

## Transmitting Genetic Risk Information in Families: Attitudes about Disclosing the Identity of Relatives

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### Summary

Attitudes about disclosing the identities of family members to a physician to ensure diffusion of genetic risk information within affected families were examined in a questionnaire study of Danish patients with  $\alpha_1$ -antitrypsin deficiency (A1AD), their relatives, and a control group of Danish citizens. The questionnaires were returned by 1,761 (82%) of 2,146 recipients; 1,609 (75%) agreed to participate and completed the questionnaire. Only 2.8% objected to disclosing the identity of children, 9.1% objected to disclosing the identity of parents, and 6.7% objected to disclosing the identity of siblings. When genetic tests are offered to a sister, 75.4% of screened individuals with severe A1AD (phenotype “piZ”) and 66.8% of piZ probands thought that the physician should say who is ill. Important reasons for informing a sister at risk were, for 58%, the opportunity to prevent disease and, for 41% of piZ-probands, the opportunity to maintain openness in the family and to avoid uncertainty. Stepwise logistic regression of background variables showed that relatives were those for whom most respondents approved the disclosure of the parents’ and siblings’ identities to enable the physician to examine them for the presence of A1AD. Women were less prone to disclose the identity of siblings. The results indicate that the genetic counselor should inquire about relatives’ identities, to ensure that they are properly informed about the known risk of severe genetic disorder, such as A1AD, for which disability can be prevented by a change of lifestyle or by careful management. Disease prevention is essential, but openness and avoidance of uncertainty in affected families are also important. Our findings imply that fully informing all relatives about the disorder and about who is actually ill should be the principal rule.

### Introduction

Detection of genes responsible for many common and serious diseases, such as breast cancer (Miki et al. 1994), raises concern about ethical issues that include respect for the individual’s autonomy and privacy (Caplan 1993; Wilcke 1998) and professional disclosure of genetic information in families (American Society of Human Genetics [ASHG] Social Issues Subcommittee on Familial Disclosure 1998). Specific genetic data reveal information not only about the specific person examined but also about the person’s relatives and future children, who may either be sick or carry the trait.

It is generally accepted that it is a doctor’s duty to inform and warn patients about reasonably foreseeable dangers arising from the use of prescribed drugs, devices, and diagnostic procedures (Berg and Hirsh 1980). It has also been stated (e.g., in the Tarasoff case) that physicians and psychotherapists must warn identifiable third parties of an impending danger identified during the course of treating a patient (Hirsh 1975).

In the Safer case, which concerned multiple polyposis, a U.S. court held that the physician should directly warn those “known to be at risk of avoidable harm from a genetically transmissible condition,” irrespective of potential conflicts between the duty to warn and the obligation of confidentiality—provided that certain conditions are met (ASHG Social Issues Subcommittee on Familial Disclosure 1998). In the Pate case, the highest state court in Florida held that the duty to warn was satisfied if the physician warned the patient that the condition (thyroid carcinoma) could be transmitted genetically (McAbee et al. 1998; Merz et al. 1998).

The fact that pulmonary insufficiency due to  $\alpha_1$ -antitrypsin deficiency (A1AD) can be prevented or reduced by an individual’s refraining from smoking has been the reason for a very active approach and information policy in Denmark, since 1978, toward relatives who are at risk of having A1AD (Wilcke 1998). The aim of the present study was to evaluate professional disclosure of genetic information about A1AD to families, which implies the use of information about relatives’ identity. In a questionnaire study, we examined the attitudes of patients with A1AD, their relatives, and a

Received November 18, 1998; accepted for publication July 16, 1999; electronically published August 9, 1999.

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group of controls toward disclosing the identity of relatives to a physician so as to ensure diffusion of precise genetic risk information within the families.

### A1AD

Severe A1AD (phenotype piZ (genotype ZZ) and a few other rare variants) is an autosomal recessive single-gene disorder that may cause serious pulmonary impairment in young and middle-aged adults. In the Scandinavian population, 1/1,600 are phenotype piZ, and A1AD is more common than cystic fibrosis (1/4,700 Danes) (Nielsen et al. 1988). However, in contrast to cystic fibrosis, not all individuals affected with A1AD (type piZ) become ill, because those who have never been smokers seldom develop lung disease (Wu and Eriksson 1988). Smokers with phenotype piZ have a very high risk of developing severe dyspnea at age ~35–40 years and of premature death due to progressive emphysema (Larsson 1978). Median survival is 50 years for smokers, whereas the survival of individuals with piZ who were never smokers is no different from that of the normal population (Seersholm and Kok-Jensen 1995). Apart from refraining from smoking (Seersholm et al. 1994), other treatments for A1AD are of dubious effectiveness.  $\alpha_1$ -Antitrypsin augmentation therapy has never been evaluated in a randomized clinical trial. Specific diagnosis based on blood samples is valid and is easy and acceptable for both carriers and affecteds (Buist 1990).

Population screening for A1AD has been done in several countries, and the adverse psychosocial effects of screening all newborns for A1AD have been extensively described by a Swedish group (Thelin et al. 1985; McNeil et al. 1986). To our knowledge, general screening for A1AD is not done in any country at present.

### The Danish A1AD Register

In Denmark, when a person with A1AD (piZ) has been identified, that person's data are reported to a central register after informed consent has been given. Soon thereafter, the proband receives a personal letter containing brief information about the deficiency and the risk for relatives of inheriting A1AD and developing lung disease (pulmonary emphysema). The proband is asked to supply the register with data on relatives with  $\geq 1\%$  risk of piZ (names, dates of birth, and addresses of parents, siblings, cousins, and children). The letter emphasizes that this information is given to the register on a voluntary basis and that the data are confidential. It also emphasizes that the purpose of the request is to inform the relatives by letter, provided consent is given, about their risk and about the consequences of piZ and to offer relatives easy access to further information and examination, free of charge, including blood tests for A1AD. The identity of the proband is disclosed to relatives on

request if consent to this has been given. In our experience this procedure accommodates individual wishes and allows for passing on information to relatives. Some probands choose to let the register approach relatives directly, whereas others distribute a copy of the A1AD register's general information to relatives without involving a physician.

## Material and Methods

### Questionnaire and Enclosed Letter of Introduction

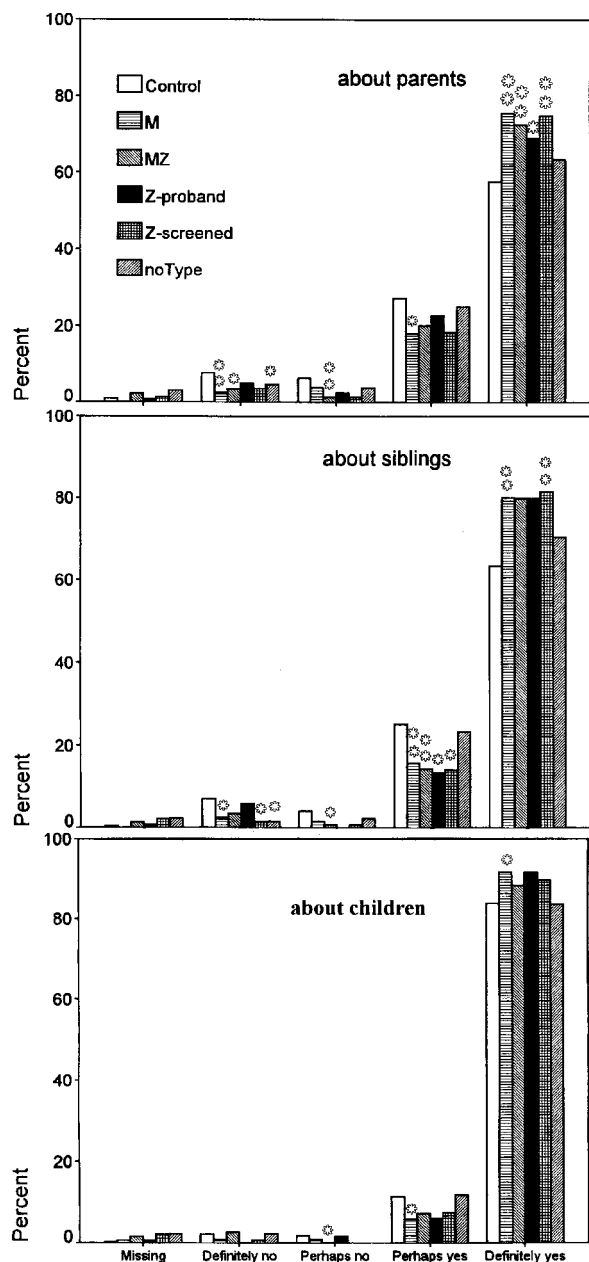
The letter of introduction we used (available in English translation on request) described A1AD, the hereditary nature of A1AD, consequences of having A1AD, options for prevention of disease (refrain from smoking), and the purpose of the study, and it stated that participation was voluntary and anonymous. The letter described a simple hypothetical situation for a 35-year-old woman, Nina, who smokes, becomes more and more short of breath, and is finally diagnosed as having A1AD. Participants were asked to answer the questionnaire as if they were Nina.

The present paper focused on two small vignettes, with Nina as proband, in which participants were asked: "Should Nina disclose the identities of her parents, siblings, and children, to enable her physician to offer them testing for A1AD?" (fig. 1), and "Should the physician tell Nina's brothers and sisters who is ill when offering them testing for A1AD?" (fig. 2). Possible answers were categorized as "definitely no," "perhaps no," "perhaps yes," or "definitely yes." Furthermore, respondents were asked to select a maximum of 3 of 11 statements related to the question, "Do you think that Nina's sister should be informed about her risk of A1AD?" (the 11 statements are shown in fig. 3).

### Study Population

The questionnaire was sent to 2,146 subjects belonging to 6 groups: (1) the "control" group: individuals randomly selected from the Danish population through the National Register of Danish citizens; (2) the "M" group: piM relatives identified by family screening; (3) the "MZ" group: piMZ relatives identified by family screening; (4) the "no type" group: nonexamined relatives with  $>1\%$  risk of piZ, who had not answered at least one written inquiry from the register; (5) the "Z-screened" group: piZ relatives identified by family screening; and (6) the "Z-proband" group: piZ probands diagnosed because of lung symptoms.

For all piM and piMZ subjects, the phenotypes were determined by isoelectric focusing (Buist 1990). For the piZ subjects, phenotype was determined by isoelectric focusing or by  $\alpha_1$ -antitrypsin blood level  $<11 \mu\text{mol/l}$ . When possible, 400 subjects with known addresses were



**Figure 1** Responses to the question, Should Nina disclose the identities of her parents, siblings, and children, to enable her physician to offer them testing for A1AD? \**P* < .01, \*\**P* < .005.

randomly drawn from each group in the register. For groups of <400 individuals, the questionnaire was sent to all subjects in the group (i.e., the Z-screened, Z-proband, and no-type groups).

The questionnaire was sent by mail in July 1996, and reminders were sent to nonresponders after 2 and 4 months. Questionnaires were answered and analyzed anonymously. Table 1 gives demographic data and re-

sponse rates for the different groups. The apparently higher number of persons with children in the M, Z-screened, and Z-proband groups was not significant after adjustment by logistic regression for the older age in these groups.

*Statistical Analysis*

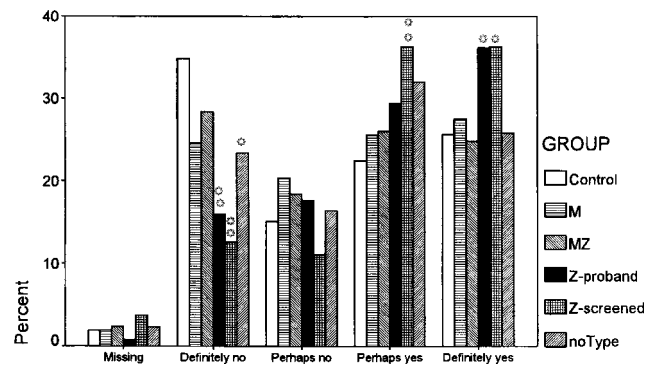
For each group, the response to each question was compared with the control group by univariate analysis. One-tailed *P* values were computed by Fisher’s exact test, and *P* values <.01 were judged significant.

To analyze whether responses were related to factors pertaining to the respondents’ personal backgrounds, we performed multivariate analysis with phenotype/group and demographic data as independent variables and with attitude responses as dependent variables in a stepwise logistic regression model (backward likelihood ratio logistic regression model, in the computer program SPSS 6.1 1993).

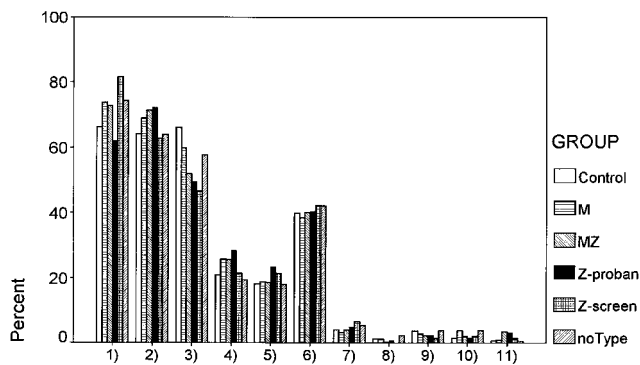
**Results**

The questionnaire was returned by 1,761 individuals (82%), of whom 1,609 (75%) agreed to participate and completed the questionnaire. Figure 1 shows that, in total, only 2.8% (44 subjects) objected to informing the physician about their children’s identity, and most belonged to the control group (24 of 44 who answered “definitely no” or “perhaps no” to the question). Regarding parents and siblings, a few more respondents objected to informing the physician—namely, 9.1% and 6.7%, respectively. Again the control group dominated: 82 of 146 objected with respect to parents, and 61 of 107 objected with respect to siblings.

Forty-three percent, 43%, and 35% felt that the physician ought to get consent from the proband before



**Figure 2** Responses to the question, Should the physician tell Nina’s brothers and sisters who is ill when offering them testing for A1AD? \**P* < .01, \*\**P* < .005.



**Figure 3** Respondents were asked to select a maximum of 3 of 11 statements relating to the question, Do you think that Nina’s sister should be told about her risk for A1AD? The precise wording of possible answers were (1) Yes, because the sister is herself at risk of having A1AD, (2) Yes, because the sister’s children are at risk of having A1AD, (3) Yes, because the lung disease can be prevented, (4) Yes, to maintain openness in the family, (5) Yes, to escape uncertainty, (6) Yes, to enable the sister to decide on her own whether she wants testing, (7) Yes, but only if the sister smokes, (8) No, one cannot stop smoking anyway, (9) No, I don’t want to force information on her, which she may not want, (10) No, because she may encounter problems when taking out life insurance, and (11) Other (please write): \_\_\_\_\_ . \*P < .01, \*\*P < .005.

approaching parents, children, and siblings, respectively. In the control group, 52% felt that consent was necessary before parents were approached, compared with 26%–42% in the other groups. In all, 54.8%—and significantly more among the Z-screened (75.4%) and Z-proband (66.1%) groups—agreed that the physician ought to disclose who is ill when offering testing to a sister (fig. 2).

Figure 3 shows reasons for informing or not informing Nina’s sister. In all, 1.5% gave only “no” responses, 3.3% gave both “no” and “yes” responses, 93.0% gave only “yes” responses, and 2.2% did not select any of these responses. In all, 58% selected “yes, because the lung disease can be prevented,” highest in the no-type group (66%) and lowest in the piZ groups (48%). In all, 35% chose “yes, to keep openness in the family” and/or “yes, to escape uncertainty,” highest for the Z-proband group (41%) and lowest for the no-type group (29%).

The stepwise logistic regression analysis showed that the phenotype/group of the respondents was significantly related ( $P < .05$ ) to their attitudes about disclosure of the identity of parents and siblings. Sex of respondents was shown to be significantly related to disclosure of the identity of siblings. This means that tested relatives M, MZ, and Z-screened were those for whom most respondents approved the disclosure of the parents’ and

siblings’ identities to the physician. Furthermore, women were less prone to disclose the identity of siblings.

**Discussion**

In all study groups there was a strong consensus that the proband ought to disclose the identity of parents (fig. 1a), siblings (fig. 1b), and especially children (fig. 1c), to enable the physician to offer them examination for A1AD. The results indicate that the genetic counselor should actively try to ensure that relatives are approached and informed about the known risk of a severe genetic disorder, such as A1AD, in which disability can be prevented by a change of lifestyle (e.g., smoking cessation) or by careful management. This is in line with results from tests for other genetic diseases with modifiable outcome (Bratt et al. 1997; Andersen et al. 1998).

Differences in attitude between patients (Z-probands), their relatives (with or without the disorder), and the control group were modest for most questions, although statistically significant for some. For all questions, the control group was most hesitant to disclose the identities of relatives to the physician and to inform relatives about their risk for A1AD.

The results suggest that attitudes about transmission of genetic information reflect individual experience and self-knowledge and that these attitudes vary, depending on whether the respondent is the ill proband, the proband’s parent, the proband’s descendant, or someone who has never heard of A1AD. With this in mind, these various groups will be discussed separately.

Among probands, 71% of piZ (Z-screened and Z-proband) respondents thought that the physician ought to tell the relatives who was ill (fig. 2). This was highly confidential information about themselves and their disease. This lack of concern about one’s own right to privacy (Wilcke 1998) may be explained by the need of sick persons for support from family and friends. Qualitative studies of hereditary intestinal cancer (Michie et al. 1996) and A1AD (the interview part of the present study) suggested that, to achieve such family support, it is crucial to maintain openness about the disease in the family and to avoid obfuscation, myths, and uncertainty among relatives. In agreement with this, 41% of the probands in the present study selected openness and avoidance of uncertainty (fig. 3) as important reasons to inform a sister. Information about personal disease is usually considered highly confidential, and this was reflected in the attitudes of the “less experienced,” when far fewer in the control group (55% compared with 75% in the Z-screened group) approved physician disclosure of who was ill (fig. 2).

Among probands, 80%–92% definitely approved disclosure of children’s and siblings’ identities (fig. 1). The

**Table 1****Baseline Demographic Characteristics**

Characteristic of Subgroup	Control (n = 847)	piM (n = 400)	piMZ (n = 400)	piZ-screened (n = 165)	piZ-proband (n = 133)	No Type (n = 201)	Total (n = 2,146)
No. of men (%)	424 (50%)	172 (43%)	194 (48%)	77 (47%)	76 (57%)	125 (62%)	1,068 (50%)
Age in years (mean ± SD)	43.9 ± 15	44.3 ± 14	43.1 ± 14	48.3 ± 13	49.6 ± 10	46.7 ± 12	44.8 ± 14
Respondents (%):							
Full response	577 (68.1%)	309 (77.3%)	341 (85.3%)	135 (81.8%)	119 (89.5%)	128 (63.7%)	1,609 (75%)
Chose not to participate	82 (9.7%)	22 (5.5%)	18 (4.5)	6 (3.6%)	4 (3.0%)	6 (3.0%)	152 (7.1%)
School education (%):							
Attending school	1	1	1	...	...	1	
Attended school:							
>7 years	19	21	21	25	36**	26	
8-9 years	18	20	18	21	21	20	
>9 years	58	53	27	50	39*	49	
Other	4	6	3	4	4	3	
Employment (%):							
Employed	65	71	71	53	29**	73	
Retired	18	17	15	37**	60**	12	
Unemployed	5	3	7	5	3	8	
Student	7	4	4	3	2	4	
Other	5	5	3	3	3	2	
Living (%):							
Alone	15	14	17	22	19	13	
With wife/husband/partner	70	75	72	70	71	79	
With children	5	7	8	6	7	6	
With siblings	1	...	1	...	...	1	
Other	8	4*	2**	2*	4	2*	
Has children (%):							
No	30	20**	27	19**	19*	20	
Yes	70	80**	73	81**	81*	80	
Smoking status (%):							
Smoke daily	33	35	35	7**	8**	48*	
Smoke, not daily	9	5	6	5	2*	2*	
Stopped ≤2 years ago	1	2	4	8**	2	2	
Stopped >2 years ago	22	26	18	53**	71**	20	
Never smoked	35	33	37	28	18**	28	
Self-reported health status (%):							
Very good	42	45	45	25**	8**	38	
Good	38	36	36	27*	15**	45	
OK	17	17	16	28*	40**	17	
Bad	3	1	3	11**	25**	...	
Very bad	0	1	...	8**	12**	...	
Meets family (%):							
Daily	22	22	15*	20	16	14	
1-2 × /week	36	40	49**	33	36	31	
1-2 × /mo	33	32	29	33	34	45	
Less often	8	7	7	13	11	11	
Never	0	0	0	1	3	...	
Meets friends (%):							
Daily	23	17	19	18	9**	16	
1-2 × /week	38	40	40	41	42	39	
1-2 × /mo	33	37	35	33	38	39	
Less often	5	5	6	7	12	6	
Never	0	0	0	1	0	0	

NOTE.—Fisher's exact test, with control group as reference. \* $P < .01$ , \*\* $P < .005$ .

proband were more moderate with respect to disclosure of parents' identities. This reluctance toward parents was also found in the interview part of the study (data not shown), and reasons given by the interviewees were that parents must be piMZ (at least if they were healthy and

smokers) and that they were older and had less opportunity to change a possible course of disease—or, as one respondent put it, "It's too late anyway." Another reason may be that affected persons want to save their parents from possible feelings of guilt about passing on the

A1AD gene to their children. Some interviewees emphasized that parents ought sometimes to know, both to avoid uncertainty as to what might be wrong with their children and to maintain openness within the family. This indicates that the consequences of informing parents compared with other relatives differ, and this suggests that it may be reasonable to leave the informing of parents to be handled as an internal family matter. The difference in attitude toward parents, siblings, and children has also been found in studies of hereditary cancer (Bratt et al. 1997).

A substantial number (35%–43%) of respondents found that the physician ought to get consent from the proband before approaching relatives. Consent seemed especially necessary before parents are approached (43% overall and 52% in the control group). However, the majority in the affected groups (i.e., M, MZ, Z-screened, Z-proband, and no-type groups) felt that the proband's consent remained irrelevant, even after correction for those responding "no" to the "disclose information" and "get proband's consent" questions. In an American study of first-degree relatives of women with breast/ovarian cancer, 56%–57% felt that the proband's consent should be required for the immediate family to receive similar risk information (Benkendorf et al. 1997). These moderate differences between studies may be explained by the different options to escape disease in A1AD and breast/ovarian cancer (i.e., avoid smoking vs. mastectomy/ovariectomy) and by cultural and educational differences between respondents, as shown by Benkendorf et al. (1997).

In this context, it may be mentioned that Denmark is situated in the northern part of western Europe and that the Danish state health insurance is based on the European health care model, which strives for equal access to health services for all. Health insurance is compulsory, is paid through taxes, and offers free health care to all, irrespective of risks, faults, employment, and economic and social status. In general, the Danish medical practice is nonpaternalistic. The interview parts of the present A1AD study and other studies (Thomsen et al. 1993) show that Danes expect to be involved in decision making and expect full information from the physician, to enable them to decide on their own.

*Relatives at risk* often have the role of observer and/or helper in families affected by chronic disease (Bury 1988; Robinson 1988). Several studies have shown that it is a huge strain to witness very close relatives, especially parents, suffering from a chronic disease and becoming more and more disabled (Turk 1979; Strauss et al. 1984). It has also been shown (e.g., for family members of patients with Huntington disease) that it is often a great relief to undergo genetic testing and so obtain knowledge about one's own risk (Tibben et al. 1993). The Huntington disease test result itself, whether favor-

able or not, does indeed increase the sense of control over the future. Thus, merely getting an answer, whether bad or good, increased the wellbeing of persons at risk of Huntington disease, compared with persons who did not undergo the predictive test (Hayes 1992; Wiggins et al. 1992). Surprisingly, it was also found that both favorable (Bloch et al. 1992) and unfavorable results caused personal and family dislocation, especially for those who had made irreversible decisions, such as not having children and running up large debts, on the basis of their belief that they would develop Huntington disease (Huggins et al. 1992). Other explanations given for adverse reactions among those found not to be carriers were "survivor guilt" and a sudden change in their understanding of themselves and in their relationships with their families and futures. Similar "functional pessimism" was found after a new genetic test indicating an extremely low risk in family members who had undergone bowel screening procedures regularly, for a long time, because of familial adenomatous polyposis (Michie et al. 1996). Long periods of uncertainty causing improper identity and family bonds among individuals with genetic risk can be avoided by facilitating the transmission of genetic risk information within families and by reducing diagnostic delay (Biesecker et al. 1993; Stoller et al. 1994; Michie et al. 1996).

It is rare for close relatives not to know anything at all about each other's serious medical conditions, and often they also know or have heard something when the disease is hereditary. This may create uncertainty and perhaps fear, especially if the knowledge is imprecise and diluted with myth. This may be an important reason to explain why tested relatives (e.g., M-, MZ-, and Z-screened groups) had the highest percentages approving proband's disclosure of the identity of relatives (fig. 1), and, furthermore, why tested relatives were most ready to dispense with the need for the proband's consent for approaching relatives. In fact, relatives approved disclosure of their own identity so that they could be informed about their genetic risk. In the case of A1AD, the majority seemed to prefer to know their risk status and the options for prevention of disease at the cost of a possible violation of their privacy. This is in agreement with preliminary results from studies of breast cancer (Winter et al. 1996) and prostate cancer (Bratt et al. 1997), showing high interest in testing and very few privacy concerns among unaffected family members at risk.

The no-type group of relatives, who had not been tested because they had not responded to the inquiry from the Danish A1AD Register, were almost as skeptical as the control group about disclosure of the identity of relatives (fig. 1). Although small, the between-group differences in attitude toward these three questions on disclosure of identities to health authorities may reflect some selection bias between tested and nontested rela-

tives (fig. 1). It suggests that it was not simply a question of laziness or "laissez faire" that relatives belonging to the no-type group chose not to be tested.

In contrast to the probands, the relatives had the option of avoiding the outbreak of disease, in this case pulmonary insufficiency. The options for prevention of debilitating disease give a person at risk for A1AD such important benefits that there is little reason to suppose that such a person would not want the benefits of knowing the risk of A1AD. Therefore, respect for relatives' right to autonomy (Wilcke 1998) confirms the view that relatives should be informed about A1AD. This was in agreement with the present result, in which as many as 39%–42% (fig. 3) indicated that the proband's sister ought to be informed, to enable her to decide for herself whether she wanted to be tested. By contrast, only 1%–4% indicated that the proband's sister ought not to be informed, because they did not want to expose her to knowledge she might not welcome (fig. 3). That only 1%–4% thought that a sister should not be informed is in agreement with a study on hereditary hypercholesterolemia, in which 3% opposed such disclosure to relatives (Andersen et al. 1998). Still, serious genetic risk information may have a major negative impact (Winter et al. 1996), and the situation in which a proband does not want to inform his or her relatives must be carefully considered, as noted in the ASHG Social Issues Subcommittee on Familial Disclosure statement (1998).

The rather large number of participants and the acceptable response rate make selection bias unlikely. The hypothetical nature of the questions must also be considered, but the responses to the questionnaire and, again, the high response rate indicate that most participants found the questions relevant and understandable.

In the Danish A1AD Register, 428 (85%) of 501 piZ probands have disclosed identity of relatives. The response rate among piZ groups (81%–90%) in the present study is similar or higher, indicating an acceptable response rate among registered piZ subjects without known relatives.

In the letter of introduction, we decided from the beginning not to mention liver disease, the second most common health problem due to A1AD. This decision was made so as not to divert participants' attention from the main issue of the questionnaire study—attitudes toward family testing of the preventable lung disease due to A1AD. Liver disease may lead to death in 1% of newborn piZ persons (Sveger 1988), but, in adulthood, death from liver disease (cirrhosis and carcinoma) is extremely rare (Eriksson et al. 1986). We believe that excluding liver disease from the discussion was necessary and would not affect respondents' attitudes.

In conclusion, the present data indicate that the genetic counselor ought to ensure that relatives are properly informed about their risk of a severe genetic dis-

order, such as A1AD, where disability can be prevented by a change of lifestyle or by careful management. Responses to the present questionnaire indicated some ambivalence even in affected families, and, consequently, the physician must exercise a good deal of flexibility and responsiveness to individual circumstances when asking for relatives' identity and when approaching relatives. The findings also indicate that openness in affected families is an important goal; this means that, in most cases, full information to all relatives about the disorder and about who is ill seem essential for successful genetic counseling.

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