Ethical aspects of research into Alzheimer disease. A European Delphi Study focused on genetic and non-genetic research

A van der Vorm,1 M J F J Vernooij-Dassen,2 P G Kehoe,3 M G M Olde Rikkert,4 E van Leeuwen,1 W J M Dekkers1

ABSTRACT

Background: Although genetic research into Alzheimer disease (AD) is increasing, the ethical aspects of this kind of research and the differences between ethical issues related to genetic and non-genetic research into AD have not yet received much attention.

Objectives: (1) To identify and compare the five ethical issues considered most important by surveyed expert panelists in non-genetic and genetic AD research and (2) to compare our empirical findings with ethical issues in genetic research in general as described in the literature.

Method: A modified Delphi study in two rounds

Results: Genetic and non-genetic research into AD generated an approximately equal number of topics with a considerable overlap. Different priorities in the ethics of both types of research were found. Genetic research raised new topics such as “confidentiality of genetic information” and “implications of research for relatives” which changes the impact and application of existing ethical topics such as “informed consent” and is judged to have more impact on both individuals and society. A difference with the results of more theoretical approaches on ethical aspects related to AD research was also found.

Conclusions: Different priorities are given to ethical issues in genetic and non-genetic research. These arise partly because genetic research causes unique and new questions, mostly related to the position of family members and the status of and access to genetic information. Differences found between the results of our empirical study and the more theoretical literature, suggest an additional value for empirical research in medical ethics.

The increasing prevalence of Alzheimer disease (AD), and the fact that its causes or a cure have yet to be discovered strongly motivate increased research efforts including that of genetic research. At present less than 5% of all AD cases have a known genetic aetiology and less than 50% harbour the ε4 allele of the APOE gene, the only recognised genetic susceptibility factor for AD.1 Although current evidence shows that non-genetic factors contribute considerably to the cause of AD, genetic variation is recognised to be an important factor in disease development and progression.1–4

There have been no ethically focused studies in genetic and non-genetic research into AD. The panel consisted of 12 experts from five countries (The Netherlands, UK, Belgium, Sweden and Luxembourg). Participants were selected for their expertise in the field of AD, genetics or ethics. Expertise was judged on educational qualifications and experience and on the basis of contributions to other studies in the field of AD.

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Representatives of the following groups were included: (1) (genetic) researchers, (2) medical doctors, (3) representatives from patient organisations (eg, Alzheimer Societies), (4) ethicists (see appendix 1 online). The aim of this procedure was to include the full range of settings relevant to the exploration of ethical aspects linked to AD research.18

In the second round the panel was extended to include 17 respondents from nine countries (participants from Greece, Spain, Romania and Israel were added in the second round). We extended the initial panel because we considered it an advantage to receive feedback on earlier findings from a wider panel. The extension of the initial panel in the second round of a Delphi study is not standard for the Delphi method, but has its place in qualitative research.19 While it might be a perceived disadvantage that panel members involved in the first round had set the agenda for the second round, this problem was minimised by allowing all participants to add topics deemed important that had been missed in the first round.

Data collection
The questionnaire of the first round was piloted in a small multidisciplinary panel. It was designed as part of a larger study which consisted of four open-ended questions related to ethical aspects of research into AD. Here we concentrate on the two questions concerned with the ethical aspects of non-genetic and genetic research into AD (see appendix 2 online). The responses to the other questions which related specifically to a consensus statement on ethics of dementia research will be reported separately.16

The second questionnaire (ie, the questionnaire forming the second round) had three aims: (1) to ensure that no relevant topics were missed during the first round; (2) to identify and prioritise the five topics from each research context considered to be most important by panel members and (3) to collect the arguments relevant to the participants’ prioritisation. This questionnaire consisted of six questions in which open questions (asking for arguments) were combined with more structured questions (asking for a rating of priorities) (see appendix 3 online). This approach resulted in quantitative information about the priorities of panel members and qualitative information about the reasons why these topics were considered more or less important.

Data analysis
The opinions collected from the first round were independently categorised by two researchers (AvdV and WD) and then discussed by four project group members (AvdV, MVD, MOR, WD) until consensus was reached. The agreed topics were integrated into the questionnaire for the second round and circulated to all participants (table 1). During the second round, priorities were scored by giving five points to the topic considered most important, four points for the topic considered second in importance and so on (see appendix 4 online for results). After the identification of priorities, we performed a qualitative analysis of the arguments given by respondents for their prioritisations. The material was entered into Kwalitan V.5.0 (Vincent Peters, Kwalitan Advies, Malden, The Netherlands) and divided into small text fragments.20 The fragments were coded such that more than one code could be assigned to one text fragment. Kwalitan facilitated the analysis of the relation between codes and text fragments and of the context of the selected codes.

RESULTS
Response rates
In the first round, 12 out of 18 questionnaires were returned (66%). The resulting topic list (see table 1) was returned to the participants together with the second round questionnaire. In the second round 17 out of 26 questionnaires were returned (65%). The main reasons for non participation were related to the pressured schedules of some of the invited experts. Non-responders mentioned “other commitments”, “sabbatical leave” or being “inundated with work at present”. One expert agreed to participate but declined to respond. Four of the invited experts did not respond at all.

Priorities identified in the second round
From the second round, 36 priorities were identified for non-genetic research and 25 priorities for genetic research respectively. The top five priorities assigned by participants in the questionnaire of the second round were further analysed (see table 2. Appendix 4 online provides information on all priorities identified).

Qualitative results of the second Delphi round
In the following sections qualitative information is presented for each of the five topics deemed most important from both genetic and non-genetic contexts (table 2). The two topics that were found to be of high priority for both types of research (“informed consent” and “proxy consent”) are covered by a single discussion.

Informed consent
Informed consent was found to be of the highest priority in both genetic and non-genetic research. Respondents gave two different opinions. First, informed consent is seen as enabling research because it is “the gateway to all research through the involvement of subjects”. Second, the need to protect vulnerable research subjects was stressed. “To be included in a research programme has many risks for a population with such a high degree of vulnerability. So, questions like informed consent, ... the possibilities of withdrawal at any time, ... and so on must be discussed and taken into account very carefully.” Furthermore, we found differences between genetic and non-genetic research. Regarding non-genetic research, it was suggested by respondents that it might be useful to have different levels of consent depending on the invasiveness of the research procedure. It was argued by some participants that in genetic research there should be a special procedure for routinely taken biomaterials, which would necessitate a classification of different types of research. For each type of research there should be a specific informed consent procedure. According to one respondent, in genetic research there must be a “strong emphasis on the protection of people, in connection to an in my opinion greater possibility of discrimination and adverse effects in obtaining insurance. Possibly, the ability to evaluate these possibilities makes more strict requirements necessary regarding someone’s competence”.

Vulnerability
Vulnerability was given a second priority in non-genetic research, but did not belong to the top five priorities in genetic research. Participants described two different types of vulnerability. The first type was associated with disease due to communication difficulties and a possibly reduced autonomy. “I think that the main problem in this field is the inability of these
patients to express their own opinion and to defend themselves against any sort of aggression.” This type of vulnerability is related to topics of informed consent and proxy consent. The other type of vulnerability is related to the risks and/or negative side effects of participation in research. “Protection of patients involved in research includes avoidance of stigmatisation and vulnerability, risks of research and respect for autonomy.”

Cost-effectiveness

Cost-effectiveness was given the third priority in non-genetic research into AD, but was not represented in the top five priorities of genetic research. One respondent described cost-effectiveness as a problem that becomes increasingly important. This raises a dilemma concerning “the right time to reduce the therapeutic programme using expensive drugs”. This problem was also mentioned by another respondent: “The key question here is who gets to make the decision about what is ‘good value for money’. … What price can be set against improved quality of life?” This respondent considered the development of an evidence base for therapeutic strategies to be extremely important in the development of new therapies. Another respondent stated that the introduction of new therapies with

Table 1 Results of the first Delphi round

<table>
<thead>
<tr>
<th>Ethical issues in non-genetic research into Alzheimer disease (AD)</th>
<th>Ethical issues in genetic research into AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
<td><strong>Topic</strong></td>
</tr>
<tr>
<td>Patient</td>
<td>Informed consent issues</td>
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<td></td>
<td>Protection</td>
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<td></td>
<td>Confidentiality for research participants</td>
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<td></td>
<td>Communication difficulties</td>
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<td></td>
<td>Respect/dignity/integrity</td>
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<td></td>
<td>Stigma</td>
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<tr>
<td></td>
<td>Vulnerability</td>
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<tr>
<td></td>
<td>False hope (related to therapeutic effects of research)</td>
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<td></td>
<td>Negative side effects/risks of research</td>
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<tr>
<td></td>
<td>Financial &amp; employment issues</td>
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<tr>
<td></td>
<td>Information on research is not suitable for patients</td>
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<td></td>
<td>Research could reduce the autonomy of patients</td>
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<tr>
<td>Family</td>
<td>Proxy consent</td>
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<tr>
<td></td>
<td>Research results may have impact on life of family members</td>
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<td></td>
<td></td>
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<tr>
<td>Medicine</td>
<td>Supervision of patients</td>
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<td></td>
<td>Availability of counselling</td>
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<td></td>
<td>Is therapy cost effective/evidence based?</td>
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<td></td>
<td>Therapeutic/preventive implications of research</td>
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<tr>
<td>Research</td>
<td>Legal issues</td>
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<tr>
<td></td>
<td>Bureaucracy</td>
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<tr>
<td></td>
<td>Applicability of research models (ie, cell/animal models)</td>
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<td></td>
<td>Availability of data for research (biobanks)</td>
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<td></td>
<td>Acquiring samples for research</td>
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<td>Access to research results</td>
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<td>Public and user engagement in research</td>
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<td></td>
<td>Research might have adverse effects on resource allocation to dementia services</td>
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<td></td>
<td>The type of causal explanation given may have social and economic implications</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>AD patients should always be considered as “moral subjects” in the research and not as “research objects”</td>
</tr>
</tbody>
</table>

Table 2 Top five priorities identified during the second Delphi round

<table>
<thead>
<tr>
<th>Ethical issues in non-genetic research into AD</th>
<th>Ethical issues in genetic research into AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Priority</strong></td>
<td><strong>Topic</strong></td>
</tr>
<tr>
<td>1</td>
<td>Informed consent</td>
</tr>
<tr>
<td>2</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>3</td>
<td>Cost-effectiveness</td>
</tr>
<tr>
<td>4</td>
<td>Therapeutic/preventive implications</td>
</tr>
<tr>
<td>5</td>
<td>Proxy consent</td>
</tr>
</tbody>
</table>
an insufficient evidence-base causes false hope and wastes money. It was also suggested that “the implementation of many therapies is always hampered by the lack of EBP [evidence based practice]”.

**Therapeutic/preventive implications**

Therapeutic/preventive implications were ranked as the fourth priority in non-genetic research, but these were not represented in the genetic research priorities list. Regarding the preventive implications of research findings, one respondent mentioned that “new data in this field will cause many questions about the willingness of people to make use of it. See… discussion[s] about smoking cessation and the plans of some people not to insure other people who cause their own risks of morbidity (should we pay for surgery for smokers?).”

**Proxy consent**

Proxy consent was the second topic to be in the priorities list of both research contexts where it was the fifth most important topic in each case. As for non-genetic research, the impact of the proxy consent procedure on the relatives was stressed. “… Information relating to the impact of research on family members and their additional concerns about their own vulnerability needs to be clarified and the differences in support they should expect from normal clinical practice and research involvement”. Nearly all respondents consider relatives as the most appropriate proxies, which prompts the question “what if there are no relatives?”. For genetic research, the fact that children might share the same genetic trait is considered an important issue. It is suggested that this might be an argument for the patient to participate in this kind of research, so that his/her children might subsequently benefit from the research results. “Here the point about proxy consent and children sharing genetic traits raises another aspect which seems very important, ie, that their interests might outweigh those of the person they are representing, when it comes to making certain decisions.”

**Confidentiality of genetic information**

Confidentiality of genetic information was found to be the second priority in genetic research and was not represented in the non-genetic research priorities. “The possibility that genetic information about patients or relatives could be spread and used against them is very high”, one respondent said. In line with the ratings above, another respondent suggested that the confidentiality of genetic information “takes precedence over the informed consent issue, because if the correct procedures and safeguards are not possible… for the protection of research participants, the collection of unprotected genetic [data] should not be considered”. It was mentioned that problems could arise “when results of genetic research pinpoint to genetic factors that make patients more at risk for side effects (negative exclusion) or on the other hand more suitable for treatment (positive discrimination)”.

**The right not to know/access to information**

“The right not to know/access to information” was found to rank as the third highest genetic research priority and was not listed for the non-genetic research priorities. There was no agreement on how much information about the research results should be given to research participants. On the one hand, “people who take part in such research should be entitled to know certain information about themselves if they wish”. On the other hand, people should have the right not to know.

**Implications of results for relatives**

“Implications of results for relatives” ranked the fourth highest priority in genetic research and was absent from the top five priorities for non-genetic research. Relatives are often unaware of possible results of predictive testing, for example unexpected non-paternity. Respondents also mentioned the possibility of discrimination against relatives on the basis of results from genetic testing (for example by insurance companies). Some respondents considered the social impact of genetic research to be greater than that of non-genetic research. One respondent stated that “roughly the same arguments for relevance [as in non-genetic research] are applicable in the field of genetics but the social impact is higher”.

**DISCUSSION**

In both genetic and non-genetic research, informed consent is considered the most important issue, but the rating differs substantially. Whereas informed consent is considered by far the most important issue in non-genetic research, there is less consensus in genetic research about morally relevant topics. One explanation for this might be the fact that genetic research is relatively new—as compared to non-genetic research. As the debate continues consensus will be reached among experts about the most important moral issues. A second explanation is that in genetic research much more interests are involved than in non-genetic research. Therefore consensus is not likely to be expected.

For the two topics prioritised in both contexts (informed consent and proxy consent) the topic changes with the context. Panel members suggest specifying the informed consent procedure. For non-genetic research the suggestion is to specify the procedure on the criterion of invasiveness. For genetic research it is suggested that there may be a separate procedure for routinely taken biomaterial. This difference might be explained by the fact that genetic research is nearly always performed with blood samples, meaning that the invasiveness will always be the same and not a useful criterion to specify the informed consent procedure. Non-genetic research is much more heterogeneous, ranging from questionnaires to clinical trials. Furthermore, there may be a greater possibility of discrimination in the context of genetic research than in the context of non-genetic research. This would make the requirements for the informed consent procedure in genetic research stricter.

Regarding proxy consent, the two contexts demonstrate differences related to the fact that family members—who are considered the most appropriate proxy decision makers—may have an interest themselves in genetic research. Because the person who has to give proxy consent may carry the same gene as their relative, a conflict of interest might arise. Although relatives may have interests in non-genetic research as well, the problem of carrier status and its influence on the ability to give proxy consent is specific to genetic research.

Several topics are prioritised for only one of the two research contexts. Cost-effectiveness and therapeutic/preventive implications are probably not prioritised for genetic research because genetic research has not yet resulted in any medication or preventive strategy. When genetic research proceeds and the results become more promising, these questions will become more prominent. It is notable that the issue of vulnerability,
which is the second important issue in non-genetic research, is not mentioned in genetic research. This may be due to the fact that in genetic research, risks for research subjects arise after the participation has ended and not as a result of procedures performed during research.18

Some of the topics that are prioritised clearly relate to the practice and nature of genetic research, for example, “confidentiality of genetic information”. In contrast, the issue of “implications of research for relatives” is not wholly specific to genetic research. However, the priorities assigned by panel members show that the position of relatives is considered to be more important in genetic research than in non-genetic research. This may be related to the “move away from autonomy” described by Knoppers and Chadwick.8 The prominent role of the family as a consequence of genetic research has also been described by Finkler et al.4 Because the family seems to be more involved in genetic research, a family consent procedure could be developed.9 A theoretical argument in favour of family consent is that the family is increasingly seen as a distinct social unit, implying that genetic information is family—and not individual—property.9 A more empirical argument, arising from this study, is that family members are involved in decisions on research participation especially when their relative is incompetent. As different family members may have conflicting interests when they have to decide about research participation, these issues should be discussed during the informed consent process instead of after conflicts have arisen.

Our study reveals a clear difference with the results of more theoretical approaches of the ethics of genetic and non-genetic research. The issues mentioned by Thomas—consent, privacy and confidentiality—are in accordance with our empirical findings, but seem to be more related to the practice (and consequences) of genetic testing and not to research.7 Knoppers and Chadwick describe reciprocity, mutuality, solidarity, citizenship and universality as five “new trends” in ethics as a result of developments in genetic research.9 These trends, formulated in a general and abstract way, were not confirmed in our study. One explanation is that the trends need more time to come forward. Another explanation is that the description of these new trends is mainly based on reflective literature within the field of ethics. The differences found between the more theoretical approaches and the results of this empirical study, suggest an additional value of empirical studies in medical ethics.

Strengths and limitations
The strength of this study is its Delphi method approach to which experts from nine countries contributed. The Delphi method is a valuable technique for exploring opinions in a new area. A possible limitation of this study is the number of participants—12 experts from different professional backgrounds participated in the first round and 17 in the second round. Although this is a small sample, larger samples do not necessarily increase reliability.29 A similarly sized panel has been useful in the past.20 The main reason for using a small panel is the relatively small number of experts in the field of ethics, genetics and AD and increasing the panel size would have resulted in an over-representation of one of the groups.

CONCLUSIONS
Different priorities were given to the ethical issues recognised to be of greatest importance in genetic research as compared to non-genetic research. The main differences observed related to the position of family members and the status of and access to genetic information, while to a lesser extent, the social impact of genetic research was deemed to be higher than of non-genetic research.

These findings are relevant for clinical practice—especially for the informed consent process for this type of research—for two reasons: (1) in general a higher level of competency is required for research having more impact, the higher social impact of genetic research will influence the informed consent process; (2) due to the stronger involvement of family members in genetic research, it may be relevant to develop a family consent procedure.

Differences were found between the results of the methodology we used, which are more concrete, and those of theoretical approaches, with a conceptual nature. This suggests an additional value for combining empirical and theoretical research methods in medical ethics.

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