Attitudes Regarding Predictive Genetic Testing in Minors: A Survey of European Clinical Geneticists

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The aim of this study is to gather information from European clinical geneticists about their practices and attitudes with regard to presymptomatic and predictive genetic testing in minors. European clinical institutes where genetic counseling is offered to patients were contacted. One hundred seventy-seven of the 287 eligible respondents (63%) answered a questionnaire. There was strongest support for testing young children when it provides a clear medical benefit, such as in the case of FAP and MEN2A. However, there is disagreement about when to provide predictive genetic testing for childhood-onset disorders for which therapeutic or preventive measures exist with some supporting the rule of earliest onset and others giving parents wider discretion. However, for childhood-onset disorders that do not have therapeutic measures, the majority of the respondents is unwilling to provide a presymptomatic or predictive genetic test. With respect to adolescents, many held a cautious position regarding presymptomatic and predictive genetic testing. Most clinical geneticists were unwilling to provide a presymptomatic or predictive genetic test for adult-onset diseases, except if it might provide a medical benefit. Although adolescents might be legally in the position to request a presymptomatic or predictive genetic test personally, the clinical geneticists are significantly more willing to provide a test if this request is made together with the minor’s parents. This variability demonstrates the need for clinical geneticists to discuss their contradicting views and to develop harmonized practices throughout Europe.

KEY WORDS: genetic testing; predictive; genetic counseling; attitudes


INTRODUCTION

In a previous article [Borry et al., 2006], we analyzed how 27 different guidelines and position articles discussed predictive and presymptomatic genetic testing in minors. Based on various social, psychological, legal, and ethical concerns, predictive, and presymptomatic genetic testing in minors remains controversial and should be addressed with caution.

The aim of this study is to gather information from European clinical geneticists about their practices and attitudes with regard to presymptomatic and predictive genetic testing in minors. Very little information has been gathered before about the European geneticists’ views of genetic testing in minors. Most empirical studies surveying clinical geneticists on this issue were undertaken more than 10 years ago [Clarke, 1994; Wertz and Reilly, 1997] and more recent studies on the issue did not include a European perspective [Wertz and Reilly, 1997; Mao, 1998; Campbell and Ross, 1998]. In particular, we were interested in whether clinical geneticists support the rule of earliest onset which states that genetic testing “should be permitted no earlier than the first possible onset of disease.”
METHOD

Procedure

With the help of the website orphanet (http://www.orpha.net), the websites of the national genetic associations and/or national contact persons, a list of clinical institutes where genetic counseling is offered to patients has been elaborated. Institutes providing only laboratory services or providing only prenatal diagnosis were not within the scope of this survey and were not included in our list. In addition, only the 27 E.U. Member States were studied. In total 312 institutes were identified and attempts made to receive one questionnaire back from every institute. Medically qualified specialists in genetics (clinical geneticists) who have offered genetic counseling to patients in the last year were asked to complete a survey of items assessing their attitudes and practices regarding genetic testing in minors. The questionnaire enumerated all of the institutes in the respondent's country and respondents were asked if they knew other institutes in their country that were not included. Data collection took place between October 2006 and March 2007. Two weeks after the questionnaire was sent out by e-mail, a reminder was made to non-responders. A second, third, and fourth and sixth reminder by e-mail were sent out with approximately intervals of 2 weeks. The fifth reminder was sent by hard copy to the non-responders. No monetary or other incentive was offered.

Questionnaire

All respondents completed a 28-item questionnaire. The survey instrument was developed especially for this study, and included a range of diseases that vary with respect to the age of onset, severity and treatability in order to incorporate the myriad of ethical concerns raised by genetic testing in minors. The questions were mostly linked to a 6-year-old child, as an exemplar of an incompetent minor whose parents or legal guardians have the legal and medical authority, or a 16-year-old adolescent. Using a 5-point Likert response scale, respondents were directed to indicate whether they are "(very) willing or unwilling to provide a presymptomatic or predictive genetic test to a 6–(or 16-) year-old child." Using a 5-point Likert response scale, the respondents were also directed to indicate whether they "(strongly) agree or disagree" with various statements. Sociodemographic factors including gender, age, country, and practice characteristics were collected. The questionnaire was reviewed by 10 experts coming from various backgrounds (patient organizations, genetics, medicine, ethics, law, social sciences, and nursing sciences) prior to its distribution.

Statistical Analysis

As the survey responses were measured on an ordinal scale, non-parametric statistics were used. The analysis was performed using SAS 9.1.3. A two-tailed Wilcoxon–Mann–Whitney U test at a 0.05 significance level has been used to compare differences in practices. A two-tailed Wilcoxon–Mann–Whitney U test at a 0.01 significance level has been used to compare differences in responses between gender, age (younger or older than 50 years) and between those who have already provided counseling for a specific disorder and those who have not. Countries were divided in four groups based on geographical regions described by the United Nations: Western European countries (Austria, Belgium, France, Germany, The Netherlands), Eastern European countries (Bulgaria, Czech Republic, Hungary, Poland, Slovakia, Slovenia, Romania), Northern European countries (Denmark, Finland, Ireland, Latvia, Sweden, United Kingdom, Lithuania, Estonia) and Southern European countries (Spain, Greece, Italy, Malta, Portugal, Cyprus). Regional differences were studied using a two-tailed Wilcoxon–Mann–Whitney U test at a 0.01 level of significance. Although the tables were presented in a 5-point Likert-type scale, this scale was recoded into a 3-point scale for the statistical analysis. For the analysis of associations between two ordinal variables, the Spearman's rank correlation coefficient was used. This coefficient takes on a value between −1 and +1 and is a measure of an association between two ordinal variables. It is interpreted much like a correlation coefficient. For these statistics the 5-point Likert-type scale was used.

RESULTS

Sample

Five supplementary institutes were identified thanks to the respondents. Of the 317 institutes we contacted, 17 institutes responded that they were only providing laboratory services, prenatal diagnosis or had finished their activities. Fourteen other institutes were excluded for the same reason, but on the indication of another respondent. Five institutes were also excluded because the staff member who responded to the questionnaire answered in name of two institutes. Of the remaining 281 institutes, 4 respondents refused to complete the questionnaire and 177 respondents returned a completed questionnaire, corresponding to a response rate of 63% (177/281) based on the number of eligible respondents. The mean age was 51 years (SD 8.7, range 30–73 years). Forty-seven percent (84/177) of the respondents were women. Responses came from 26 different European countries.

Practices Regarding Presymptomatic and Predictive Genetic Testing in Minors

The questionnaire listed 10 autosomal dominant disorders and asked respondents whether they have ever provided a genetic test in practice to an asymptomatic healthy minor younger than
16 years. Over half (57%) acknowledged testing for familial adenomatous polyposis (FAP) and 47% for multiple endocrine neoplasia 2A (MEN2A) in an asymptomatic minor younger than 16 years (see Table I). In contrast, almost none of our respondents had provided a test for Alzheimer disease (0%), breast cancer (2%), Huntington disease (4%) in an asymptomatic minor.

Attitudes About Presymptomatic and Predictive Genetic Testing in Minors

Respondents were then asked their attitudes towards testing both a 6-year-old and a 16-year-old for these 10 disorders. As shown in Figure 1, most respondents were very unwilling or unwilling to provide a presymptomatic or predictive genetic test for Alzheimer disease (ApoE4) (97%), breast cancer (96%) or Huntington disease (97%). This also held for the 16-year-old child, although to a lesser degree. The majority of the respondents were also very unwilling or unwilling to provide such a test for Charcot-Marie-Tooth disease (77%), hereditary hemochromatosis (75%), inherited thrombophilia (60%), myotonic dystrophy (62%) and retinitis pigmentosa (66%). For each condition, unwillingness decreased when the child was described as 16 years of age. The majority of respondents supported testing 6-year-olds for FAP and MEN2A.

Gender and age did not influence the responses. However, the results of the Wilcoxon–Mann–Whitney U test indicate that the respondents (z = -4.9636, two tailed P < 0.0001) who have ever provided genetic counseling for MEN2A are significantly more in favor of providing a presymptomatic or predictive genetic test to a 6-year-old child for this disorder. A geographical analysis shows that respondents from Northern and Western European countries have more experience with counseling for MEN2A than respondents

| TABLE I. Frequencies and Percentages of Clinical Geneticists That Have Ever Provided Counseling or Testing for Presymptomatic or Predictive Genetic Conditions to an Asymptomatic Minor Younger than 16 Year Old (N = 177) |
|-----------------------------|-----------------------------|
|                             | Provided counseling N (%)   | Provided counseling and testing N (%) |
| Alzheimer disease (ApoE4)   | 57 (32)                    | 0 (0)                                |
| Breast cancer (BRCA 1,2)    | 125 (71)                   | 2 (1)                                |
| Charcot-Marie-Tooth disease | 147 (83)                   | 19 (11)                              |
| Familial adenomatous polyposis | 116 (66)               | 66 (37)                              |
| Hereditary hemochromatosis  | 124 (70)                   | 15 (8)                               |
| Huntington disease          | 140 (79)                   | 6 (3)                                |
| Inherited thrombophilia (Factor V Leiden) | 119 (67) | 28 (16) |
| Men2A                        | 91 (51)                    | 43 (24)                              |
| Myotonic dystrophy (Steinert)| 143 (81)                   | 33 (19)                              |
| Retinitis Pigmentosa         | 136 (77)                   | 14 (8)                               |

**Figure 1.** The willingness of clinical geneticists to provide a presymptomatic or predictive genetic test to a 6-year-old child (percentages). AD = Alzheimer disease; BRCA = Breast cancer; CMT = Charcot-Marie-Tooth; FAP = Familial adenomatous polyposis; HH = Hereditary hemochromatosis; HD = Huntington disease; IT = Inherited thrombophilia (Factor V Leiden); MEN2A = Multiple endocrine neoplasia; MD = Myotonic dystrophy (Steinert); RP = Retinitis pigmentosa; Y = Year.
from Southern and Eastern European countries ($\chi^2 = 29.9908$, $P < 0.0001$) which correlates with greater willingness to provide a genetic test.

We also observed that respondents from Northern and Western European countries have greater experience with counseling for hemochromatosis ($z = -4.110$, two tailed $P < 0.001$) and were significantly more unwilling to provide such a test for hemochromatosis than respondents from Southern and Eastern European countries ($z = 3.1969$, two tailed $P = 0.0014$). In contrast, for inherited thrombophilia we observed that respondents from Eastern European countries were more willing to provide such a test than respondents from Northern ($z = -3.3076$, $P = 0.0009$), Southern ($z = 2.9181$, $P = 0.0035$) or Western European countries ($Z = 3.0593$, $P = 0.0022$), and this could not be explained by differences in counseling experience.

Age of the respondents did not explain response variability. Gender, however, influenced the answer patterns. The Wilcoxon–Mann–Whitney U test showed that men were more willing to provide a predictive genetic test for Huntington disease to an adolescent than were women ($z = -2.8043$, $P = 0.050$). This is also the case for breast cancer if we would put the significance level at 0.05 instead of 0.01 ($z = -1.9596$, $P = 0.05$).

A comparison of the medians for 6- and 16-year-old minors shows that for all diseases studied the respondents are more willing to provide a presymptomatic or predictive genetic test to a 16-year-old asymptomatic minor than to a 6-year-old child. For example, respondents were significantly more willing to provide the same test to a 16-year-old child for six of the seven diseases studied the respondents are more willing to provide a genetic test. Thirty-five percent of the respondents agrees that “minors of 16 and 17 years” are requesting this test together with their parents ($z = 4.1215$, $P < 0.0001$). There was no significant difference in willingness to test for MEN2A between 6- and 16-year-olds, but this may be explained on the basis that the information is often clinically useful as young as 6 years old and most of the clinical geneticists were supportive of predictive testing at both ages ($z = -1.9764$, $P = 0.0481$).

Experiences and Arguments About Predictive Genetic Testing in minors

In Table II, we observe that there exists a broad disagreement about whether a 16-year-old minor should be able to receive a predictive genetic test. Thirty-five percent of the respondents agrees strongly or somewhat with the statement that “minors of 16 and 17 years” are mature enough to request a predictive or presymptomatic genetic test for an adult-onset disease personally, while 41% strongly disagrees or disagrees somewhat. Respondents were significantly more in favor of providing this test if the minor requests this test together with his parents ($z = -4.1037$, $P < 0.0001$). Furthermore, 87% of clinical geneticists agree or strongly agree that presymptomatic and predictive genetic testing should only be available at the age that is considered to be adequate for starting medical surveillance. The results of the Wilcoxon–Mann–Whitney U test indicate that the clinical geneticists from Southern and Eastern European countries agree are less likely to agree to offer a presymptomatic or predictive genetic test if asymptomatic minors of 16 and 17 years are requesting this test personally without the consent of their parents than their colleagues from Northern and Western European countries ($z = -2.7223$, $P = 0.0065$). No difference is observed between these groups when asymptomatic minors of 16 and 17 years are requesting this test together with their parents ($z = 0.5564$, $P = 0.5779$). Gender and age did not influence the responses.

### DISCUSSION

This research provided an overview of the attitudes of clinical geneticists with regard to presymptomatic and predictive genetic testing in minors. The respondents’ attitudes clearly indicated a cautionary position towards presymptomatic and predictive genetic testing in minors. There was strongest support for testing young children when it provides a clear medical benefit, such as in the case of FAP and MEN2A.

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However, there is disagreement about when to provide predictive genetic testing childhood-onset disorders for which therapeutic or preventive measures exist with some supporting the rule of earliest onset and others giving parents wider discretion. However, for childhood-onset disorders that do not have therapeutic measures, the majority of the
respondents is unwilling to provide a presymptomatic or predictive genetic test.

The main reason for providing or supporting predictive testing in an asymptomatic minor was the presence of direct medical benefit through medical intervention or preventative measures. This is completely in line with existing policy documents [Borry et al., 2006].

Although the respondents were more eager to provide a presymptomatic genetic test for adult-onset diseases to 16-year-old adolescents on personal request than to 6-year-old children on parental request, the majority is still very or somewhat unwilling to provide this test for breast cancer or Huntington disease in adolescence. The exclusion of minors from predictive genetic testing for breast cancer and Huntington disease is mostly based on the grounds of the lack of clear medical benefits of testing at that age, together with concerns regarding the possibility of third party pressures in the request and the potential of psychosocial harms [Binedell et al., 1996]. The geneticists were also mixed in their attitude about whether minors of 16 and 17 years old are mature enough to request a predictive or presymptomatic genetic test for an adult-onset disease personally. Previous research [Lucassen and Houlston, 2000] on predictive genetic testing for breast cancer also showed the controversial character of such testing. Although in various countries adolescents may have the legal and/or mental competence to request an adult-onset presymptomatic or predictive genetic test for any or all of these conditions, the geneticists’ responses suggest that they will encourage deferring testing.

There was more disagreement among the clinical geneticists for other adult-onset disorders. For myotonic dystrophy (Steinert), thrombophilia (Factor V Leiden), and hemochromatosis the respondents expressed an unwillingness to test a 6-year-old child, but there was greater heterogeneity regarding their willingness to provide a presymptomatic or predictive genetic test for a 16-year-old minor. The variety in answers regarding myotonic dystrophy might be explained by the extreme variability of the disorder, in both severity and age at onset [Fokstuen et al., 2001]. Factor V Leiden testing has been recommended for women with a family history of thromboembolism that are contemplating or using oral contraceptives or are pregnant [Grody et al., 2001]. Nicolaides et al. [2005] recommended that genetic testing was important in asymptomatic first degree relatives of individuals with proven symptomatic thrombophilia. In particular, this is important for females in the child-bearing years. Hereditary hemochromatosis is a common autosomal recessive disorder of iron metabolism and has a symptom onset usually beyond 30 years of age [McDonnell et al., 1999]. However, the ideal age to test those at risk of the disease is a matter of debate [Delatycki et al., 2004], with some advocates for and against early testing. This debate is also reflected in the responses to our questionnaire.

Although 87% of the clinical geneticists strongly or somewhat agreed on the fact that presymptomatic and predictive genetic testing in minors should only be available at the age that is considered to be adequate for starting medical surveillance, 32% of the respondents were very or somewhat willing to provide a predictive genetic test for FAP to a 6-year-old child. This attitude contradicts the rule of earliest

<table>
<thead>
<tr>
<th>TABLE II. Statements Regarding Presymptomatic and Predictive Genetic Testing in Minors*</th>
<th>1. Strongly disagree, n (%)</th>
<th>2. Disagree somewhat, n (%)</th>
<th>3. Neither agree or disagree, n (%)</th>
<th>4. Agrees somewhat, n (%)</th>
<th>5. Strongly agree, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) It is my experience that minors of 16 and 17 years old are mature enough to request a predictive or presymptomatic genetic test for an adult-onset disease personally (N = 173)</td>
<td>28 (16)</td>
<td>43 (25)</td>
<td>42 (24)</td>
<td>50 (29)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>(b) Asymptomatic minors of 16 and 17 years should be offered a presymptomatic or predictive genetic test if they request this test personally without the consent of the parents</td>
<td>28 (16)</td>
<td>47 (28)</td>
<td>27 (16)</td>
<td>61 (36)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>(c) Asymptomatic minors of 16 and 17 years should be offered a presymptomatic or predictive genetic test if they request this test together with their parents</td>
<td>13 (8)</td>
<td>28 (16)</td>
<td>26 (15)</td>
<td>73 (43)</td>
<td>31 (18)</td>
</tr>
<tr>
<td>(d) Presymptomatic and predictive genetic testing should only be available at the age that is considered to be adequate for starting medical surveillance</td>
<td>2 (1)</td>
<td>11 (6)</td>
<td>10 (6)</td>
<td>70 (41)</td>
<td>78 (46)</td>
</tr>
</tbody>
</table>

Frequencies and percentages (n = 171).

*All statements have 171 respondents unless specified.
onset and implies that the timing of testing for childhood-onset diseases remains controversial [Ross, 2002].

Counseling experiences significantly influenced the answers of the respondents regarding testing for MEN2A. Clinical geneticists who are experienced in genetic counseling for MEN2A are more willing to provide a presymptomatic genetic test to a 6-year-old child. This favorable position might be explained by the fact that a positive test for MEN2A leads to a highly effective clinical intervention. Early detection of the malignant mutation can lead to intervention by thyroidectomy, which has been shown to be well tolerated even by most young children. Disagreement might exist however about the age that thyroidectomy might be performed, some recommending 5 years, while others recommending 10 years [Brandi et al., 2001].

In accordance with the recommendations of the European Society for Human Genetics [European Society of Human Genetics, 2001], the respondents are unwilling to provide a presymptomatic genetic test at the age of 6 for Charcot-Marie-Tooth disease and retinitis pigmentosa, two conditions that may present in childhood but for which no treatment is available. Other guidelines [Borry et al., 2006], however, have emphasized that for childhood-onset disorders for which no preventive or therapeutic measures exist, parental discretion might be appropriate, because parents should be entitled to make a decision in this context.

CONCLUSION

Most clinical geneticists remain unwilling to provide a presymptomatic or predictive genetic test for adult-onset diseases, except if it might provide a medical benefit. In this case clinical geneticists are significantly more willing to provide such a test to an adolescent if this is requested together with the parents of the minor. These discrepancies demonstrate the need for clinical geneticists to discuss their contradicting views and to develop harmonized practices throughout Europe.

REFERENCES


