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Review

Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers

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The objective of this study is to review ethical and clinical guidelines and position papers concerning the presymptomatic and predictive genetic testing of minors. The databases Medline, Philosopher's Index, Biological Abstracts, Web of Science and Google Scholar were searched using keywords relating to the presymptomatic and predictive testing of children. We also searched the websites of the national bioethics committees indexed on the websites of World Health Organization (WHO) and the German Reference Centre for Ethics in the Life Sciences, the websites of the Human Genetics Societies of various nations indexed on the website of the International Federation of Human Genetics Societies and related links and the national medical associations indexed on the website of the World Medical Association. We retrieved 27 different papers dealing with guidelines or position papers that fulfilled our search criteria. They encompassed the period 1991–2005 and originated from 31 different organizations. The main justification for presymptomatic and predictive genetic testing was the direct benefit to the minor through either medical intervention or preventive measures. If there were no urgent medical reasons, all guidelines recommend postponing testing until the child could consent to testing as a competent adolescent or as an adult. Ambiguity existed for childhood-onset disorders for which preventive or therapeutic measures are not available and for the timing of testing for childhood-onset disorders. Although the guidelines covering presymptomatic and predictive genetic testing of minors agree strongly that medical benefit is the main justification for testing, a lack of consensus remains in the case of childhood-onset disorders for which preventive or therapeutic measures are not available.

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Since their introduction, genetic tests and their widespread application have been considered carefully, with special attention focusing on the release of information about the test and test results, the confidentiality of genetic information, the voluntariness of the request, the responsibility towards blood relatives and the psychological impact of the test. An even more cautious approach has been envisaged when considering such testing in children and adolescents. This caution originates from the fear that testing in childhood or adolescence could create devastating social, emotional, psychosocial and educational consequences in minors. Some have suggested that genetic testing might harm a child's self-esteem, create depression or anxiety, distort the family perception of a child or stigmatize a child (1, 2). Authors have also stressed that testing children can breach the confidentiality (3, 4) and the privacy of genetic information (5), ignore the specific moral status of the child (6) and downplay respect for the autonomy of the child or adolescent (7–9). Testing might also ignore the right of the child not to know (10) and

ignore recent pleas to integrate children and adolescents into medical decision making (7, 11–16). For the sake of clarity, we define minors in this review as all persons who have not reached legal age (which in most countries is 18 years). This includes newborns, babies, children, teenagers and adolescents.

Genetic tests are often discussed in different settings and for different types of disorders: newborn screening; heterozygote or carrier testing; diagnostic testing; prenatal diagnosis; predictive testing for monogenic, late-onset disorders (e.g. Huntington disease) and susceptibility testing for late-onset disorders that have complex genetic and environmental interaction (e.g. coronary heart disease). The ethical discussion is different from one context to another.

In a previous study (17), we reviewed guidelines and positions papers on carrier testing in minors (e.g. in families affected by an autosomal recessive or X-linked disorder) and found that there is a consensus on postponing carrier testing until the child can give proper informed consent. The guidelines disagreed in three different areas. First, although most guidelines limited the role of the genetic counsellor to educating parents about inherited disorders so that they clearly understood the significance of genetic testing and could responsibly inform their child about potential genetic risks at a later date, one guideline stressed that it is the responsibility of both the family and the healthcare system to ensure that carrier testing is offered when the child is older. Second, although all guidelines agreed that children preferably should not undergo carrier testing, ideally postponing it until later in life, some guidelines underscored that persistent refusal to comply with a parental request for the carrier testing of a child (e.g. in cases when the parents cannot deal with the anxiety of not knowing the carrier status of their child) may have a more negative impact on the child and his family than would complying with the request. In addition, under the interpretation that early knowledge of one's carrier status might help a child to learn to cope with this information at an early age and might reduce the anxiety and uncertainty experienced by parents about their child's carrier status, some guidelines acknowledged that testing in minors may be warranted. Third, guidelines disagreed about the communication of incidentally discovered carrier testing (e.g. during diagnostic testing, screening or prenatal diagnosis, or in a research context). Meanwhile, some guidelines recommended that such information should be conveyed to the parents, and others recommended that this information should not be disclosed to parents or to other third parties.

In this study, we focus on presymptomatic and predictive genetic testing in minors. Presymptomatic and predictive genetic testing refers to the possibility of tracing a genetic defect before the presentation of symptoms. The first term refers often to those situations in which an abnormal test result will almost inevitably lead to the development of the disease later in life (e.g. Huntington disease); the second term often refers to a broader range of situations in which the risk for a disorder is substantially increased or reduced but without necessarily implying any degree of certainty (e.g. hereditary breast cancer). In most of the guidelines we examined, this distinction was not made. Therefore, the words predictive and presymptomatic are used here in a broadly interchangeable manner. The objective of this study is to systematically review national and international normative documents (without legal authority) regarding presymptomatic and predictive testing and to analyse the recommendations towards testing in minors. Special attention will be devoted to areas of discussion and disagreement.

Materials and methods

Data sources

We searched the databases Medline, Philosopher's Index, Biological Abstracts, Francis, Web of Science, Current Contents and Google Scholar using the following search term strategy: (Child OR childhood OR adolescen* OR infant OR young OR paediatric OR pediatric OR newborn OR minor) AND (predictive OR presymptomatic OR pre-dispositional OR susceptibility) AND (ethic* OR guideline OR position OR bioethic* OR moral OR autonomy OR normative OR statement OR report OR recommendation). We also searched the websites of numerous national bioethics committees (listed on the websites of WHO and the German Reference Center for Ethics in the Life Sciences), the websites of the Human Genetics Societies of different nations (listed on the website of the International Federation of Human Genetics Societies and related links) and the websites of national medical associations listed on the website of the World Medical Association.

Study selection

Articles were candidates for our review if they contained guidelines or were position papers

emanating from international and national organizations, national bioethics committees and professional associations that explicitly addressed predictive and presymptomatic testing of minors and provided clear guidelines on the issue. We focused our search on general, not disease-specific, statements and excluded guidelines that focused on genetic testing related to adoption. In our study, we included only guidelines written in English or guidelines translated into English by the guideline developers.

Data extraction and synthesis

In contrast to systematic reviews focusing on the relevant research on the accuracy and precision of diagnostic tests, the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative and preventive regimens, our systematic review of normative positions has two aims. Our first aim is to assemble 'a reliable and comprehensive account of the facts of the matter and to identify and clarify concepts that are relevant to the valuation of the ethical implications of those facts' (18). Our second aim is to organize 'these concepts into an argument (a coherent set of reasons that together support a conclusion for how one should or should not act)' (18). This systematic review of normative ethical positions towards predictive and presymptomatic testing is based on a formal tool developed by McCullough et al. (18).

Results

Guidelines and position papers

We retrieved 27 different guidelines or position papers (Table 1) pertaining to predictive testing of minors for childhood-onset and/or adult-onset diseases. These covered the period 1991–2005, with a peak in number of articles in the period 1994–1998 (13 of the 27 guidelines). The

Table 1. Overview of guidelines with title, guideline developer and year of publication

Year	Guideline developer	Title
1991	National Consultative Ethics Committee for Health and Life Sciences (France)	Opinion regarding the application of genetic testing to individual studies, family studies and population studies. (Problems related to DNA 'banks', cell banks and computerisation.)
1992	German Society of Human Genetics	Statement on post-natal predictive genetic diagnosis
1993	Swiss Academy of Medical Sciences	Genetic investigations in humans
1994	Institute of Medicine	Assessing genetic risks. Implications for health and social policy
1994	Working Party of the Clinical Genetics Society (UK)	The genetic testing of children. Report of a working party of the Clinical Genetics Society
1995	American Medical Association	Testing children for genetic status
1995	American Society of Human Genetics and the American College of Medical Genetics	Points to consider: ethical, legal and psychosocial implications of genetic testing in children and adolescents
1995	National Consultative Ethics Committee for Health and Life Sciences (France)	Opinion and recommendations on 'Genetics and medicine: from prediction to prevention'. Reports
1995	German Society of Human Genetics	Statement on genetic diagnosis in children and adolescents
1995	Genetic Interest Group	GIG response to the UK Clinical Genetics Society report 'The genetic testing of children'
1996	German Society of Human Genetics	Position paper of the German Society of Human Genetics
1996	Japanese Society of Human Genetics	Guidelines for genetic testing, using DNA analysis.
1997	National Human Genome Research Institute	Promoting safe and effective genetic testing in the United States
1998	British Medical Association	Human Genetics: choice and responsibility
1998	Advisory Committee of Genetic Testing (UK)	Report on genetic testing for late-onset disorders
1998	Australian Medical Association	Human genetic issues
1999	Italian National Bioethics Committee	Bioethical guidelines for genetic testing
2000	Canadian College of Medical Geneticists	Position statement – genetic testing of children
2000	European Society of Human Genetics	Provision of genetic services in Europe – current practices and issues. Recommendations of the European Society of Human Genetics
2001	Danish Council of Ethics	Genetic investigation of healthy subjects – report on presymptomatic gene diagnosis
2001	American Academy of Pediatrics	Ethical issues with genetic testing in paediatrics
2001	Japanese Society of Human Genetics	Guidelines for genetic testing
2002	Human Genetics Society of Australasia	DNA presymptomatic and predictive testing for genetic disorders
2003	Canadian Paediatric Society	Guidelines for genetic testing of healthy children
2003	Belgian Society of Human Genetics	Guidelines for predictive genetic testing for late-onset disorders
2003	Genetics-Medicine-Related Societies (Japan)	Guidelines for genetic testing
2005	Human Genetics Society of Australasia	Child testing policy

guidelines originated from 31 different organizations. Most guidelines were issued by genetic associations and societies (12), medical (10) and paediatric (2) associations or societies, a consumer group (1), national bioethics committees (3) and other independent bodies related to governmental structures (3), such as the Institute of Medicine, the Advisory Committee of Genetic Testing and the National Human Genome Research Institute. The retrieved guidelines were developed in Europe (14), the United States (5), Japan (3), Australia (3) and Canada (2). Nine guidelines were devoted exclusively to the issue of genetic testing of minors, and 18 guidelines covered this issue in general guidelines about genetic testing.

Recommendations towards testing of minors

All guidelines clearly advanced the idea that medical benefit is the main justification for testing of minors for adult-onset or childhood-onset diseases. Sixteen guidelines (19–34) that did not make a clear distinction between childhood-onset and adult-onset diseases formulated in a similar way that predictive genetic testing should only be performed for persons of legal age, in principle, except for disorders for which preventive or therapeutic actions could be initiated.

The remaining 11 guidelines (35–45) that distinguished childhood-onset from adult-onset diseases clearly proposed in similar words that, when considering specifically predictive and presymptomatic tests for late-onset disorders, such testing is only recommended when 'established, effective, and important medical treatment' (43) can be offered or when testing 'provides scope for treatment which to any essential degree prevents, defers or alleviates the outbreak of disease or the consequences of the outbreak of disease' (41). The rationale behind this option is that predictive testing for adult-onset disease 'should be delayed until the person is old enough to make an informed choice' (38).

Guidelines (36–40, 42–44) explicitly dealing with predictive and presymptomatic tests for childhood-onset disorders considered testing 'clearly appropriate where … there are useful medical interventions that can be offered (e.g. diet, medication, surveillance for complications)' (37). The rationale is that medical benefit to the child should be the primary justification for genetic testing in children and adolescents. The availability of preventive or other therapeutic measures leads, in some cases, even to the requirement to perform a genetic test (39).

The situation is less clear for childhood-onset disorders for which preventive or other therapeutic measures are not available. Although putting forward the idea that medical benefit is the main justification for testing, five guidelines (35–37, 39, 42) considered testing in this context appropriate because generally 'parents should have discretion to decide about genetic testing for childhood diseases that are unpreventable and untreatable …. Since with unpreventable and untreatable genetic diseases there are both benefits and risks to genetic testing and neither the benefits nor risks clearly outweigh each other, parents generally should be allowed to decide about testing for their children'. For these guidelines, testing was considered appropriate on the condition that 'testing would be in the child's best interests' (42). Because 'best interests' cannot be understood in this context as a medical benefit, it should be understood here as a psychological or social benefit.

This view seems to be at odds with the view of the European Society of Human Genetics: 'A predictive genetic test is indicated during childhood if the onset of a disorder can be expected at this age *and* [our italics] if medical measures can be taken to prevent the disease or its complications or to treat the disease'. It also appears to differ from the view of the German Society of Human Genetics: 'A predictive genetic diagnosis is indicated during childhood if the onset of a disorder can be regularly expected at this age *and* [our italics] if medical measures can be taken to prevent the disease or its complications or to treat the disease' (38, 43). The difference between these two statements and the statement of the Working Party of the Clinical Genetics Society is limited to the use of the conjunctions *and* or *or*: 'The predictive genetic testing of children is clearly appropriate where onset of the condition regularly occurs in childhood *or* [our italics] there are useful medical interventions that can be offered (e.g. diet, medication, surveillance for complications)' (37). The consequences of using a one or the other conjunction may be important. The use of the conjunction *and* in the first case seems to describe two criteria before proceeding to testing, while use of the conjunction *or* in the second case seems to describe two different situations in which testing is acceptable.

Recommendations towards the timing of testing for childhood-onset diseases

Testing is recommended when the results are of 'immediate' relevance (25, 26, 31) for a child's

health or may offer 'timely' (19, 22, 30, 42) 'medical benefit'. The operational meaning of the words immediate and timely was not specified. Only three guidelines clearly related the moment of testing to the start of preventive or therapeutic measures. The Belgian Society of Human Genetics clearly points out that 'in principle predictive testing should only be available at the age that is considered to be adequate for starting medical surveillance' (27). The British Medical Association (44) also warns that a careful consideration is required if there is a 'long period of time between the request for testing and the estimated onset of symptoms'. Finally, the UK alliance of patient organizations Genetic Interest Group (GIG) (36) advanced the idea that ultimately 'parents are responsible for the welfare of their children, and at the end of the day, most of them are better equipped to decide what is in the best interest of a particular child, and the family as a whole, than are outsiders'. As a consequence, the GIG states that parents should be able to decide about the best moment of such testing.

Recommendations towards the timing of testing for adult-onset diseases

Although in most countries, a person's 18th birthday draws the legal line between childhood and adulthood, no guideline used this as a strict rule for accepting or refusing genetic testing for adult-onset diseases. In all guidelines, it was emphasized that age 'should be given flexible consideration' (31) and that genetic tests should be deferred as much as possible to the moment adolescents are 'competent to make a free informed decision' (27). 'The degree of maturity and state of development' (43) and 'conditions of competence, voluntariness, and adequate understanding of information' (19) were considered crucial criteria in the assessment of adolescents' requests for genetic testing. Furthermore, all guidelines stressed that children should receive education and counselling appropriate to their age and maturity. Postponing testing was not considered as a reason to avoid discussing the issues of genetic risk and/or genetic testing with younger children (37).

In light of the legal context in which they have been written, two guidelines described specific age limits regarding genetic testing. The British Medical Association (44) accepts that adolescents between 16 and 18 years of age may themselves request predictive testing for a late-onset disease. Under special circumstances, the British Medical Association also accepts that people younger than 16 years may consent to presymptomatic testing for adult-onset disorders if they have 'a very high level of capacity'. The Danish Council of Ethics (41) sets a limit at 15 years of age. Before a child reaches the age of 15 years, the parents are considered to be 'the one with the competence to make the decision concerning the performance of presymptomatic genetic testing'; between 15 and 18 years of age, a child 'should itself determine whether it wishes to have presymptomatic genetic testing undertaken'.

Discussion

Predictive and presymptomatic genetic testing in minors is the subject of many more sets of guidelines than carrier testing in minors. Contrary to our previous review dealing with carrier testing in which we were able to include 14 guidelines (17), for the present review, we were able to include 27 guidelines and position papers. Professional societies and associations have clearly devoted more attention to predictive and presymptomatic genetic testing in minors than to carrier testing. On the one hand, this might be due to the fact that more consensus exists on the policy regarding predictive testing of minors than on carrier testing of minors. Some commissions might indeed have decided to decline discussing carrier testing of minors in their statements because no agreement could be reached. On the other hand, predictive and presymptomatic genetic testing in minors might be considered more controversial than carrier testing in minors and in greater need of clear recommendations.

Despite the numerous guidelines published and the variety of guideline developers, we observed a remarkable degree of unanimity. It is clear that the availability of medical benefit is the most important justification to perform predictive and presymptomatic genetic testing in minors, regardless of the onset of the disease. The absence of medical benefit is the most important justification to defer testing until the adolescent or adult is able to make a personal decision on this matter after a full discussion and exploration of the issues.

Although the guidelines seem mostly clear, practical difficulties may arise when trying to implement them. First, the distinction between adult-onset and childhood-onset disorders might not always be clear. The fact that some adult-onset disorders may have some juvenile phenotypes (e.g. Huntington disease) may complicate

the clinical-ethical assessment of a case. Theoretical categories may not be suitable for clinical practice. Second, the value of some preventive and therapeutic measures may be uncertain or a matter of discussion. This might put pressure on the justification of performing particular genetic tests in minors. Third, the concept of best interests is central in ethical discussions about genetic testing in minors. The general character of the concept, however, creates difficulties in interpretation when applied to real cases. It is often unclear what type of interests is being promoted and whether there is a hierarchy in interests. Various interests or presumed interests may not be compatible. Conflicts may arise between the best interests of an individual child and the best interests of the family as a whole or in the best interests of other family members. In addition, discussion can arise about who can decide about what is serving the best interests of child. The parents are expected to make the best decision for their children, but healthcare professionals have the ethical and legal responsibility to intervene in a child's interests if parents are not able to decide for their child or if parental decisions may harm the child. Fourth, guidelines should always be assessed in the particular local legal context and cannot always be translated to another cultural setting. It is clear that the previous Danish law on patients' rights (46) directly determined the professional recommendation that competent patients between 15 and 18 years of age may personally give informed consent to genetic testing, after having informed the person holding parental authority and letting him participate in the decision making. The Family Law Reform Act (47), in turn, contextualizes the British Medical Association's recommendation that young people between 16 and 18 years of age are presumed to be competent to give consent to genetic testing, without any necessity to obtain consent from parent(s) or guardian(s). Furthermore, the common law, under influence of the Gillick case, rejects the position that consent from parents is always needed before treating children younger than 16 years. When a young person, who has sufficient understanding and intelligence to understand fully what is proposed, gives consent to treatment, consent from parents is not legally necessary although parental involvement is mostly encouraged. Other countries, such as France, have urged in their law (48) to inform minors and let them participate in decision making in proportion to his or her degree of maturity. Fifth, several guidelines recommend that assessments of competence and maturity in young people should be made, but little advice is given about how to make such assessments. It has been urged that a far more comprehensive definition of maturity, linked to age and developmental stage, is required for assessing young people at risk who request predictive testing (49).

A remarkable observation is that not all guidelines distinguish between childhood-onset and adult-onset diseases. This is strange because the guidelines that make the distinction show that these are very different situations and may lead to different recommendations, particularly when there are no preventive or therapeutic measures. On the one hand, the focus on adult-onset diseases, and, in particular, on Huntington disease since the introduction of genetic tests has probably led to some short sightedness in relation to diseases with a different age of onset and may explain the limited attention given to childhood-onset diseases. On the other hand, various committees that have issued these guidelines might have had difficulties in reaching consensus in providing recommendations on genetic testing in such a situation and therefore might have decided to defer the issue.

Although an important level of consensus appears through the various guidelines and position papers, areas of conflict and discussion that we noted are connected to genetic testing in childhood. First, testing for childhood-onset disorders for which preventive or other therapeutic measures are not available remains an issue of discussion. Such testing would not be performed if we were to follow general recommendations only to perform testing in cases having a medical benefit. The use of the conjunction *and* in the guideline of the German Society of Human Genetics and the European Society of Human Genetics suggests that two conditions (i.e. childhood onset *and* medical benefit) should be present before testing is acceptable. This is a striking difference from the recommendation of the Working Party of the Clinical Genetics Society that describes two different situations in which testing is acceptable (i.e. childhood onset *or* medical benefit).

Second, the timing of testing for childhood-onset diseases remains a potential field of discussion. Although practice shows that testing is mostly forbidden earlier than the age of first possible onset of the disease (e.g. Familial Adenomatous Polyposis) (50), the professional recommendations are open to various interpretations. Furthermore, the GIG (36) claims that parents should be able to decide about the best moment of such testing and not professionals

according to recommendations such as the 'rule of the earliest onset', which suggests that 'genetic testing should be permitted at an age no earlier than the age of first possible onset' (51) of the disease. Conflicts have already arisen on the issue that parents should be able to decide about testing and have access to the genetic information of their children when there is no urgent medical indication to do so (52).

Although we retrieved 27 different guidelines or statements that discussed the presymptomatic or predictive testing of minors, only one statement was written by a consumer group. This apparent lack of representation from patient organizations may be because we focused our search on general guidelines rather than on disease-oriented guidelines (e.g. Huntington disease). Nevertheless, even after contacting various geneticists and groups of patient and parent organizations such as the GIG (UK) and the Dutch Genetic Alliance (Vereniging Samenwerkende Ouder- en Patiënt-enorganisaties – VSOP), we did not succeed in identifying policy documents on childhood genetic testing from disease-specific family support groups. Future research (e.g. surveying patient organizations on that issue) could help identify whether these groups have developed policies that may not be available online or may not be widely disseminated.

In conclusion, although the guidelines regarding presymptomatic and predictive genetic testing of minors agree strongly that medical benefit is the main justification for testing, clarification is required concerning the case of childhood-onset disorders for which preventive or therapeutic measures are not available.

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