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ORIGINAL RESEARCH

Prospective Evaluation of Predictive DNA Testing for Huntington's Disease in a Large German Center

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Abstract We present a prospective study of counselees seeking predictive testing for Huntington's disease at the Huntington Center North Rhine-Westphalia (Bochum, Germany) between 2010 and 2012. The aim was to observe the decision-making process of at-risk individuals and explore their experiences following the decision as well as the impacts of positive and negative mutation results. Data were collected using two standardized questionnaires as well as via a semi-standardized telephone interview one year after the initial counseling session. Seventy-two individuals participated in at least one of the three phases of the survey, including 31 individuals in the telephone interview. Sociodemographic data were in accordance with previous reports. The process of predictive testing was generally perceived in a positive manner, with almost all interviewees reporting a balanced emotional state one year after initial counseling, regardless of the decision for or against the test. The most important reasons named in favor of or against testing were assembled as well as different aspects regarding the satisfaction with the reached decision. In line with and expanding previous observations on gender-related differences in decision-making, our results suggest that gender-related aspects should be more strongly taken into account in genetic counseling during the predictive testing and counseling processes.

Keywords Huntington's disease · Predictive testing · Genetic counseling · Decision-making · Motivation · Gender differences

Introduction

Huntington's disease (HD; MIM 143100) is a rare autosomal dominant neurodegenerative disorder with a prevalence of 10–13 per 100.000 in Western populations (Bates et al. 2015). The main symptoms include motor disturbances, typically characterized by involuntary movements, cognitive and psychiatric features. Age of onset is mostly between 30 and 50 years of age, with a reported range of 2 to 85 years (Zielonka et al. 2015). HD progressively leads to increasing dependency in daily life and finally to death within 15–20 years after onset. Some therapeutic options are available to relieve symptoms and improve the quality of life, and ongoing trials currently explore new strategies for slowing disease progression (Shannon and Fraint 2015; Wild and Tabrizi 2014). However, so far there is no cure for HD.

HD is caused by an expanded CAG repeat block in the first exon of the *HTT* gene (MIM 613004) on the short arm of chromosome 4. (The Huntington's Disease Collaborative Research Group 1993). CAG repeat lengths of 40 or more are fully penetrant, whereas repeat lengths between 36 and 39 exert variable penetrance (Bates et al. 2015). Expanded alleles as well as intermediate alleles in the range between 27 and 35 CAG trinucleotides are unstable and prone to

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expand (mainly) during male meiosis (Trottier et al. 1994). Patients with symptoms of HD can undergo diagnostic testing (DT), and identification of an expanded *HTT* allele (≥36 repeats) confirms the diagnosis. Individuals who are at risk of being carrier for such an expansion due to their family history, but do not show symptoms of the disease, on the other hand, may undergo predictive testing (PT), possible via direct DNA analysis since 1993 (The Huntington's Disease Collaborative Research Group 1993). This test result is virtually 100% accurate in detecting mutation carriers, yet prediction of disease onset and severity is not possible. Interestingly, the overall request for PT turned out to be substantially less frequent than originally expected, with rates between 10 and 20% of all at-risk individuals in various studies (Paulsen et al. 2013).

PT can provide pivotal information for decision-making such as family planning, and it resolves uncertainty, but is also associated with substantial social and psychological challenges. Therefore, an international protocol for PT including several pre-test sessions was developed (Tibben 2007) as recommended by the guidelines (International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea 1994), which are regularly revised according to recent research results (MacLeod et al. 2013). The protocol aims to support and protect at-risk individuals and their families. The proposed minimum age for PT is 18 years (which is also the age of legal responsibility in Germany), but genetic counseling without testing may be performed for minors (MacLeod et al. 2013). In our center, PT for HD consists of at least three sessions with a geneticist and one additional session with a psychiatrist/ psychologist/ psychotherapist as has been described recently (Arning et al. 2015). In the first counseling session the purpose of the visit from the individual's perspective is addressed, a detailed family history taken and a pedigree drawn. Further, detailed information about the disease, its genetic background and the testing process is provided. Additionally, the individual's motivations and possible consequences of a future test are addressed with a focus on the process of decision-making rather than the decision itself (Shiloh 1996). The main aspects of all sessions are subsequently summarized in written form and forwarded as a personal letter to the counselee. If the counselee wants to proceed with PT, a psychiatrist/ psychologist/ psychotherapist visit is arranged in order to evaluate how the counselee would cope with the future information. After a minimum time period of four weeks after initial counseling, a second counseling session and blood draw take place. Thereafter, an additional date for result disclosure can be fixed upon request by the individual at risk. The counselors receive results in a sealed envelope to ensure neutrality in case of a change in decision of the individual at risk. On the day of result disclosure a second blood draw is offered in order to confirm the first result. Additional counseling sessions are possible any time upon request. In Germany, predictive genetic counseling and testing for HD are generally available for at-risk individuals, and all costs are covered by their health insurance. Anonymous testing is possible upon request.

Since decision-making for PT and subsequent coping with the test result are complex issues, several studies have aimed to explain the factors beneath. Family planning is accepted as one of the major reasons to seek PT (Evers-Kiebooms et al. 2002). An Australian study investigated factors related to timing of PT in detail (Trembath et al. 2006). Another large study focused on reasons to withdraw from PT (Wedderburn et al. 2013) and recent studies have aimed to explore the consequences of PT results (Forrest Keenan et al. 2015; Gong et al. 2016). However, these studies mostly consist of either large, retrospective evaluations (Dufrasne et al. 2011; Evers-Kiebooms et al. 2002; Trembath et al. 2006; Wedderburn et al. 2013), including one at our own center (Arning et al. 2015), or of psychological qualitative interviews with very few participants (Forrest Keenan et al. 2015; Gong et al. 2016). Prospective evaluations with regard to decision-making have rarely been performed yet; an Italian study reported avoiding uncertainty about the future as a main motivation for PT and emphasized the importance of pre-PT sessions in decision-making, since a high percentage of participants decided to withdraw from PT (Mandich et al. 1998).

The aim of this study was to prospectively follow the decision-making process of individuals at risk in our center and explore their experiences following the decision as well as the impacts of mutation test results.

Materials and Methods

Study Design

This prospective study was conducted with counselees considering predictive HD testing at the Huntington Center North Rhine-Westphalia in Bochum (Germany) between January 1st 2010 and December 31st 2012. Inclusion criteria comprised a positive family history of HD, age 18 or over and willingness and capacity to give informed consent. Exclusion criteria were obvious signs compatible with the presence of HD, prediagnosed severe depression or other current severe mental illness, inability to give informed consent and poor knowledge of the German language. All participants gave their informed consent. Approval of the Ethics Committee of the Ruhr-University Bochum (Germany) was obtained.

Data were collected through a questionnaire consisting of three parts, designed by a multidisciplinary team of geneticists, neurologists and psychologists. The first part (phase 1) served to obtain sociodemographic data and was filled out by the counselor during or immediately after the initial counseling session. It comprised gender, age, prior risk, length of time the risk had been known, family history and age of onset of

affected relatives as well as level of prior exposure to HD (categorized according to whether the candidate had never observed HD symptoms, been exposed only to early symptoms or observed also advanced stages and/or death of a family member due to HD). The second part (phase 2) was filled out by the counselee at home in the first few weeks following the counseling session in order to obtain detailed information about the decision-making process, attitudes and experiences through multiple-choice, scaled and open-ended questions.

The third part (phase 3) consisted of a telephone interview performed 12–15 months after the initial counseling session by an experienced female psychiatrist according to a semi-structured interview guide. The broad topics included family, partnership, friendship, work environment and insurances. Mainly open-ended questions about possible changes in these aspects of life after counseling and/or PT were used in order to assess the counselees' emotional states and everyday life problems related with HD. Questionnaires (in German language) and data can be obtained by the authors upon request.

Statistical Analysis

Collected data of phases 1 and 2 were analyzed using SPSS 22.0 for simple descriptive statistics, cross tabulations, linear regression and correlation analyses. Descriptive statistics are presented as means and standard deviations (SD) for continuous variables and proportions for categorical variables. The statistical significance for cross tabulations was assessed using t tests for continuous variables and chi-square or Mann-Whitney U tests for descriptive variables. Cut-off value for statistical significance was $p < 0.05$.

The open-ended questions of the telephone interview transcripts (phase 3) were analyzed and presented as categorical variables such as positive and negative responses according to the common themes and key words. Additionally, coefficient and correlation analyses with the data of all three phases were performed in order to establish a predictive model regarding the satisfaction with the decision in favor of PT.

Results

During the 3-year period, a total of 130 individuals sought genetic counseling in our center to get informed about predictive HD testing. Of these, 15 were excluded from the analyses because of pre-diagnosed manifest depression, other psychological issues regarding the survey or poor language skills. Forty-three participants did not give their informed consent for the study. Therefore, 72 individuals (55.4%) were included in our survey and participated in at least one of the three phases. Not all counselees completed all three questionnaires and/or the interviews. The numbers of participants for the three study phases are visualized in Fig. 1.

Phase 1: Sociodemographic Data

Among the 72 participants, 69 (95.8%) gave informed consent for carrying out phase 1 of the survey, and the sociodemographic data of these individuals are summarized in Table 1. The cohort comprised 49 (71%) female and 20 (29%) male participants, with a mean age at initial contact of 33 years (SD = 12.1 years). Most counselees (80%) were married or had a partner, and 76.8% were accompanied by a second person for initial genetic counseling, 36.7% of female and 50% of male participants by their partners. In total, 40.6% of participants had one child or more at the time of initial contact. However, 43.5% of all counselees, regardless of whether they already had children or not, expressed their wish to have children in the future, whereas 15.9% were indecisive about family planning. Among both latter groups, the wish for future children at this time was reported to be dependent on a favorable PT result in 61% of cases. None of the participants (or their partners) was pregnant at the time of genetic counseling.

Most participants (84.1%) had an *à priori* risk of 50%. Among those, more participants with an affected mother (56.9%) than an affected father (31%) sought genetic counseling; however, females with an affected mother tended to refrain more often from testing than males with an affected mother (57.1% vs. 33.3%, respectively). Comparing the age of onset of the parents by univariate analysis of variance (ANOVA) did not show significant differences between groups. Some participants (12.1%) could not directly identify an affected parent, but at least one sibling was affected. The mean age of onset was 47 years (SD = 8.0) among affected parents and 48.5 years (SD = 12.0) among affected siblings. Roughly half of the counselees had exclusively experienced some early psychologic and/or motor symptoms of HD (52.5%) in their relatives, and 42.6% had observed severe illness and/or death of family members with HD. Very few (4.9%) participants reported no prior exposure to HD in their families.

While initially 76.8% of participants had expressed their wish to get tested, only 60.9% finally decided in favor of PT (two thirds female, one third male). Only one of the participants who decided to get tested has not (yet) picked up the test result more than 4 years after the blood draw. Of the other 41 participants, 78% received their result in the company of their partners and the others together with the unaffected parent or a friend. In total, 29 of 41 results (70.7%) harbored normal *HTT* alleles, whereas for 12 (29.3%) counselees an expansion was proven. Further differentiated according to *à priori* risk, all five individuals with a risk of 25% and two thirds with a risk of 50% received a normal result.

The mean number of years that an at-risk individual had known of their own risk before presenting for counseling was 5.3 years (SD = 8.1). Those counselees with 50% *à priori* risk tended to have known their risk for longer time than those with 25% risk or less (5.6 vs. 3.1 years). Additionally, the

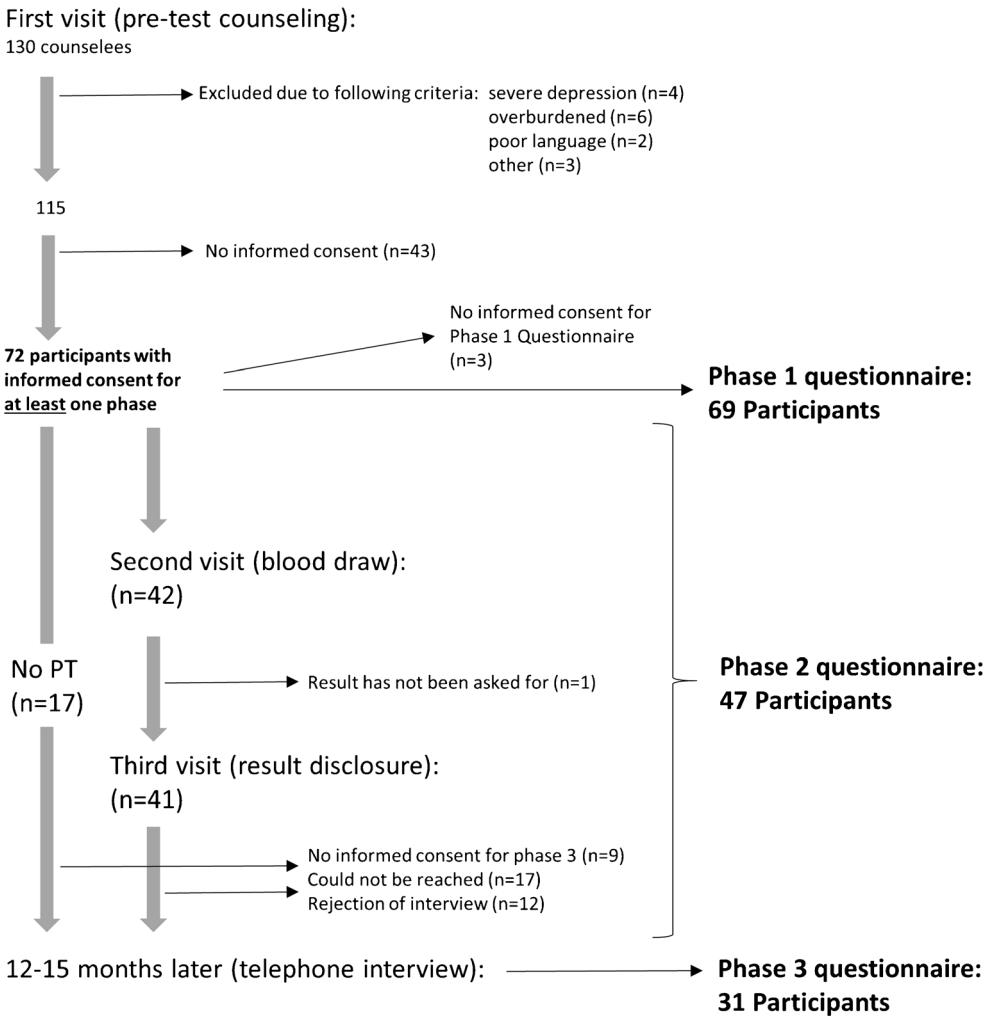

Fig. 1 Flow chart illustrating the design of the prospective study and the numbers of participants in each of the three phases. The numbers of counselees excluded due to different criteria as well as the numbers of participants at each point of contact (bottom, left hand side) and the numbers of participants with available data for each phase (bottom, right hand side) are shown. The data of "second and third visit" or "no PT" is only available for 69 participants who had given their informed consent for phase 1. PT: predictive testing

clients having observed severe illness tended to know their risk longer than those having observed only early symptoms (6.6 vs. 4.5 years). Further, counselees who decided in favor of PT tended to know their risk longer than those who decided against (6.2 vs. 3.7 years, $p = 0.273$). However, among the cases in whom data were available, 50.8% learned of their risk 1 year or less before the initial counseling session. Of those, 60% decided in favor of PT, which corresponds to the overall percentage of tested individuals.

Phase 2: Survey 4–6 weeks after Counseling

Among the 72 participants, a total of 70 gave their informed consent for carrying out phase 2, but only 47 (67.1%) of these returned the survey. For 44 of these 47 participants, sociodemographic data is available. A comparison between responders and non-responders revealed that the majority of those who sent the survey back finally decided in favor of PT, while the majority in the other group decided against PT. This difference is statistically significant and not influenced by gender ($p = 0.03$; Table 2).

When asked about their information sources before genetic counseling, most counselees (93.4%) claimed they informed themselves via the internet, but 46.6% had also been informed by a clinician. Moreover, 53.3% of participants had already had contact with at-risk individuals who had decided in favor of PT, but the majority (60%) denied any influence on their own decision. Most participants also claimed that they did not feel pressured to take the test by their partner or family (means of 4.95 and 5.40, respectively, on a scale from 0 to 6, with 6 representing absence of pressure). However, regarding the influence of the partner we observed a significant difference between males and females (means of 3.53 and 5.89, respectively; $p = 0.003$), suggesting that men feel more pressure from their partners than females. Males also tended to feel more pressure from their family (parents or siblings) compared to females (means of 4.86 and 5.77, respectively; $p = 0.114$). When participants were asked for an individual assessment of their general coping capacity in our questionnaire, though, we got similar results for men and women (means of 2.21 and 2.60, respectively, on a scale from 1 to 6 with 1 representing full coping abilities).

Table 1: Descriptive characteristics of the study sample

	∑	tested	not tested	*p*-value*
∑	69	42	27	-
Age (*n*=69/42/27)[#](mean)	33.0	34.8	30.2	0.125** (n.s.)
Gender (*n*=69/42/27)				
female	49 (71%)	28 (66.7%)	21 (77.8%)	0.321 (n.s.)
male	20 (29%)	14 (33.3%)	6 (22.2%)	
Marital status (*n*=65/39/26)				
single	13 (20%)	5 (12.8%)	8 (30.8%)	0.076 (n.s.)
partnered	52 (80%)	34 (87.2%)	18 (69.2%)	
Children (*n*=69/42/27)				
yes	28 (40.6%)	18 (42.9%)	10 (37%)	0.631 (n.s.)
no	41 (59.4%)	24 (57.1%)	17 (63%)	
Family planning (*n*=69/39/19)				
not finished	30 (43.5%)	21 (53.8%)	9 (47.4%)	0.643 (n.s.)
finished	28 (40.6%)	18 (46.2%)	10 (52.6%)	
undecided	11 (15.9%)			
Family planning is dependent on test result (*n*=41/23/9)				
yes	25 (60.9%)	20 (87%)	5 (55.6%)	(U=-1.901) 0.183 (n.s.)
no	7 (17.1%)	3 (13%)	4 (44.4%)	
undecided	9 (22%)			
Companion present in the first session of genetic counseling (*n*=69/42/27)				
yes	53 (76.8%)	31 (73.8%)	22 (81.5%)	0.461 (n.s.)
no	16 (23.2%)	11 (26.2%)	5 (18.5%)	
Initial wish in favor of PT (*n*=69/39/18)				
yes	53 (76.8%)	39 (100%)	14 (77.8)	(U=-3.026) **0.002**
no	4 (5.8%)	0	4 (22.2%)	
undecided	12 (17.4%)			
À priori risk (*n*=69/42/26)				
50%	58 (84.1%)	37 (88.1%)	21 (80.8%)	0.407 (n.s.)
25%	10 (14.5%)	5 (11.9%)	5 (19.2%)	
other	1 (1.4%)			
Affected parent (*n*=58/32/19)				
mother	33 (56.9%)	17 (53.1%)	16 (84.2%)	(U=-2.224) **0.026**
father	18 (31%)	15 (46.9%)	3 (15.8%)	
not known	7 (12.1%)			
age of onset (mean) (*n*=44)	47.0	47.5	46.2	0.598**
age of diagnosis (mean) (*n*=43)	54.5	54.3	54.8	0.883**
Since how many years is the participant aware of the risk? (mean) (*n*=59/38/21)	5.3	6.2	3.7	0.273** (n.s.)
Siblings (*n*=69/42/27)				
yes	59 (85.5%)	35 (83.3%)	24 (88.9%)	(U=-.635) 0.525 (n.s.)
no	10 (14.5%)	7 (16.7%)	3 (11.1%)	
number of (mean) (*n*=59)	2.49	2.48	2.50	0.982**
Affected siblings (*n*=59/34/24)				
yes	13 (22%)	11 (32.4%)	2 (8.3%)	(U=-2.142) **0.032**
no	45 (76.3%)	23 (67.6%)	22 (91.7%)	
not known	1(1.7%)			
age of onset (mean) (*n*=12)	48.5	47.0	56.5	0.332**
Contact to affected family members (*n*=69/41/27)				
yes	45 (65.2%)	37 (90.2%)	26 (96.3%)	(U=-.929) 0.353 (n.s.)
rarely	18 (26.1%)			
no	5 (7.2%)	4 (9.8%)	1 (3.7%)	

Table 1 (continued)

	∑	tested	not tested	*p*-value*
not known	1 (1.5%)			
Affected people are known (*n*=61/32/26)				
with mild symptoms	32 (52.5%)	19 (59.4%)	13 (50%)	0.475 (n.s.)
with severe symptoms	26 (42.6%)	13 (40.6%)	13 (50%)	
nobody	3 (4.9%)			
Other family members had already genetic counseling (*n*=69/37/27)				
yes	40 (58%)	25 (67.6%)	15 (55.6%)	0.327 (n.s.)
no	24 (34.8%)	12 (32.4%)	12 (44.4%)	
not known	5 (7.2%)			
Other family members were already tested (*n*=69/36/26)				
yes	21 (30.4%)	14 (38.9%)	7 (26.9%)	0.326 (n.s.)
no	41 (59.4%)	22 (61.1%)	19 (73.1%)	
not known	7 (10.2%)			

*Chi-Square or Mann-Whitney U tests used for categorical variables and for differences in proportions unless otherwise indicated by "**".

**Student's *t*-test used for differences between means.

"n" is always shown as numbers of total/tested/not tested individuals.

"n.s.": not significant

PT: predictive testing

Comparing the subjective information level before and after the first counseling session, there is an obvious increase in how much the participants feel informed about HD (means of 2.7 and 1.3, respectively, on a scale from 1 to 6, with 1 representing "very well informed" and 6 representing "badly informed"). Only 9 participants reported the same information level after counseling, while all others felt better informed afterwards.

Most participants (93%) reported that they had already been convinced about their decision for or against PT before the counseling session, and the vast majority (86.5%) did not change this decision afterwards. Nevertheless, 15.2% of those who had initially expressed their wish for PT did not continue the process so far. An impact of the counselor on decision-making was not evident, since 44 of 45 participants expressed that counseling was performed in a non-directive way. Overall, the most important motivations against PT were the fear that the risk for others (e.g. the offspring) would increase after the test and the fear of an unfavorable mutation result, followed by the considered, willful decision "not to know" (Fig. 2b). On the other hand, the most important motivations in deciding for PT were the ability to plan private life and to eliminate uncertainty, followed by the hope to lack the mutation, to sort out the risk for already born children and to be able to plan their professional life/career (Fig. 2a). When asked whom they would inform about their test result, most counselees named their partner (78.5%), followed by their children and their clinician (multiple answers possible).

We also wanted to find out if the participants experienced problems in their life (such as establishing partnerships or friendships, making a career, obtaining bank credits or insurance) as being more difficult than for individuals without a family history of HD. Here, the participants almost uniformly denied special problems concerning these aspects, with an exception of 15% of the clients each for building up partnerships and obtaining insurance. The majority of participants (63.8%) were in the process of making important decisions in their life during the time of genetic counseling, including family planning (34.7%), career decisions (26.1%) or other important life aspects (25.6%, for example building a house, getting married, studying or moving abroad). However, they overall denied a strong effect of the PT result on their decisions. The mean age of participants involved in family planning was 27.7 years. In the age group of ≥28 years, participants tended to express a higher willingness to have children even after an unfavorable result than participants <28 years; however, statistical significance was not reached ($p = 0.096$).

The majority of participants reported that they openly talk about HD in their family; nevertheless, 27.6% reported that

Table 2 Comparison of participants who returned the survey and who did not, stratified by their PT decision and gender

	Survey returned	Survey not returned	
In favor of PT	31 (70.5%)	11 (44%)	$p = 0.03$
Against PT	13 (29.5%)	14 (56%)	(significant)
Female	30 (68.2%)	19 (76%)	$p = 0.491$
Male	14 (31.8%)	6 (24%)	(not significant)
Total	44	25	$n = 69$

PT predictive testing

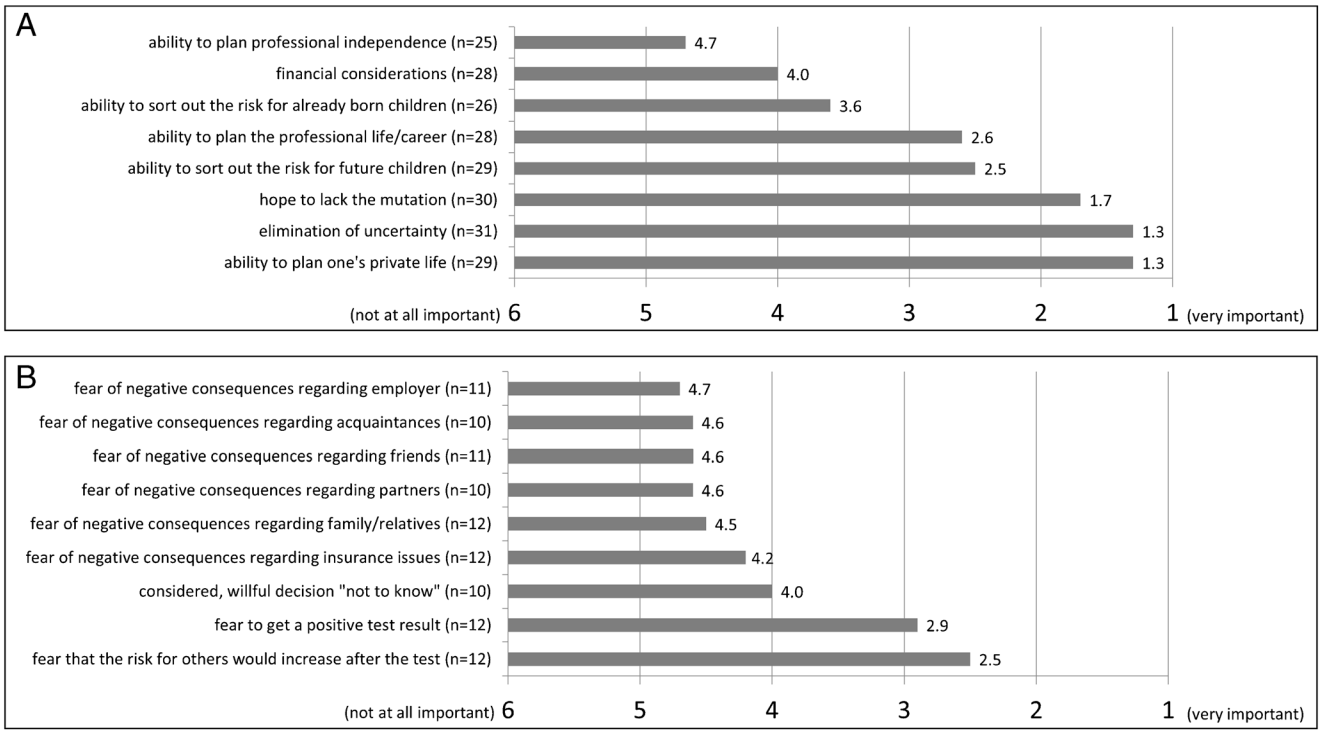

Fig. 2 Main motivations in decision-making in favor of (**a**) and against (**b**) predictive testing for HD, as revealed from phase 2 of the survey (4–6 weeks after counseling). The counselees were asked to assess the impact of the listed motivations on a scale from 1 to 6, with 1 meaning "very important" and 6 meaning "not at all important". The numbers of participants, who answered each question, as well as mean values for each type of motivation are shown. Only the answers of tested participants are included for (**a**) and those of untested participants for (**b**). HD: Huntington's disease

this topic mostly remains concealed. Almost all counselees (95.6%) stated that they knew the affected individual(s) in their family personally. When asked about the most terrifying symptoms of HD, loss of cognitive functions was the most frequent answer (multiple answers were possible), and listlessness and social isolation was chosen as the most severe burden with a mean of 4.1 (scale from 1 to 6, with 6 representing the most severe burden). Visiting a psychologist as part of the PT protocol was not regarded as particularly wearing by most (70.4%) of the participants.

Phase 3: Telephone Interview

Informed consent for the telephone conversation had originally been obtained from 60 counselees, but the interview was actually conducted with only 31. The remaining individuals either rejected to be interviewed (12) or did not answer the phone or call back in spite of multiple calls by the interviewer (17). The majority (8) of those who rejected the interview have not undergone PT (yet); the remaining four had undergone testing and were found to lack the *HTT* mutation.

Twenty of the 31 participants of the telephone interview had in the meantime attended the second session with the counselor and given a blood sample for PT. Of those, 19 had already completed the whole procedure and knew their mutation status at the time of the interview (7 mutation positive: group A, 12 mutation negative: group B), while one individual had not retrieved the result yet. We grouped this latter individual together with the remaining eleven participants that had only attended the first counseling session and decided against PT for the moment (12 mutation status unknown: group C). 21 of the 31 counselees who were interviewed on the phone had returned the post-counseling questionnaire (phase 2). Among those, six participants belonged to group A, nine to group B and six to group C. 50% of group C (mutation status unknown) did not send back the questionnaire.

At the beginning of the interview, the participants were asked to report their emotional state experienced since the last genetic counseling session (either initial counseling or result communication). The majority (25/30, 83.3%) reported an overall positive emotional state, while only two participants from group C reported a negative emotional state. The remaining three participants (two from group A and one from group C) particularly emphasized that they had felt bad for some time after the counseling/PT, but reported a positive emotional state at the time of telephone interview. When asked whether they had told their family, partner, friends, employer and insurance company about their result of PT (for groups A and B) or that they were in a genetic counseling session (group C), the

majority of participants reported positive reactions, regardless of whom they had informed (Fig. 3). Most counselees (29/31; 93.5%) shared the information with their family. 24 of 31 interviewees were in a partnership, and all of those shared the information with their partners. On the other hand, only a few told their employer (33% of women, 11% of men) or insurance agent (9.5% of women, 0% of men) about PT.

Overall, none of the participants expressed regret after PT. In fact, a few participants who had rejected PT even expressed that they would decide otherwise now. However, they avoided giving a recommendation for others and uniformly emphasized that the decision for or against PT is highly personal. Participants in group C were additionally asked about their main reasons not to undergo PT. In order to analyze the statements further, we categorized the answers according to intrinsic reasons (such as concentrating on short-term goals like graduating from school or passing exams, willful decision "not to know" or fear of a possibly inconvenient test result) and extrinsic reasons (such as postponing the test due to lack of time, fear of negative consequences for the family and increasing the risk for family members). According to this categorization, 41.7% reported an intrinsic, 33.3% an extrinsic reason, and one participant named a combination of both types of reasons. The most frequently reported long-term problems included the right manner to convey the information of PT results to the children and (in second place) to decide on family planning.

In order to obtain an idea about characteristics of counselees prone to be satisfied with their decision for PT in the end, the combined information from all three questionnaire parts were analyzed using linear regression analyses. The likelihood of choosing PT (again) at the time point of being questioned was chosen as dependent variable. Gender, age, familial or partner pressure, the likelihood of considered, willful decision "not to know", coping ability and wanting children were used as predictive variables. Overall, the regression model reached statistical significance ($F_{(7,13)} = 7.65$; $p = 0.012$), and a high r2 value indicated that a substantial amount of variance in the dependent variable could be explained by the predictors (r2 = 0.899). The highest beta-value was observed for the likelihood of a considered, willful decision "not to know" ($\beta = -0.78$), indicating that counselees who had not endorsed the desire "not to know" from the beginning, were most likely to be content with their decision for PT throughout the process. The regression analysis further revealed that a prototypical counselee, who is prone to be content with his/her decision and would choose PT (again), is female ($\beta = 0.24$), of a higher age ($\beta = -0.24$), has strong

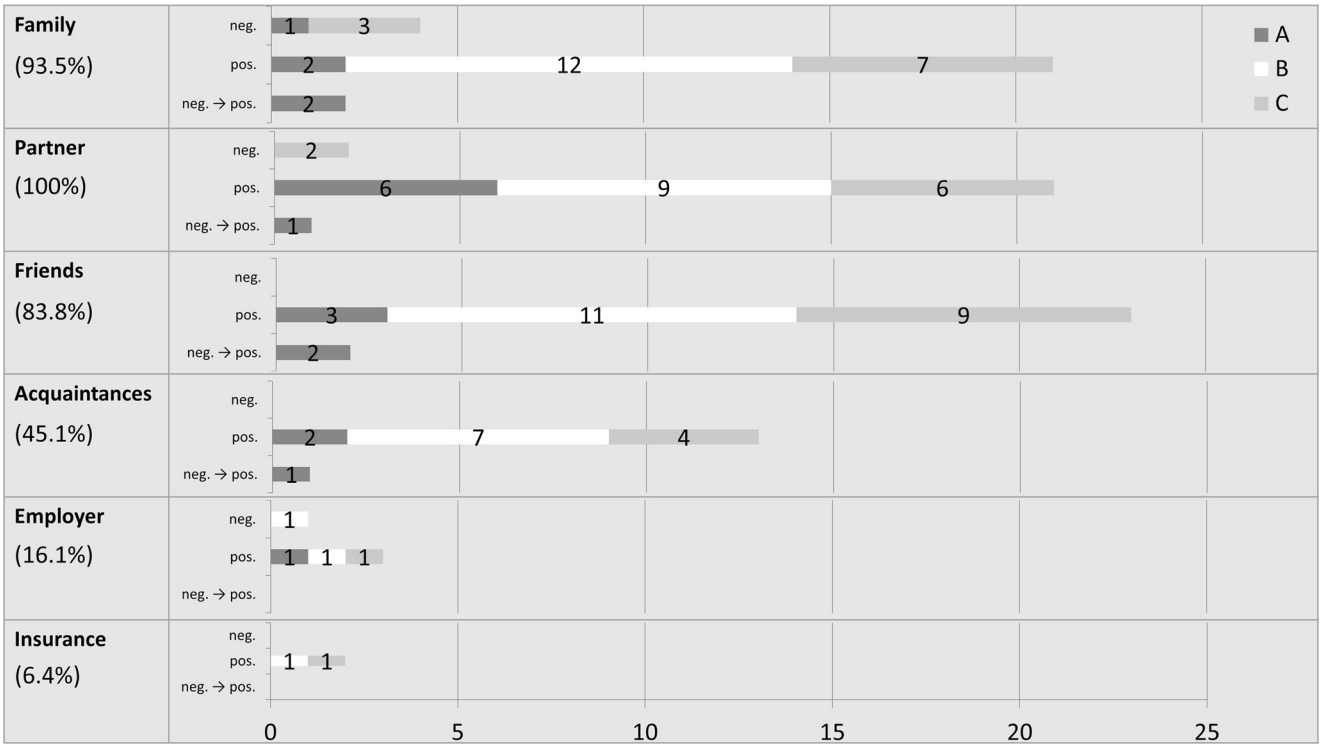

Fig. 3 Rates of disclosure of *HTT* mutation result (groups A and B) or the fact of having been counseled (group C) to family, partner, friends, employer and insurance agent, subdivided in positive and negative reactions, as revealed from the telephone interview. All participants informed their partners, if they were in a relationship. Most participants informed their family and close friends, but to a lesser degree the acquaintances and only rarely the employer or insurance company. Overall, just a few definitively negative reactions (neg.) were reported. Pos.: positive reaction, neg.: negative reaction, neg. → pos.: initially negative reaction converting to positive after a while, **a** *HTT* mutation, **b** no *HTT* mutation, **c** mutation status unknown

ability to cope with psychological burden (β = −0.32), is not under pressure of his/her family (β = −0.43) or partner (β = 0.35) and wants to have (further) children (β = −0.11).

Discussion

With a duration of three years our study represents a prospective evaluation regarding decision-making and coping strategies as well as individual perception of the counseling protocol during the process of PT for HD. We are aware of the limitations of this study, i.e. small number of participants and high drop-out rates, especially regarding the telephone interview. However, other cohort studies using postal surveys or telephone interviews showed similarly low response rates (Smith et al. 2013; Taylor 2005). We therefore regard our results as exploratory as well as hypothesis-generating and as a basis for more extended prospective evaluations.

The sociodemographic data collected in phase 1 of our study mostly correspond to the results of earlier investigations, with a mean age at first counseling in the mid-30s (31.6–40.4 years in other studies) (Dufrasne et al. 2011; Evers-Kiebooms et al. 2002; Trembath et al. 2006), mostly individuals with a 50% risk and more females than males at risk seeking PT (Dufrasne et al. 2011; Evers-Kiebooms et al. 2002; Trembath et al. 2006; Wedderburn et al. 2013). Similar to earlier studies (Dufrasne et al. 2011; Trembath et al. 2006), more participants than statistically expected received a favorable test result, which could be explained by the theory of self-selection, suggesting that non-carriers may be emotionally more stable and thus overrepresented in the group of individuals actively seeking PT (Codori et al. 2004; Maat-Kievit et al. 2000). Likewise, they might also be more willing to participate in research studies on this topic. However, our prospective approach revealed some additional interesting observations about decision-making and coping strategies during the PT process. Most importantly, looking back one year after initial counseling, none of the participants regretted their decision for PT and almost all, regardless of whether they underwent PT or not, reported a positive emotional state, although a few had felt bad for some time after counseling and/or PT. These findings are in line with recent studies on the impact of a positive test result on young adults' life, where also none of the participants regretted their decision for PT (Gong et al. 2016; MacLeod et al. 2014), as well as with the outcome of larger retrospective evaluations (Dufrasne et al. 2011).

The decision for or against PT often includes complex, conscious as well as unconscious motivations, and usually more than one reason is mentioned by the participants (Evers-Kiebooms et al. 2002). The most important motivations for a decision in favor of PT named in the present study were the ability to plan private life and to eliminate uncertainty, aspects that have also been highlighted in other studies before (Dufrasne et al. 2011; Tibben 2007; Williams et al. 2010b). On the other hand, assessment of motivations against PT is more complicated in retrospective studies and can usually only be assumed from the original files, when the participants do not return to the counseling center. For example, "not the right time" or "unknown" reasons were retrospectively recognized in an Australian survey (Wedderburn et al. 2013). Here prospective study designs are advantageous. The most important motivations against PT named shortly after counseling in our study (phase 2 of the survey) were the fear of an increasing risk for others (e.g. offspring) and the fear to obtain an unfavorable *HTT* mutation result, followed by the considered, willful decision "not to know". However, even though the risk for children was an important aspect, one year after counseling overall intrinsic (i.e. by the counselee individually named) reasons outweighed extrinsic (i.e. externally imposed reasons to refrain from testing), as would be expected and hoped for in a personal decision such as PT. Interestingly, life aspects, which were in theory expected to be more difficult to cope with by individuals at risk (such as career, insurance etc.), were not experienced in this way by our participants. Even though the majority of participants were in the process of making important decisions in their life (e.g. family planning, career considerations etc.) at the time of genetic counseling, most of them denied a strong effect of the future test result on their decision. This suggests that the impact of PT for HD on certain life time decisions and the fear of genetic discrimination and insurance problems may not be as important in our German cohort as reported for other countries (Erwin et al. 2010; Williams et al. 2010a; b). Unlike foreign studies describing insurance discrimination in one third of participants (Bombard et al. 2009), our participants also did not report significant discrimination. This difference could be explained by the social policy in Germany, which provides health care for all and forbids any institution from requesting that an at-risk individual have PT. Needless to state that the counselees are informed about possible negative consequences regarding PT during the counseling session. Unlike other studies emphasizing the importance of family planning as a main motivation for PT (Evers-Kiebooms et al. 2002), we could not show such a significant effect. This could be due to limited prenatal options regarding the HD risk of a future child in Germany at the time of the survey (2010–2012): prenatal genetic testing is no longer allowed in Germany for adult-onset diseases since 2010, while preimplantation genetic testing has only been available since 2014, and it is not covered by health insurance. However, participants ≥28 years tended to express a higher willingness to have children even after an unfavorable result than participants <28 years, suggesting that the age of counselees needs to be taken into account in this respect.

The overall positive and encouraging statements towards PT and the observed lack of regret, even after having learnt about an unfavorable *HTT* mutation result, may be explained

by the fact that the PT procedure is already designed to avoid severe negative consequences through multiple pre-PT counseling sessions, in which all possible consequences are discussed (Dufrasne et al. 2011). Positive statements are also in line with the fact that – contrary to initial assumptions - very few catastrophic reactions have been described after PT worldwide. Rather, the majority of studies reported "benefit" from testing for both carriers and non-carriers concerning various aspects of life (Paulsen et al. 2013). We established some predictive aspects for contentment with one's decision in this regard, including female sex, a higher age, strong coping abilities, lack of pressure imposed by the family or partner as well as the general wish to have children. However, it has to be considered that there may be substantial bias in prospective evaluations such as the present study, since individuals with psychological or other problems related to PT or an unfavorable test result may not be willing or capable to fill in questionnaires or answer telephone interviews. In this respect, we also found that the majority of participants, who sent back the questionnaire in phase 2 of our survey, in the end decided in favor of PT, while most non-responders decided against PT. This result could suggest that participants who have already decided against PT may not want to be confronted with this topic anymore, again pointing to selection bias in prospective studies for an emotionally difficult topic like PT for HD.

With increasing international experience concerning PT, gender-specific aspects evolved as an important factor in decision-making for PT (Arning et al. 2015; Taylor 2005). Similar to previous studies (Taylor 2005; Wedderburn et al. 2013), more female than male persons at risk applied for PT in the present study. Several explanations were suggested which include greater involvement of women in health services and reproductive decisions as well as their higher ability to confront and express themselves about emotionally difficult situations (Taylor 2005). Yet, when we tried to evaluate these hypotheses by asking for the general (individually perceived) coping capacity in our questionnaire, the results for men and women did not differ substantially. This finding is in contrast to the study by Taylor (2005), where women tended to express higher perceived coping abilities than men. This discrepancy may be explained by the fact that both evaluations were based on small numbers, and for our study one might speculate that only men with high coping abilities were willing to send back the questionnaire. An important limitation of both studies in this aspect is the absence of an objective evaluation system for coping capacities of participants, which can lead to some predescribed bias due to social desirability effects and/or higher self-confidence among men (Weisberg et al. 2011).

More participants with an affected mother (56.9%) than an affected father (31%) sought genetic counseling in the present study, as has been described before (Arning et al. 2015; Scuffham and MacMillan 2014; Trembath et al. 2006). It was suggested that individuals inheriting a potentially further expanded *HTT* allele via an affected father may develop symptoms earlier and thus, less frequently present for PT (Trembath et al. 2006). However, females with an affected mother tended to refrain more often from testing than males with an affected mother in our study (57.1% vs. 33.3%, respectively). This phenomenon could be a reflection of the demographics of the participants or the age of onset of the participants' parents; however, we did not find significant differences between groups in this respect. The same phenomenon was recently observed in a retrospective cohort study evaluating PT in our center between 1993 and 2009. It was hypothesized that females may be more satisfied than men with the prospect of (most probably) inheriting the same CAG repeat length as their mothers and thus, having a disease course similar to their mothers (Arning et al. 2015). On the other hand, one could speculate that the influence of an affected mother may be stronger in the decision-making process of their sons, since men tended to feel more pressure to undergo PT from their family as discussed below. This is in line with the findings of Scuffham and MacMillan (2014) who suggested that affected mothers may positively influence their sons to seek genetic testing because of their typical care-giving role (Scuffham and MacMillan 2014). The effect of each parent should therefore be explored individually in further studies.

Overall, participants did not experience considerable pressure to have PT by their partners or families in the present study. However, here again we identified a significant gender difference, suggesting that men feel more pressure from their partners than females. An important role of female partners in the health-seeking behavior of men has generally been observed (Taylor 2005). Some authors even suggested that some males may undergo genetic testing in general against their will because of pressure through family members (Hallowell et al. 2006; Liede et al. 2000). Our results cannot support the latter hypothesis for HD, but nevertheless underline the important role of female partners in decision-making for PT. Taylor (2005) also found gender differences regarding the disclosure of results, with women being more likely to disclose their results to others than men. Because of the small number of participants we were unable to confirm this conclusion in the present survey. Overall, however, the growing evidence for gender differences in various areas related to PT suggests that gender-specific aspects should be more strongly taken into account in genetic counseling.

Last, but not least, in our study we tried to evaluate the individual perception of the PT protocol for HD over a period of up to one year from initial counseling. Overall, genetic counseling was experienced as informative and non-directive, and an influence of the counselor on decision-making was uniformly denied. However, most participants reported that they had already decided about PT before the counseling and did not change their mind afterwards (although a few obviously did not return despite their earlier wish for PT). In

this respect, our results emphasize the important impact of the internet on decision-making, since 93.4% had already sought information via the internet before the first counseling session. This percentage is even greater than reported for breast cancer surgery [69%, (Schmidt et al. 2016)]. In fact, the establishment of a comprehensive and effective web-based educational tool supporting informed decision-making for people at risk of HD has already been evaluated and was generally approved (Hawkins Virani et al. 2013). Similar decision aids via internet have also been developed for other genetic counseling issues such as screening and diagnostic testing for fetal anomalies (Åhman et al. 2016). Internet-based information distribution has even greater meaning for younger people, since it is compatible with their lifestyle. The Huntington Disease Youth Organization (HDYO) has already met this point by establishing an international online platform available for kids, teens and young adults affected by HD (http://de.hdyo.org/). Likewise, the HDBuzz webpage (http://en.hdbuzz.net/) allows distribution of the latest HD research news, written by scientists but in plain language. Additionally, the patient organization for HD in Germany designed a new homepage (http://www.dhh-ev.de/) containing clearly stated and continually updated information in German language.

In conclusion, our data from a prospective study on PT in HD suggest that the process of PT is generally experienced in a positive manner, with the vast majority of participants reporting a positive emotional state one year after the initial counseling session regardless of their decision for or against PT. Furthermore, by extending previous observations of gender-specific aspects in decision-making we submit that these gender-related differences should be more seriously taken into account in genetic counseling. Appreciating the importance of internet-based information for decision-making, reliable online sources should be mentioned in the pre-test counseling session. Our findings could serve as a basis for more extended prospective evaluations (potentially involving international consortia) with higher numbers of participants and longer follow-up intervals.

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Compliance with Ethical Standards

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Human Studies and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. The Ethics Committee of the Ruhr-University Bochum (Germany) approved the study protocol.

Animal Studies No animal studies were carried out by the authors for this article.

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