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# Huntington's Disease and the ethics of genetic prediction

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## Author's abstract

*What ethical justification can be found for informing a person that he or she will later develop a lethal disease for which no therapy is available? This question has been discussed during the past twenty years by specialists concerned with the prevention of Huntington's Disease, an incurable late-onset hereditary disorder. Many of them have played an active role in developing experimental testing programmes for at-risk persons. This paper is based on a corpus of 119 articles; it reviews the development of their reflection and includes an outline of the ethical problems identified and the solutions adopted in pre-clinical protocols. Seen in a broader perspective, the experience of presymptomatic testing for Huntington's Disease has given medical geneticists the opportunity to clarify their ethical position in the as yet little explored field of predictive medicine.*

## Introduction

Advances in genetic research have put modern medicine in the uncomfortable position of being able to foresee future conditions that it cannot treat. Unlike more familiar medical situations in which diagnosis of a disorder leads to therapeutic initiatives, genetic knowledge is not, in the majority of cases to which it applies today, the prelude to curative measures. Despite this serious drawback, research is flourishing and therapeutic benefits are hoped for in the near future. In the meantime, a basic ethical question has to be addressed by medical geneticists: should an incurable hereditary disease be diagnosed before symptoms appear? This problem is particularly acute in the case of adult-onset disorders. If predictive information is technically possible, what ethical justification can there be for communicating it to the person concerned?

These questions are not entirely new: they have been central to the debate pursued during the last twenty years in connection with efforts to elaborate a reliable method of determining whether the descendants of

persons suffering from Huntington's Disease will themselves develop the condition. Huntington's Disease is a devastating, incurable late-onset hereditary disease of the central nervous system characterised by the progressive aggravation of involuntary movements and loss of cognitive faculties, frequently accompanied by psychiatric disturbances. The first symptoms generally appear between ages thirty-five and forty-five; over a period of fifteen to twenty years the affected person gradually becomes totally incapacitated and unable to communicate. Each child of an affected person has a 50 per cent risk of inheriting the gene responsible for the disorder and thus becoming affected himself. However, attempts to prevent the transmission of the disease have so far failed because there has been no way of identifying affected persons before the onset of symptoms, by which time they have usually reproduced. For offspring aware of their risk, the prolonged period of waiting for onset places them in a situation of anguished uncertainty with regard to their own future, while all members of the family suffer from an enormous burden of economic, social and psychological problems. The rate of suicide among affected persons is much higher than among the general population, though it is not clear whether this is a direct consequence of the disorder itself or a reaction to initial awareness of the prospect of unavoidable deterioration.

A search in the following databases: Medline, Bioethics and the Cumulative Index of Medicine, yielded a corpus of 119 articles dealing explicitly with the ethical issues of presymptomatic testing for Huntington's Disease for the period 1970 to mid-1990. All but three (1,2,3) are in English. Although initial discussion of presymptomatic testing can be traced back to the early 1970s, the topic attracted little attention in medical circles until the discovery of the first genetic marker for the disease in 1983 and the initiation of experimental testing in 1986. Since then the increase in the number of articles written by the various specialists concerned, notably medical geneticists, psychologists and genetic counsellors, has been spectacular. These articles represent an original example of concerted professional efforts to explore the ethical issues in predictive medicine and elaborate an

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## Key words

Huntington's Disease; medical genetics; pilot tests; medical ethics.

ethical professional approach. Because genetic knowledge is likely to be used for predicting other late-onset diseases in the future, a presentation of this first debate over the prevention of Huntington's Disease through presymptomatic testing, can be of general interest.

Experimental testing programmes, involving communication of information concerning an increased (or decreased) risk of Huntington's Disease to voluntary at-risk adults, began in 1986 despite the existence of diverging opinions among affected families, their associations and the medical community as to the ethical justification of this procedure. Those involved in the trials in the United States, Canada and Great Britain, consider the provision of such predictive information as a legitimate medical activity and the majority of the articles in the corpus express this point of view. But even in these countries some practitioners familiar with the disease and members of affected families think that knowing one's future risks does more harm than good. They prefer waiting until a cure or effective preventive therapy becomes available before resorting to presymptomatic testing. Their opinion is represented in only a few articles here. In other countries, such as France, where experimental testing has not been carried out and the questions have scarcely been examined, similar misgivings may be shared by many more health professionals than a cursory examination of the corpus might suggest.

The first part of my review outlines the growth of professional interest in presymptomatic testing for Huntington's Disease and describes the status of those participating in the debate. In the second part, the ethical issues dealt with since the 1983 discovery and the solutions adopted for experimental testing are presented. Final comments concern new issues identified as testing shifts from a research to a clinical context.

### **I.1: Growth of interest in presymptomatic testing for Huntington's Disease**

Period	Years	Number of articles
1	1970-1973	11
2	1974-1983	22
3	1984-mid 1990	86
	Total	119

1984-1990: number of articles by year			
1984	7	1988	9
1985	8	1989	19
1986	10	1990 (to June)	12
1987	21		

Period 1: The first professional discussion of ethical problems took place in the early 1970s. It was prompted by a series of experiments involving the

administration of levodopa to adult offspring of persons affected by Huntington's Disease who wanted genetic counselling concerning their own risk of transmitting the disease to future children. Debate focused on two major problems: first, the legitimacy of this particular research design, and second, the question of professional responsibility with regard to the subjects involved in the experimentation. Disagreement over the justification of this test, which produced the symptoms of Huntington's Disease in certain subjects, was amplified by disagreement over the justification of *any* kind of presymptomatic testing for the disease. The idea was advanced that disclosure of information predicting the future would place an unbearable psychological burden on the subjects. For some this was sufficient reason for abandoning the entire project until a cure was available, whereas for others it meant that extreme prudence would need to be exercised in the search for a useful testing procedure. Discussion took place within the community of concerned researchers at the World Federation of Neurology's Centennial Symposium in 1972 (4,5,6) as well as in general medical journals (7,8,9,10,11,12,13). It is worth noting that the first family association, the American Committee to Combat Huntington's Disease, founded in 1967, was represented at the symposium.

Period 2: Prior to 1983, discussion of ethical problems remained speculative, even though reference was often made to the need to avoid the errors of the earlier levodopa tests (14,15,16,17,18). However, during the late 1970s and early 1980s impetus for presymptomatic testing came from two major sources. In the first place, the American Federal Commission to Control Huntington's Disease and its Consequences (19,20) expressed approval of research for a screening test which would relieve at-risk candidates from the anguish of uncertainty and allow them to make critical life decisions on the basis of adequate knowledge concerning their own future. Secondly, the first opinion surveys carried out among affected families (21,22,23,24) revealed that a majority were in favour of a predictive test for the same reasons and would make use of it when it became available. During this period the lay movement developed, with national associations being founded in North America, Europe and Australia. In several instances their co-operation facilitated the organisation of the surveys, thus providing an essential link between researchers and Huntington's Disease families.

Period 3: In the Autumn of 1983, the discovery of the first genetic marker for the disease was announced. This breakthrough in fundamental research opened the way for elaborating a linkage test based on examination of the DNA of at-risk individuals and other appropriate family members. Speculation gave way to the preparation of an experimental protocol and discussion of the ethical problems raised by this experimental use of genetic techniques for presymptomatic diagnosis. Response to this challenge

is reflected in the overall increase of the number of articles during this period. A peak was reached in 1987, the year following the initiation of the first pilot tests. Since that date the articles include reports of these tests and reflections on the generalisation of testing as a clinical service.

## I.2: The authors

### a) INVOLVEMENT WITH HUNTINGTON'S DISEASE (TOTAL 119)

Fifty-three articles (44.5 per cent) are written by professionals engaged in the pilot tests; 46 (39 per cent) by medical practitioners potentially concerned with affected families; 17 (14 per cent) by interested observers, for example scientific journalists and ethicists; the remaining 3 (2.5 per cent) come from representatives of the lay associations and/or members of affected families. In several cases information on various aspects of the pilot tests is provided by different members of the same research team. The total number of different authors (or first authors in the case of more than one) is 82.

### b) ORIGIN BY COUNTRY (TOTAL 119)

United States 55; Great Britain 33; Canada 11; Belgium 5; Australia 5; Others 10. The predominance of Anglo-Saxon specialists, representing the countries where testing began, is evident. Colleagues from other countries are conspicuously absent. Though not necessarily a problem as long as testing remains experimental, their lack of involvement in the pilot-test experience, which has benefited from intense collaboration among different specialists and between specialists and representatives of the lay associations, may complicate the establishment of satisfactory testing procedures in countries where attitudes to disease and doctor/patient relationships are grounded in different cultural contexts.

### c) MEDICAL DISCIPLINES REPRESENTED (TOTAL 119)

The type of journal is followed by the number of articles: general medical 45; genetics (medical, human) 37; neurology 12; biomedical ethics 7; general science 5; psychology, psychiatry 5; others 8.

Genetic technology applied to at-risk people has placed the greatest ethical burden on professionals working in medical genetics – researchers, medical geneticists, psychologists or genetic counsellors – rather than on the neurologists who have been traditionally concerned with Huntington's Disease patients. It is interesting to note that despite the specific characteristics of this rare disease, discussion has not been limited to specialised journals. The important number of articles appearing in general medical journals (such as the *New England Journal of Medicine*, *Lancet* and the *British Medical Journal*) suggests that the ethical issues associated with Huntington's Disease illustrate classic problems in medical ethics and have been brought to the attention of the medical community as a whole.

## II. Ethical issues raised by the marker test 1984-1986: preliminary questions

Following the discovery of a genetic marker for Huntington's Disease, reflection on presymptomatic testing took place against a backdrop of well-known ethical standards governing biomedical practice in such matters as experimental design, laboratory procedures and experimentation with human subjects (see, for example, (25)). However, these familiar guides for professional conduct were challenged by the emergence of the new genetic diagnostic techniques. More specifically, when the authors examined the scientific, medical and social context within which the pilot tests were to be elaborated, the issues they identified implied a reconsideration of traditional guidelines with respect to the following subjects:

- 1) the objectives of medical genetics;
- 2) the selection of candidates for testing;
- 3) the nature of the genetic techniques involved, ie the linkage test.

### 1) OBJECTIVES OF MEDICAL GENETICS

Because Huntington's Disease is a particularly devastating hereditary disorder which, until a cure is found, can only be avoided if potential carriers do not have children, the question of the appropriate professional attitude with respect to reproduction decisions has been a constant preoccupation. In the first decades of the century, coercive eugenic sterilisation programmes, based on scientific research, were proposed to eliminate the disease. Later, genetic counselling clinics were organised, but despite consensus on the principle of non-directivity in counselling for hereditary disorders, health professionals tended to adopt a directive approach when dealing with Huntington's Disease families. It is not surprising then that once a marker test seemed probable questions were raised over the true goal of presymptomatic testing, and, by extension, of medical genetics in general: would it be used as a means to eradicate the disease, by justifying eventual professional pressure on affected persons to limit their reproduction? Or could it be used to improve the quality of life of at-risk persons? Another question concerned doctors' professional responsibility towards their patients. Should it extend no further than the at-risk individual or should it encompass other family members as well, since they must co-operate if the candidate is to be tested?

The way in which the specialists determined their position on both these issues seems to have depended not only on their interpretation of professional deontology but also upon their involvement with affected families via the lay associations. In fact, during this period co-operation between the two groups developed, increasing professional understanding of the complex repercussions of the disease on family relationships and the many motives underlying the

demand for testing. The increasing number of surveys carried out by the geneticists, again with the assistance of the lay associations, to determine the attitudes and intentions of at-risk persons and their families with regard to predictive testing (28,29,30,31,32,33,34,35, 36,37,38,39,40,41) reflects their growing recognition of the lay viewpoint during this period. A novel orientation of medical genetics for Huntington's Disease emerged from these inquiries. Its objective was no longer defined solely by the problem of limiting the reproduction of at-risk persons. Rather its purpose would be to take into account the interests and expectations of at-risk people and provide them with information and support which would enable them to make informed decisions in all areas of their lives, including founding a family but also in other personal and professional matters. (See exchange in (26) and (27).)

### 2) SELECTION OF CANDIDATES FOR TESTING

The specific characteristics of Huntington's Disease – a late-onset condition with neurological and psychiatric complications that become progressively more severe, and the unusually high rate of suicide among affected persons – created particularly delicate problems relating to the selection of candidates for testing. It was recognised that nothing was known about the possible impact of predictive information, positive or negative, on at-risk persons. However, although current management of the disease was known to be less than fully satisfactory, owing not only to the absence of therapy but also to widespread medical ignorance and frequent cases of misdiagnosis, the specialists admitted that these failings were partially offset by the important role played by family associations in communicating medical information and providing social support for affected families (1,42,43,44,45,46,47,48,49).

### 3) THE LINKAGE TEST

The marker test presents certain limitations which make it an imperfect diagnostic tool. It does not detect the defective gene; its accuracy is not absolute; it is not applicable to all at-risk people; it requires an accurate diagnosis of the disease in the relative presumed to be affected; the result is not always informative, and when it is, it says nothing about *when* the first symptoms will appear. These limitations raised the ethical issue of the scientific reliability of the marker test as such and its exclusion of certain candidates from testing. For those who would be admitted to testing, the questions of access to DNA samples from other family members and lack of professional experience in disclosing this kind of information were most often cited as the most difficult ethical dilemmas needing to be resolved before testing procedures could be implemented (42, 43,50,51,52,53,54).

## 1986: Pilot tests and ethical solutions

Briefly outlined, these are the problems the specialists identified as they advanced towards experimental

presymptomatic testing. In fact, the most original feature of their debate was not so much the solutions they adopted as the *way* in which they developed them: a way based on continuous exchange of views with the lay associations, made possible by the existence of structures facilitating communication and co-operation. The associations participated in elaborating the experimental protocols and since then have played an active role during the testing period by providing social support for test participants and their families and sharing in the discussion of unexpected problems arising during testing. Although most authors have recognised that this partnership is essential, few have gone so far as to realise that it also contributes to the *ethical* legitimacy of the pilot tests (see, for example, (1,45)).

Concerning the protocols themselves, the explicit legitimising premise has been that the reasons for testing and the decision to be tested rest with the at-risk person alone (26), who must be of an age to give informed consent. Pre-eminence has thereby been given to the ethical principle of individual autonomy (55), illustrated by frequent references to notions such as *informed decision*, implying *consent to* or *refusal of* the test, the *right to know* and the *right not to know*, *voluntary participation*, the *right to privacy* and *confidentiality of results*. On the scientific level, emphasis has been placed on the cautious introduction of new markers to increase the accuracy of the linkage test and make testing available to a greater number of individuals (56). DNA banks have stored genetic material not only to attend to the immediate needs of voluntary candidates but also to preserve the chances of future testing for a person who at present does not wish it.

The testing procedure consists of a series of meetings with the research team during which each candidate first prepares himself for the predictive information, and then receives support as he reacts and integrates the test result. The testing period can last up to two years, during which the candidate is assisted by the various members of the research team: psychologist, genetic counsellor and medical geneticist (1,56,57,58, 59,60,61,62). Prior to the communication of the test result, he is given the opportunity to rehearse his reactions to different results and explore the resources at his disposal for the post-test period. He undergoes frequent psychosocial assessment in order to evaluate his responses to the information and provide him with psychological support when necessary. Sensitivity to the problem of suicide has reinforced the provisions made for comprehensive counselling during all stages of the testing procedure (31,63,64,65). By closely following the subjects, the specialists hope to improve their understanding of how individuals cope with good or bad news, so as to develop strategies for helping future candidates when the test is available as a clinical service. The articles containing information on the policy adopted by various research protocols (1,56,57, 58,59,60,61,62) include details of specific measures intended to protect the candidates. These ethical

standards have also been outlined in a set of guidelines resulting from continued collaboration between the lay associations and the professionals. It is hoped that they will be used to regulate future testing programmes (66, 67, 68).

Preliminary results indicate that the first test subjects have not experienced catastrophic reactions when confronted with their test result (49, 56, 57, 58, 61, 62, 69, 70, 71, 72). However, in the course of testing a number of previously unforeseen problems have arisen (for example, a number of would-be candidates were unaware that they were already clinically affected; parents sometimes asked for testing of their children), which have led the research teams once more to clarify their ethical priorities in the light of these circumstances (2, 55, 73, 74, 75, 76, 77).

### III. Clinical testing

Clinical testing may have begun already in the last months. However, in this corpus it is generally assumed that the passage from research to clinical application has not yet taken place. It is worth noting that in contrast to the consensual ethical position prevailing for the pilot tests, the authors discussing clinical testing introduce diverging opinions, based on their appreciation of actual legal dispositions (27, 43, 78, 79, 80, 81). There may be situations where the priority accorded to the at-risk person may have to be balanced against other people's rights. In fact, these articles question the permanence of the principles which have proved effective in the experimental setting. The number of articles dealing with problems in these terms is likely to increase as clinical testing is developed; already in the present corpus certain questions challenge the principles governing access to testing and disclosure in the pilot tests. Counsellors may be obliged to provide the test against their own personal judgement. Other family members may have the right to information on an individual's genetic status. The doctor may be obliged to disclose information concerning an individual whose occupation may place the lives of others in danger. Third parties such as the at-risk person's employer or insurance company may in certain circumstances have the right to ask for the information produced by the test.

### Conclusion

As long as information is lacking concerning the long-term impact of disclosure on pilot-test candidates and their families, a definitive evaluation of this experiment and the answers elaborated for the ethical questions formulated at the beginning of this review – Should adult-onset diseases be diagnosed before symptoms appear? What ethical justification can there be for communicating predictive information to the person concerned? – cannot be effected. It is thus probably premature to recommend that the procedure become an 'ordinary' medical service. What needs to be examined now are the actual social consequences of

transferring the experimental conditions of presymptomatic testing to a clinical setting.

Genetic diagnostic tools are now being developed for other late-onset diseases, not all of which are hereditary. Ethical issues ought to become the subject of public debate as their resolution will affect not only the future role of medical geneticists but also the social integration of a growing number of people identified as presymptomatic patients. The experimental stage of testing for Huntington's Disease is coming to an end: we should not forego the attempt to define a social ethic for genetic procedures which accommodates the legitimate interests of both the individual and the community.

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### Editor's note

As the author does not directly refer in her paper to references beyond (81) only these have been published. However, the entire corpus of 119 articles on which the paper is based can be obtained by writing to: Mme Gwen Terrenoire, Centre de Sociologie de l'Éthique, Centre National de la Recherche Scientifique, 59 Rue Pouchet, 75849 Paris Cedex 17, France.

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