questions may lead to supposed wants and needs, while informing may direct towards the use of the information rather than to neglect it. Are counsellors always obliged to increase the options available and to present every possible option? What is the aim? Perhaps the aim lies in the starting point of genetic counselling.

(2) A COUNSELLOR OUGHT TO PROVIDE FACTUAL INFORMATION IN A NON-DIRECTIVE WAY

Sometimes, strictly adhering to the admonition to be morally neutral in the selection and transmission of information leads counsellors simply to dump information onto their clients, as stated by Caplan.[10] But is "informing about the facts" in order "to choose and act" an exercise in truth dumping in which every fact, every option, every risk, and every benefit is unleashed? Is it really possible to be non-directive and inform about every possible event? Non-directive is not the same as morally neutral. Informing is not as value free as it sometimes seems to be, certainly not for the one who receives the information. Information from a doctor has a prescribing element. If a genetic counsellor thinks he/she ought to inform a couple of all findings, even if the findings are uninformative or difficult to interpret, he/she creates an environment in which the decision "to do" something with the test results seems wiser than "to do nothing".

(3) COUNSELLORS OUGHT TO TELL THE TRUTH AND RESPECT THE AUTONOMY OF THE COUNSELLEE

It seems a universal rule to tell the truth, the whole truth, and nothing but the truth, in order to give the patient the opportunity to act freely. But when it is unclear what "the truth" is, this rule can easily lead to a sort of technical imperative. Not an imperative in the sense of "we have got the technology so we ought to use it" but in the sense of "we have used the technology so we ought to inform about all the results in every possible detail". However, informing a counsellee does not always promote his autonomy, because autonomy is impossible in cases of inadequate and incomplete understanding.

(4) ONE OUGHT TO AVOID A LEGAL CLAIM

Fearing legal claims will probably direct the counsellor's choices too. Our medicine seems to become more and more "defensive". Globalisation of our world has greatly speeded up transfer of knowledge. Nowadays, scientists strive to use "the best method in the world" to solve a given problem. There is a continuous exchange of knowledge and, as a result, also of moral rules and values. However, moral ideas and ideals are not universal and depend, among other things, on law, insurances, economic factors, public policy, etc. Exchanging opinions, arguments, reasons, and motives remains important, but we must avoid the possibility of legal claims in one country directing the decisions and actions in another. In the contact between counsellor and counsellee moral values are often more important than legislation. We must prevent legal rules from harming those who are supposed to be protected by those rules.

Conclusion

Of course, respecting the counsellees' autonomy means informing them of the medical facts, in order to give them the opportunity to choose between alternatives. However, to repeat our questions: what are the relevant medical facts and, most of all, to what extent should the doctor be responsible? Sometimes it seems "chance" no longer exists nowadays, it seems "fate" has completely changed to "fact". The danger that one, as a counsellor, risks is to feel infinitely responsible, not because one has caused something, but because one did not try to avoid it. If we feel responsible for all the facts, we want to deal, one way or another, with those facts. However, we have to realise that our capacities are limited, particularly the

capacity to understand and foresee all the consequences of our actions. We should not take more responsibility than we are able to bear.

As long as we do not know what the right decision is, we have to proceed carefully. Thousands of years ago the Greek physician Gorgias stated: "man can not know the past entirely, he can not overlook the present entirely and he can not foresee the future". Nowadays everything seems to be calculable and predictable, but destiny is still capricious and life is still precarious. Counsellors want to tell the truth but unfortunately they do not always know what the truth is, as illustrated by the mutability of CAG repeats. They do not know how great the chance is that the repeats will expand. If counsellors do not know how to interpret certain facts, they are not able to give their counsellees the right interpretation either. The field of genetics becomes more and more a field of risk estimates and therefore the question will become more how "certain" a risk percentage is, and most of all which uncertain percentage is worth mentioning. In "minimal risk" situations (in this example when unaffected parents or partners are involved) it is wise for the counsellor to refrain, to keep his uncertainty to himself, to tell his patients the things he is pretty much sure of, and to keep silent about the things in which "chance" and "luck" play an important role. This is because the advantages for the counsellee are limited in those kinds of situations. If a counsellor has doubts about the value of ambiguous knowledge, the solution cannot be left to the responsibility of the counsellee. The question is if it is always justified to give "all available" information to counsellees, presuming that "knowing" is always better than "not-knowing", and on the assumption that counsellees are able to cope with and master all kinds of uncertainties.

This point of view does not only have consequences for counsellors, but also for counsellees and, ultimately, for the whole of society. Do the latter accept and respect the limitation of the doctor's responsibility and accept the limitations of technology? Resources should be invested into researching the wants, needs, and expectations of (potential) counsellees. Do they want information about every single hypothesis and every single exception? What do they really want and expect from genetics and what are counsellors able and willing to give?

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