

# Psychological Impact of Predictive Genetic Testing for Inherited Alzheimer Disease and Frontotemporal Dementia

## The IT-DIAfN Protocol

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**Aim:** Our aim was to evaluate the psychological impact of predictive genetic testing in individuals at-risk for inherited dementia who underwent a structured counseling and testing protocol.

**Methods:** Participants were healthy at-risk relatives from families with at least one affected patient, in whom a disease-associated genetic variant had been ascertained. A comprehensive psychological assessment (personality, anxiety and depression, quality of

life, coping strategies, resilience and health-related beliefs) was administered at baseline, at 6 months and 12 months follow-up.

**Results:** Twenty-four participants from 13 families were included. Sixteen participants underwent blood sampling and genetic analysis; 6 resulted to be carriers of pathogenic variants (1 in *PSEN1*, 1 in *PSEN2*, 4 in *GRN*). Carriers showed higher score on the Resilience Scale for Adults (RSA) – social competence, and on Multidimensional Health Locus of Control – internal, than noncarriers ( $P=0.03$  for both). Ten at-risk relatives who completed the follow-up showed improvement in RSA – planned future ( $P=0.01$ ) with respect to baseline.

**Discussion:** Our case series showed that at-risk individuals undergoing predictive testing showed benefit on personal life and no detrimental impact on a broad range of psychological outcomes. Higher social skills and lower internal health locus of control in carriers may be an early psychological correlate of preclinical dementia.

**Key Words:** Alzheimer disease, frontotemporal dementia, genetic counseling, genetic testing, psychological outcomes

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Over the last decades, several genes have been identified in inherited dementia, namely *PSEN1*, *PSEN2*, and *APP* in autosomal dominant Alzheimer disease (AD),<sup>1</sup> and *MAPT*, *GRN*, and *C9orf72* in frontotemporal dementia (FTD).<sup>2</sup> Once a gene variant that is causal of AD or FTD is identified in a family, relatives may decide to undergo predictive genetic testing to determine whether they are at-risk of developing the manifest disease. This opportunity should be carefully evaluated because of the ethical, social and psychological implications that could follow the knowledge of the state of risk.<sup>3</sup> Although several concerns were raised about the risk of unfavorable psychological reactions, research studies demonstrated that the use of a standardized genetic counseling protocol minimizes negative responses.<sup>4</sup> This observation was reported also in a few studies involving small series of families with AD and FTD.<sup>5,6</sup>

The current guidelines on genetic counseling and testing for AD and FTD<sup>7</sup> were mainly based on the large body of evidence produced during the decades of experience with Huntington disease (HD). These guidelines recommend a consultation with a psychologist or psychiatrist in case of presymptomatic testing, but there was no indication about psychological domains that should be assessed. Longitudinal studies examining the psychological impact of predictive testing in hereditary neurodegenerative diseases focused on the psychological constructs of anxiety, depression, distress, wellbeing, and general health.<sup>8,9</sup>

Furthermore, there are psychological components that have not been included as clinical outcome measures in the predictive testing literature. These include, but are not limited to, illness perception, self-esteem, resilience, and coping strategies.<sup>8</sup> Psychological outcomes related to the course of life, decisions in a family, and future planning were equally important, but scarcely addressed.<sup>10</sup> Gaining insight into the full psychological characteristics that can influence the decision to undergo the predictive genetic analysis and impact the outcome of testing is of utmost importance to implement the procedure in clinical practice. This need becomes even more critical with recent diffusion of next-generation sequencing in neurology clinics.<sup>11</sup>

In Italy, within the Italian Dominantly Inherited Alzheimer and Frontotemporal Network (IT-DIAfN) project, a network of research centers with expertise in hereditary dementia developed a consensus protocol for genetic counseling and testing of affected individuals and healthy at-risk relatives with familial AD or FTD.<sup>12</sup> Local protocols were surveyed and harmonized across the Italian participating centers, referring to the current guidelines on genetic counseling and testing for late-onset neurodegenerative diseases. A multidisciplinary team of health professionals – a geneticist, a neurologist or geriatrician with a consolidated background in neurodegenerative disease, and a psychologist or psychiatrist with expertise in counseling – provided care at all stages of the protocol in order to facilitate fully informed and autonomous decision making.<sup>7</sup> The IT-DIAfN protocol was implemented within a research framework in centers participating in the IT-DIAfN network, showing that the procedure was feasible and safe in terms of occurrence of catastrophic events.<sup>13</sup>

The aim of this study is to investigate the psychological impact of predictive genetic testing in healthy at-risk relatives, based on data collected with a comprehensive psychological assessment.

## METHODS

Eligible individuals were healthy at-risk relatives of patients carrying a known pathogenetic variant for AD or FTD. Families with inherited dementia had been selected from a clinical series of consecutive patients admitted to two IT-DIAfN centers (IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy, in collaboration with Briolini Hospital of Gazzaniga, Bergamo, Italy, and IRCCS Fondazione Istituto Neurologico Carlo Besta, Milan, Italy). The results from the series of affected individuals were previously reported.<sup>13</sup>

We included thirteen families (6 AD and 7 FTD) with a known pathogenetic mutation, namely: 3 in *PSEN1* (M233T, G184G, L392V); 2 in *PSEN2* (M239I); 1 in *MAPT* (P301L); 7 in *GRN* (6 T272fs, 1 C157fs). We estimated from pedigrees that 56 first-degree relatives at 50% risk were potentially eligible for the IT-DIAfN protocol. Eighteen were siblings, 37 adult children, and 1 child under the age of 18. Twenty-four of these 56 at-risk relatives asked for predictive genetic testing and were enrolled from November 2014 to March 2019. A written informed consent was obtained from all participants.

The IT-DIAfN protocol was described in detail elsewhere.<sup>12,13</sup> Briefly, the counseling protocol for healthy at-risk relatives consisted of: (i) at least 2 pretest consultations, including the psychological assessment; (ii) blood sampling; (iii) disclosure of the genetic test result; (iv) follow-up. Participants were offered follow-up visits, including psychological assessment, at 1 (T1), 6 (T6) and 12 months (T12) from the disclosure of the genetic test result. According to the current guidelines<sup>3</sup> and to the IT-DIAfN protocol,<sup>7,13</sup> the

multidisciplinary team comprised a geneticist and a psychologist or psychiatrist with expertise in counseling, and a neurologist or geriatrician with expertise in neurodegenerative diseases. Figure 1 shows the flow of the genetic counseling and testing procedure.

Psychological assessment included scales of personality traits, anxious symptoms, depressive symptoms with evaluation of past or present suicidal thoughts or attitudes (Beck Depression Inventory – BDI<sup>14</sup>; Hamilton Depression Rating Scale – HDRS<sup>15</sup>), quality of life (12-Item Short Form Health Survey – SF-12<sup>16</sup>; World Health Organization Quality of Life-short version<sup>17</sup>), coping strategies, resilience (Resilience Scale for Adults – RSA)<sup>18</sup> and health-related beliefs (Multidimensional Health Locus of Control – MHLOC scale).<sup>19</sup> All the scales were self-administered, except HDRS. Details on the protocol are available as supplementary methods (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>).

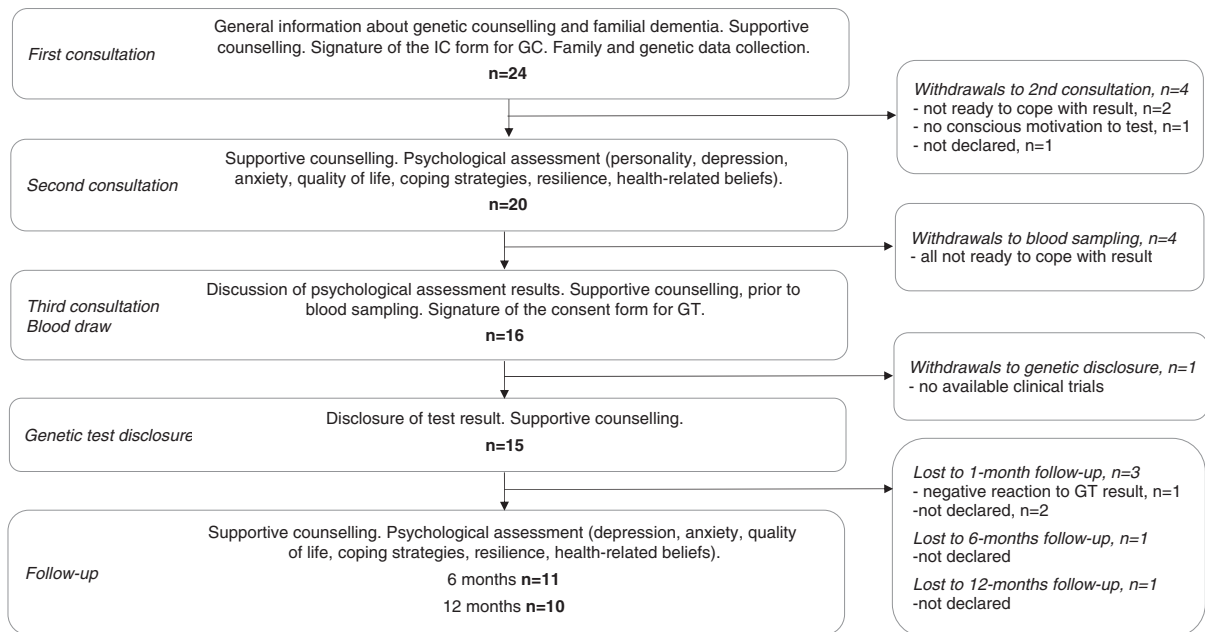
Years to expected disease onset (YEO) was computed as the difference between age of at-risk relatives at first consultation and mean age of symptoms onset for the disease-associated genetic variant identified in the family. For the *PSEN1* M233T and *PSEN2* M239I mutations we used the mean age at onset reported by Ryman<sup>20</sup> (33.7 and 50.7 y, respectively), and for the *MAPT* P301L, *GRN* T272fs and *GRN* C157fs, those reported by Morris<sup>21</sup> (53.0, 62.7, and 58.4 y, respectively). For the *PSEN1* G184G genetic mutation, the mean age of onset (47.7 y) was computed from literature.<sup>22–24</sup> For the *PSEN1* L392V genetic mutation, we did not find pertinent information in the literature and estimated age at onset (44.0 y) from data kindly provided by the Dominantly Inherited Alzheimer Network (DIAN) Expanded Registry of the Washington University in Saint Louis (personal communication).

Genetic analyses included only the relevant variant identified in the affected family member and were performed by using standard Sanger sequencing.

Statistical analysis was performed using the Statistical Software SPSS 25.0. *P*-values <0.05 were considered significant, with no correction for multiple testing according to the exploratory design of the study. Education was collected as a categorical variable: middle (secondary school graduate), high (high school graduate), and university. For 1 at-risk relative, the information about education was not provided (annotated as missing data). Data on 20 at-risk relatives who underwent psychological assessment at baseline were analyzed. We defined different group comparisons based on: (i) genetic disclosure (disclosed vs. not disclosed); (ii) genetic status (carriers vs. noncarriers); (iii) T12 follow-up (completed vs. not completed); (iv) YEO (first tertile vs. second and third tertile). Differences in sociodemographic and psychological features between groups were tested using Mann-Whitney test for continuous variables and  $\chi^2$  test for categorical variables. For psychological features, we used a series of analyses of covariance using age, education and diagnosis as covariates. Differences in psychological scales between baseline and T6 and between baseline and T12 were evaluated using the Wilcoxon test.

## RESULTS

The 24 at-risk relatives enrolled in the IT-DIAfN protocol were middle-aged (mean age  $39.2 \pm 11.7$  y, age range: 19 to 69), more frequently female (63%), and high educated (83% were high school or university graduates). The family diagnosis was equally distributed among



**FIGURE 1.** Flow of the genetic counselling (GC) and genetic testing (GT) process.

participants (46% AD and 54% FTD). Twelve individuals (50%) were married.

Four participants left the protocol after the first consultation, 2 of them feeling not ready to cope with a potential unfavorable genetic test result, one not having a conscious motivation to test, and 1 without any motivation (withdrawals to second consultation). Five participants left the protocol after the second consultation, because of the inability to cope with the potential emotional impact of an unfavorable genetic test result ( $n = 4$ ) (withdrawals to blood

sampling), and unavailability of clinical trials with experimental drugs ( $n = 1$ ) (withdrawal to disclosure) (Fig. 1).

The comparison between 15 at-risk individuals who chose to receive the disclosure and 5 who did not (4 withdrawals to blood sampling and 1 withdrawal to genetic disclosure – Fig. 1) showed that the latter was less educated (middle, high, university graduates: 7%, 29%, 64% vs. 20%, 80%, 0%, respectively,  $P < 0.05$ ). Participants who chose to know their genetic status showed lower scores on the physical domain of the SF-12 ( $51.9 \pm 7$  vs.  $57.6 \pm 2.6$ , respectively,  $P < 0.05$ ), but the difference was no longer significant after adjustment for age and education ( $P = 0.11$ ). Supplementary Table 1, <http://links.lww.com/WAD/A380> reports the full sociodemographic and psychological data comparisons (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>).

Table 1 shows that the at-risk subjects closest to the expected disease onset ( $YEO \leq 4$ ;  $n = 7$ ) were all from AD families, while the remaining ( $YEO \geq 5$ ;  $n = 13$ ) were mainly from FTD ( $P < 0.001$ ). As expected by definition, age significantly differed between groups ( $P < 0.05$ ). Participants with 4 or less YEO showed higher scores on the WHOQOL-environmental health and MHLOC-powerful other scales with respect to those with  $YEO \geq 5$  ( $73.1 \pm 14.3$  vs.  $60.1 \pm 12.6$ , and  $22.7 \pm 2.1$  vs.  $19.5 \pm 2.5$ , respectively,  $P < 0.05$ ), but the difference remained significant after adjustment only for the MHLOC-powerful other scale ( $P = 0.23$  and  $< 0.05$ , respectively). Supplementary Table 2, <http://links.lww.com/WAD/A380> reports all psychological data comparisons (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>).

Sixteen participants underwent blood sampling and genetic analysis; six were carriers of pathogenic variants (1 in *PSEN1*, 1 in *PSEN2*, 4 in *GRN*). Sociodemographics were similar between carriers and noncarriers (Table 2). Carriers showed higher scores on social competence dimension of the RSA ( $P < 0.01$ ) and near significant lower scores on the internal MHLOC scale ( $P = 0.056$ ) than non-carriers. Both the  $P$ -values resulted significant after

**TABLE 1.** Sociodemographic and Psychological Features of 20 Healthy at-risk Relatives (see “Second Consultation” Box in Fig. 1) Included in IT-DIAfN Protocol by Years to Expected Disease Onset at Baseline

	Years to Expected Disease Onset		<i>P</i> *
	$\leq 4$ , $n = 7$	5–23, $n = 13$	
<b>Sociodemographics</b>			
Age (y)	$48.0 \pm 12.4$	$35.8 \pm 10.4$	0.019
Sex (female), <i>n</i> (%)	4 (57)	4 (31)	0.251
<b>Education, <i>n</i> (%)</b>			
Middle	1 (14)	1/12 (8)	
High	2 (29)	6/12 (50)	
University	4 (57)	5/12 (42)	0.652
<b>Family diagnosis, <i>n</i> (%)</b>			
Alzheimer disease	7 (100)	2 (15)	
Frontotemporal dementia	0	11 (85)	$< 0.001$
<b>Psychological scales</b>			
<b>Health-related beliefs</b>			
MHLOC-powerful others	$22.7 \pm 2.1$	$19.5 \pm 2.5$	0.041

\* $\chi^2$  or Mann-Whitney test for sociodemographics. Age-adjusted and diagnosis-adjusted analysis of covariance for psychological scales: only significant results were shown.

IT-DIAfN indicates Italian Dominantly Inherited Alzheimer and Frontotemporal Network; MHLOC, multidimensional health locus of control.

**TABLE 2.** Sociodemographic and Psychological Features of 16 Healthy at-risk Relatives (see “Third Consultation/Blood Draw” Box in Fig. 1) Included in IT-DIAfN Protocol by Genetic Status at Baseline

	Genetic Status		P*
	Carriers, n = 6	Noncarriers, n = 10	
Sociodemographics			
Age (y)	41.8 ± 9.9	40.1 ± 9.6	0.635
Sex (female), n (%)	4 (67)	6 (60)	0.790
Education, n (%)			
Middle	1 (17)	0/9 (0)	
High	1 (17)	4/9 (44)	
University	4 (66)	5/9 (56)	0.300
Psychological scales			
Resilience			
RSA – social competence	26.8 ± 2.9	21.3 ± 3.6	0.032
Health-related beliefs			
MHLOC – internal	22.7 ± 2.7	26.1 ± 2.3	0.033

\* $\chi^2$  test or Mann-Whitney test for sociodemographics; age-adjusted and education-adjusted analysis of covariance for psychological scales: only significant results were shown.

IT-DIAfN indicates Italian Dominantly Inherited Alzheimer and Frontotemporal Network; MHLOC, multidimensional health locus of control; RSA, resilience scale for adults.

age-adjustment and education-adjustment ( $P < 0.05$ ) (Table 2). No other significant difference in psychological scales were found. Supplementary Table 3, <http://links.lww.com/WAD/A380> reports the full data comparisons (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>).

Of the 15 at-risk individuals who chose to undergo the genetic disclosure, 10 continued the protocol until T12 and 5 withdrew before T12. Sociodemographics did not differ between the 2 groups. Two of 10 (20%) who completed the T12 were carriers of a pathogenic variant, versus 3 of 5 (60%) who were lost to follow-up ( $P = 0.17$ ).

Participants who completed T12 showed significant improvement in planned future dimension of the RSA ( $P < 0.05$ ) and marginally significant improvement in HDRS score ( $P = 0.051$ ) (Fig. 2). Supplementary Fig. 1, <http://links.lww.com/WAD/A380> reports the diagram for raw data (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>). Supplementary Figure 2, <http://links.lww.com/WAD/A380> shows that no other significant psychological differences were

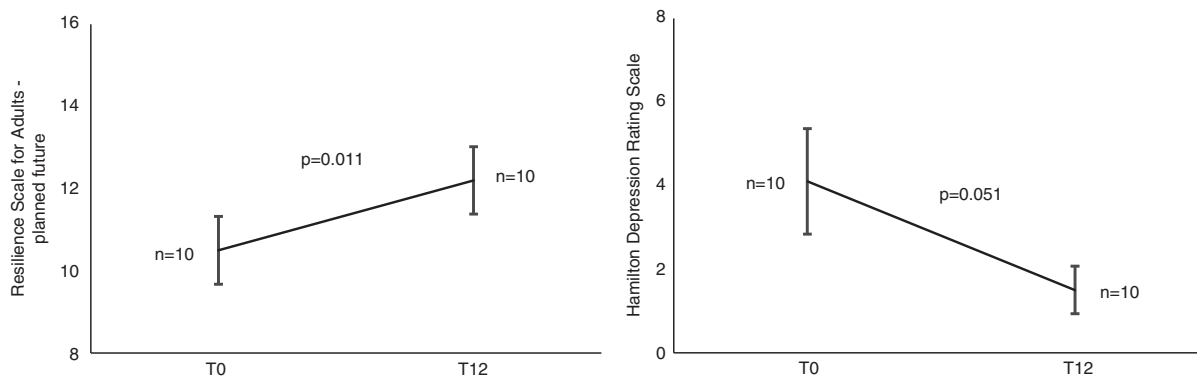
found between T12 and the baseline (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>). Of note, depressive symptoms measured by the BDI scale did not improve at T12 relative to the baseline. No significant psychological differences were found between T6 and T0.

Among those who did not complete the follow-up plan, 3 (2 carriers and 1 noncarrier) were lost to T1; 1 carrier stated to be unable to cope with the genetic test result (7%), 2 (1 carrier and 1 noncarrier) did not provide any motivation (14%). One carrier was lost to T6 and one noncarrier was lost to T12, because of undeclared reasons (Fig. 1). Participants who withdrew at any stage showed significantly higher scores on the social competence domain of the RSA scale with respect to those who completed until T12 ( $26.5 \pm 2.6$  vs.  $21.8 \pm 4.0$ ,  $P < 0.05$  after adjustment for age and education). Supplementary Table 4, <http://links.lww.com/WAD/A380> reports the full sociodemographic and psychological data comparisons (Supplemental Digital Content 1, <http://links.lww.com/WAD/A380>).

## DISCUSSION

This study describes the psychological outcome of a structured genetic counseling and testing protocol for familial AD and FTD in a small series of at-risk individuals for inherited dementia. We found that at-risk relatives who learned their genetic status had no detrimental psychological impact, while showing improvement in future planning and depressive symptoms at 1-year follow-up. A quantitative scale demonstrated that the awareness of increased risk of inherited dementia is associated with improved future planning. Tibben et al<sup>25</sup> reported similar findings in asymptomatic carriers of HD, who showed qualitative feeling of more control over future and better future planning. A retrospective study in 20 individuals at-risk for familial amyotrophic lateral sclerosis undergoing a semistructured phone interview revealed that some individuals reported positive changes in their lives, and results would inform future planning.<sup>26</sup> Because of the small number of our at-risk relatives who completed the T12 follow-up, and the small number of carriers (2 of 10), we cannot finally test if this result was different between carriers and noncarriers, but the inspection of raw data (supplementary material, <http://links.lww.com/WAD/A380>) suggested that both groups ameliorated.

We found that at-risk relatives who learned their genetic status had fewer depressive symptoms at 1-year follow-up. In HD, longitudinal studies with follow-up until 24 months reported variable results in carriers and



**FIGURE 2.** Significant differences between baseline (T0) and 12 months follow-up (T12) on scales measuring depressive symptoms (HDRS) and resilience (RSA).  $P$  on Wilcoxon test.

noncarriers,<sup>27,28</sup> but a longer (until 10 y) follow-up study reported that carriers became more pessimistic when approaching the age of onset.<sup>29</sup> Of note, we found an improvement when depressive symptoms were evaluated with the HDRS, but not with the BDI. The most relevant difference between the two scales is that the former was clinician-administered, the latter self-administered. For the clinical purpose of the IT-DIAfN protocol, the HDRS was administered in unstructured form, that can reduce test-retest reliability. Moreover, the clinician who administered the scale was not blinded to genetic status of at-risk relatives, leading to a potential bias.

When comparing at-risk relatives who requested genetic disclosure with those who declined, we did not find differences in term of personality characteristics, psychological resources or coping skills. Instead, studies in HD showed that participants who actively sought predictive testing might be more motivated and better equipped to handle adverse emotional reactions,<sup>30</sup> and that non-participants were more pessimistic about their future than participants.<sup>31</sup>

In our series, higher education was associated to greater ability to deal with the process of genetic counseling and testing. No difference in education between applicants and nonapplicants was shown in the first studies on predictive genetic testing in HD.<sup>30,31</sup> Our finding is in line with plenty of studies demonstrating the favorable effect of education on health outcomes, regardless of the disease and health care setting, according to the empirically tested theory of fundamental determinants of health (eg, World Health Organization report<sup>32</sup> and the citations therein).

Our analysis suggested that carriers of a disease-associated variant had lower internal health locus of control (LOC) and more social skills than noncarriers. LOC reflects the extent to which individuals perceived internal or external factors as influencing the outcome of events in their life, specifically health outcomes when the MHLC scale is used. It was demonstrated that older adults who perceive low internal LOC show poor memory performance<sup>33</sup> and that patients with mild cognitive impairment have low internal cognitive control beliefs associated with changes on amygdala connectivity.<sup>34</sup> In our cohort, 4 of 6 individuals were carriers of a genetic variant causing FTD. FTD is characterized by early disturbances in social behavior and alterations in interpersonal interactions, including active searching of social interactions.<sup>35</sup> As functional brain changes start decades before cognitive symptoms in genetically-determined dementias,<sup>36</sup> low internal LOC and high social skills may be interpreted as an early psychological correlate of underlying disease state in individuals with preclinical dementia. Decruyenaere and coworkers evaluated the perceived age at onset of HD in the affected parent, and found that a closer perceived proximity of the HD onset was associated with more depression and anxiety in the test participants.<sup>37</sup> In our clinical series, we found no significant differences in anxiety or depression, but we showed that at-risk individuals who are close to the expected age of onset had high scores on the powerful others-health LOC. These individuals might perceive circumstances outside of their control to have a greater impact on their health than own behaviors, as already shown in progressive chronic diseases.<sup>38</sup> As the MHLOC scale does not allow to identify which event or person the construct refers to, we speculated that trust in the counseling team or in other supporting persons may reflect an adaptive mechanism aimed to provide psychological protection from adverse

reactions. Possible differences in psychological characteristics of asymptomatic at-risk individuals as a function of proximity of the disease onset were not extensively investigated in familial AD and FTD and warrant investigations on larger series.

We found that participants who were lost to follow-up after the genetic test disclosure showed higher social skills than those who completed the protocol until T12. Individuals with higher social competence could be able to activate a network of social contacts after the test disclosure. Alternatively, the difference could be related to the presence of preclinical cases of FTD in the group of lost-to-follow-up. However, we cannot exclude that a less favorable outcome occurred in participants who were lost to follow-up, mainly in carriers. One of 2 carriers who withdrew after genetic disclosure experienced elevated distress, as already reported in FTD cases.<sup>39</sup> The carrier who was lost to T6 did not declare the reason of withdrawal, but feelings associated with intrusion and avoidance were reported at 1-month follow-up. According to the principle of patient autonomy and to the nondirective approach of genetic counseling (Jamal et al<sup>40</sup> for a recent review), we did not attempt to persuade the participant to follow-up, nor were justifications required if the participant declined the invitation to follow-up. In a study of presymptomatic testing for HD, carriers who withdrew after genetic disclosure showed, at the baseline, significantly higher hopelessness, intrusion and avoidance scores and lower psychological wellbeing scores than carriers who completed follow-ups.<sup>29</sup> These findings underline the need for a broad psychological assessment to identify vulnerable individuals and offer the appropriate genetic counseling procedure.

The major limitation of this study stems from the limited clinical sample size, resulting in low power of inferential statistics and limited generalizability of the results. Therefore, we regard to the present investigation as an exploratory study. Moreover, the study did not address potential adverse consequences of predictive testing beyond the individual level, such as social discrimination. This issue should be extensively addressed, starting from the general discussion about genetic discrimination in AD and FTD.<sup>41</sup> The measures of psychological constructs used in this study were not disease-specific for inherited dementia – this limitation was acknowledged also in studies evaluating the psychological impact of genetic testing in HD.<sup>9</sup> Moreover, the specific setting and procedures are expected to influence the psychological impact of the counseling protocol. Since the inception of predictive genetic testing in families with inherited neurodegenerative disorders, it appeared that self-selection is common in different settings and plays an important role in preventing catastrophic consequences of an unfavorable test result, as suggested by the low uptake of predictive testing for HD.<sup>30</sup> This study was designed on the basis of current clinical recommendations for inherited neurodegenerative diseases,<sup>3</sup> and self-selection of participants was an intrinsic source of bias.

Given these limitations, yet some practice implications can be drawn from our experience. Establishing robust predictors of outcome after predictive testing is the main objective of all studies investigating the impact of genetic testing in at-risk individuals. To date, the psychological status at the time of decision to undergo the predictive genetic test is considered the best predictor of post-test distress.<sup>37</sup> The association between high education level and positive attitude toward test disclosure found in

our cohort can be interpreted in line with current knowledge, as education, in turn, is associated with better socioeconomic status and facilitates access to high-quality health care. Nevertheless, education, as well as the background psychological conditions, are pre-existing factors that cannot be modified in clinical interventions such as genetic counseling and testing.

Therefore, we endorse the recommendation to offer predictive genetic testing within a well-structured, extensive counseling protocol. In the absence of actionable predictors of unfavorable outcome, we should rely on genetic counseling as the appropriate framework to assess risk factors, to allow reflection and self-evaluation, and promote informed and autonomous decisions. In other terms, a rapid testing protocol, as well as the direct-to-consumer setting, still appears unsafe. Our preliminary finding that preclinical FTD may influence the attitude of counselees adds a further caveat. Escaping from any risk of reductionism, we keep in mind that genetic testing in inherited dementias is far from solving all uncertainties that at-risk individuals have to cope with.<sup>42</sup> Studies facing this complexity using comprehensive measures of outcomes in large cohorts of at-risk individuals are warranted.<sup>39</sup>

In conclusion, the results of our clinical series of at-risk relatives from families with inherited AD and FTD showed that the decision to undergo a structured protocol of predictive genetic testing was not harmful as measured on a broad range of psychological outcomes, and might be beneficial on life planning and depressive symptoms. However, several uncertainties remain. Larger studies are warranted to confirm these preliminary results and establish recommendations on the most appropriate and effective psychological assessment to be included in best-practice guidelines for genetic testing of inherited AD and FTD.

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