

# Patients' choices and opinions on chorionic villous sampling and non-invasive alternatives for prenatal testing following preimplantation genetic testing for hereditary disorders: A cross-sectional questionnaire study

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## Abstract

**Objective:** The aim of this study was to investigate choices of and reasoning behind chorionic villous sampling and opinions on non-invasive prenatal testing among women and men achieving pregnancy following preimplantation genetic testing (PGT) for hereditary disorders.

**Methods:** A questionnaire was electronically submitted to patients who had achieved a clinical pregnancy following PGT at the Center for Preimplantation Genetic Testing, Aalborg University Hospital, Denmark, between 2017 and 2020.

**Results:** Chorionic villous sampling was declined by approximately half of the patients. The primary reason for declining was the perceived risk of miscarriage due to the procedure. Nine out of 10 patients responded that they would have opted for a non-invasive prenatal test if it had been offered. Some patients were not aware that the nuchal translucency scan offered to all pregnant women in the early second trimester only rarely provides information on the hereditary disorder for which PGT was performed.

**Conclusion:** Improved counseling on the array of prenatal tests and screenings available might be required to assist patients in making better informed decisions regarding prenatal testing. Non-invasive prenatal testing is welcomed by the patients and will likely increase the number of patients opting for confirmatory prenatal testing following PGT for hereditary disorders.

## Key points

### What is already known about this topic?

- Invasive prenatal testing is often declined due to the associated risk of miscarriage, and non-invasive alternatives may increase the number of patients accepting prenatal testing
- Doctor-patient communication on prenatal testing has been reported as difficult and patients' knowledge about limitations of prenatal tests have been reported as suboptimal

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- These aspects in the context of preimplantation genetic testing (PGT) for hereditary disorders are not well investigated

**What does this study add?**

- This study details patients' opinion and choices of invasive and non-invasive prenatal testing following PGT for hereditary disorders
- Non-invasive alternatives may increase the number of patients accepting prenatal testing from 50% to 90%, potentially alleviating concerns during pregnancy and increasing the chance of detecting a misdiagnosis from PGT
- The study supports previous reports, that communication on the topic is difficult and that patients' knowledge about limitations of prenatal tests is inadequate

## 1 | INTRODUCTION

Preimplantation genetic testing (PGT) is an option for couples at risk of transmitting a known hereditary disorder to their offspring. PGT entails assisted reproductive technology to generate preimplantation embryos from which embryonic material can be biopsied and subjected to genetic testing, thereby allowing differentiation between affected and unaffected embryos. Other options available to avoid transmitting a hereditary trait are gamete donation and adoption, however, a biological relation is often of importance for couples. PGT allows couples to achieve pregnancy with their own biological child while drastically reducing the risk of passing on the hereditary disorder. The risk of passing on a hereditary disorder despite PGT is estimated to be <1% according to the two most recent data collections published by the European Society of Human Reproduction and Embryology (ESHRE) PGT, based on data from PGT centers across Europe.<sup>1,2</sup> While the risk of misdiagnosis is low, the consequences are severe in the case of an undetected misdiagnosis resulting in the birth of a child affected by physical and/or mental disability at birth or later in life. For this reason, a confirmatory prenatal test following PGT is recommended by our clinic, and patients are therefore informed about the option of prenatal testing as described in the latest good practice recommendations from the ESHRE PGT Consortium.<sup>3</sup> In addition to detection of misdiagnosis, prenatal testing may also help alleviate potential stress or anxiety experienced by patients during pregnancy.

As the topics of genetics can be complicated, thorough guidance on both PGT and prenatal testing should be provided to help patients make an informed choice. Doctor–Patient communication is an important but difficult task.<sup>4</sup> It has been shown that although doctors believe that the delivered information was understood by patients, this might not be the case for a lot of patients,<sup>5</sup> and inadequate communication skills has been raised as an issue in relation to prenatal care.<sup>6</sup> While some communicative challenges might be common to health care in general, others might be related to the type of healthcare or degree of difficulty associated with the specific treatment and/or condition. For a couple to understand the concepts and limitations of PGT and whether to opt for prenatal testing, a certain level of understanding of genetics and the procedures is necessary. Health literacy has been shown to play an important role in

reproduction behaviors and to impact decision making and outcomes,<sup>7</sup> emphasizing the need for proper counseling, especially given the complexity associated with understanding genetics. Given the complexity of the treatments and screening procedures available during pregnancy, especially the type of genetic information that can be obtained from different tests, research with the aim of evaluating how patients perceive the information given might help to improve counseling and help patients in their decision making.

The current gold standard for prenatal testing following PGT is chorionic villous sampling (CVS) which entails biopsy of placental tissue and subsequent genetic analysis for the hereditary disorder. The procedure is invasive in nature, and it is associated with a low risk of miscarriage, which is estimated to be <1%.<sup>8</sup> Although the risk is not significantly different from the background risk of miscarriage,<sup>8</sup> the discomfort associated with the procedure and the perceived risk of miscarriage by patients represent challenges. This stems from the fact that the perceived risk by patients may differ from the actual risk. In this regard, proper counseling is obviously important, but patient-related factors, such as education,<sup>9</sup> may also affect how risk is perceived. The (perceived) risk of miscarriage and the discomfort associated with the CVS procedure have been reported to be important reasons for declining prenatal testing.<sup>10</sup> Similar concerns have been reported from patients at our PGT center, although so far it has not been quantified or qualified. If these are in fact the primary reasons for declining prenatal testing, non-invasive alternatives are likely to be embraced by patients resulting in higher adherence to prenatal testing, as previously described.<sup>11–14</sup> We recently published a proof of concept on cell-based non-invasive prenatal testing (cbNIPT) following PGT for monogenic disorders showing promising results.<sup>15</sup> However, the difficulties associated with communicating information to patients might only increase as the number of prenatal test options increases (e.g. CVS, cell-free fetal NIPT and cbNIPT). One study reporting on patients' opinions about non-invasive testing for chromosomal abnormalities using cell-free fetal DNA compared to conventional prenatal screening (e.g. the quadruple screen test) showed that while patients were in favor of obtaining more information on the genetic status of the fetus, navigating the complexity of the decision making process was challenging.<sup>16</sup> Thus, the increasing array of possible prenatal options means that more information has to be provided to patients, complicating the task of

pre-test counseling that health care providers face. This calls for initiatives to ensure that health care providers are properly informed on NIPT and capable of relaying relevant information to patients.<sup>17</sup>

In Denmark, both PGT for hereditary disorders and invasive prenatal testing by chorionic villus sampling or amniocentesis are offered without costs to the patient within the public health care system. This means that the patient's decision making with respect to both PGT, and prenatal testing is less likely to be affected by financial factors. Socioeconomic status has previously been reported to affect uptake of prenatal testing, both invasive and non-invasive.<sup>18</sup> Currently, in the context of prenatal testing for a hereditary disorder, only invasive prenatal testing is publicly funded in Denmark, as non-invasive prenatal testing has not been implemented into routine clinical practice.

The aim of this questionnaire survey was to investigate the reasoning behind patient decision making on prenatal testing by CVS following PGT and how a non-invasive alternative would affect decision making. Additionally, the questionnaire also aimed at investigating how patients experience counseling with respect to prenatal testing following PGT.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient cohort

Patients who achieved a clinical pregnancy following PGT-treatment between January 1, 2017, and December 31, 2020, at the Center for Preimplantation Genetic Testing at Aalborg University Hospital were invited to participate in the questionnaire survey. A clinical pregnancy was defined as the presence of a fetal heartbeat by ultrasound monitoring in gestational week 7–8. Both the female receiving controlled ovarian stimulation (COS) treatment and their partners were invited.

### 2.2 | Prenatal testing

Patients and their partners were informed on the option of prenatal testing by CVS during preclinical consultation prior to initiating PGT. Prenatal testing by CVS is available at no cost to all patients following pregnancy achieved by PGT.

### 2.3 | Questionnaire design

The questionnaire was designed using a commercial online platform (SurveyXact, <https://www.surveymxact.com/>). All questions were in Danish. The questionnaire was designed so that participants had to provide an answer to each question before being presented with the next question in order to ensure that all questions were answered. To reduce the risk that participants would not complete the questionnaire because none of the presented answers to a given question were deemed appropriate, the option to answer “do not know” was

offered for some questions. Conditional branching was used to present relevant questions depending on previous answers and to allow different questions and/or different phrasing of questions for women receiving treatment and their partners (e.g., “your pregnancy” vs. “your partner's pregnancy”). Since we wanted to investigate if there was any difference between women receiving treatment and their partner, each participant was asked to state their role at the beginning of the questionnaire. The questionnaire was designed to gather information about (1) relevant preclinical history prior to initiating PGT, (2) treatment characteristics and clinical results from their PGT-treatment, (3) thoughts and concerns during pregnancy, (4) patient experience from preclinical consultations, (5) their choice and reasoning with respect to CVS and (6) their opinion on non-invasive prenatal testing. An English translation of the entire questionnaire can be found in the **supplementary materials and method section**. Unfortunately, after distribution of the initial version of the questionnaire, it was discovered that three essential questions with respect to the participants choice of CVS had been wrongly conditioned. To solve this, the questionnaire was corrected and the participants who had answered the questionnaire prior to the mistake being corrected ( $n = 165$ ) were invited to answer the three questions in a separate questionnaire.

### 2.4 | Questionnaire distribution

Invitations to take part in the questionnaire survey were distributed electronically via a Danish national mailing system (“E-boks”), where each citizen has his/her own secure mail account tied to their unique personal identification number (PIN). This allowed efficient distribution of invitations from a list of PINs. The invitation included a description of the study and study aims, contact information in case any question should arise, and a link to the online-based questionnaire. The invitations were written in Danish. The questionnaire was distributed on February 19, 2021, and the additional questions on March 12, 2021 and ended on May 1, 2021.

### 2.5 | Analysis

Only fully completed questionnaires were included in the data analyses. Answers from the three additional questions were manually combined with the questionnaire if they were all completed. The responses were analyzed separately for women receiving treatments and their partners as well as combined for all respondents. For questions with discrete answers, the number and percentage of each answer were calculated and presented with an exact 95% confidence interval (CI<sub>95</sub>). For questions where the respondent was asked to fill in a number, mean(s) with standard deviation(s) or median(s) with 10th and 90th percentiles were reported for normally and non-normally distributed data, respectively. Whether statistically significant differences were present was evaluated from comparison of the calculated 95% confidence intervals or by Chi<sup>2</sup>-test (without Yates

correction) when required (such as in cases of overlapping confidence intervals but where none of the two estimates were encompassed by the confidence interval of the other).

### 3 | RESULTS

The questionnaire was distributed to 314 respondents, of which 203 (64.7%) completed the initial set of questions. Of those 203 respondents, 172 (84.7%) also completed the additional questions. Hence, 54.8% of all respondents completed the initial set of questions as well as the additional questions.

Baseline characteristics and relevant pre-PGT medical history for respondents can be seen in Table S1. Of the 203 respondents, 61.6% ( $n = 125$ ) were females and 38.4% ( $n = 78$ ) male. All female respondents had gone through PGT with a partner, and none had used gamete donation. With respect to who was carrier of the genetic disorder, 48.8% ( $n = 99$ ) and 42.9% ( $n = 87$ ) of female and male respondents were carriers, respectively, while 10.3% ( $n = 21$ ) reported the genetic disorder to be carried by both the male and the female. Of all respondents, 17.7% ( $n = 36$ ) reported having a child affected by the genetic disorder prior to initiating PGT. The median number of pregnancies prior to initiating PGT was 0 (10th/90th percentile: 0/3). In total, 48.5% (48/99) of respondents were not aware that they were carrying a hereditary disorder when attempting to achieve a pregnancy prior to initiating PGT (61.9% [39/63] and 52.8% [19/36] for female and male respondents, respectively). Of the 58 respondents that were aware of their risk of passing on the genetic disorder, 70.7% (41/58) opted for CVS during pregnancies achieved prior to PGT (74.4% [29/39] and 63.3% [12/19] for female and male respondents, respectively). Of those, 75.6% (31/41) of participants reported at least one instance where the CVS showed the fetus to be affected by the genetic disorder (79.3% [23/29] and 66.7% [8/12] for female and male respondents, respectively). In all cases, a decision was made to terminate the pregnancy. Among respondents reporting that they were aware of their risk of passing on a hereditary disorder, 11.0% (CI<sub>95</sub> 6.0%–18.1%, 13/118) reported having an affected child prior to initiating PGT; a significantly lower percentage compared to the 32.4% (CI<sub>95</sub> 23.0%–47.3%, 22/64) of respondents who were not aware of their risk of passing on a hereditary disorder (Table S2).

PGT treatment characteristics and clinical results reported by participants can be seen in Table S3. The average age of female and male respondents at the time of initiating PGT was 29.4 and 31.2 years. A median of two COS, two oocyte retrievals, two transfers and one achieved pregnancy were reported with 75.9% (154/203) of respondents reporting having a child as a result of PGT (81.6% [102/125] and 66.7% [52/78] of female and male respondents, respectively). A median of one child following PGT was reported.

Respondents' thoughts and concerns during pregnancy are detailed in Table 1. Of the 203 respondents, 52.7% ( $n = 107$ ) reported having a desire during pregnancy to verify that the fetus had not inherited the disorder (50.4% [63/125] and 56.4% [44/78] for female and male respondents, respectively), with 38.4% (78/203) of

respondents reporting being concerned during pregnancy that the fetus had inherited the disorder despite PGT (40.0% [50/125] and 35.9% [28/78] for female and male respondents, respectively). Concerns and a desire for verification were not statistically different between sexes. With respect to whether the respondent felt their partner shared his/her concern, 66.7% (52/78) reported that they felt that their concern with respect to whether the fetus had inherited the disorder or not was shared by their partner. A significantly higher proportion of male respondents reported that their partner shared their concern compared to female responders (82.1% [23/28] vs. 58.0% [29/50], respectively,  $\text{Chi}^2(1, N = 78) = 4.7, p = 0.03$ ).

Respondents' choices and reasoning behind CVS are shown in Table 2. Of the respondents, 43.6% (75/172) opted for CVS (42.6% [46/108] and 45.3% [29/64] for female and male respondents, respectively), 55.2% (95/172) did not opt for CVS (56.5% [61/108] and 53.1% [34/64] for female and male respondents, respectively), and 1.2% (2/172) reported having both accepted and rejected CVS in multiple pregnancies (0.9% [1/108] and 1.6% [1/64] for female and male respondents, respectively). With respect to their choice of CVS, 95.1% (195/203) of participants reported that their partner agreed with the decision (95.2% [119/125] and 94.9% [74/78] of female and male respondents, respectively). Of the respondents reporting that they desired verification that the fetus had not inherited the disorder, 74.2% (66/89) opted for CVS (76.8% [43/56] and 69.7% [23/33] for female and male respondents, respectively). Of those who did not have a desire for verification, 9.6% (7/73) opted for CVS (4.4% [2/46] and 18.5% [5/27] of female and male respondents, respectively). The difference in choice of CVS with respect to whether verification was desired was statistically significant for both males and females.

The two primary reasons for choosing CVS were to allow for termination of pregnancy in case of an affected fetus (69.3% [52/75], 69.6% [32/46] and 69.0% [20/29] for all, female and male respondents, respectively) and due to recommendations from the clinic (56.0% [42/75], 67.4% [31/46] and 37.9% [11/29] for all, female and male respondents, respectively; Table 2). A smaller proportion of respondents chose CVS so they could be prepared in case the fetus had inherited the disorder as they did not consider termination of pregnancy to be an option for them (13.3% [10/75], 8.7% [4/46] and 20.7% [6/29] for all, female and male respondents, respectively). A smaller proportion of respondents reported other reasons or an abnormal result of the nuchal translucency scan as reasons for CVS. Other reported reasons included the respondents wanting to know whether the fetus had inherited the disorder or not, without elaborating on whether termination of pregnancy was an option or not. The reason most frequently stated for not choosing CVS was the risk of miscarriage associated with the procedure (69.5% [66/95], 70.5% [43/61] and 67.7% [23/34] of female and male respondents, respectively; Table 2). Termination of pregnancy not being an option was reported by 32.6% (31/95) of respondents as a reason for declining CVS (32.8% [20/61] and 32.4% [11/34] of female and male respondents, respectively). Nineteen percent of respondents (18/95) reported that they were convinced that a normal result from the nuchal translucency scan was sufficient (23.0% [14/61] and 11.8%

TABLE 1 Patient thoughts and concerns during pregnancy

			N	Percentage	CI <sub>95</sub>
Did you have a desire during the pregnancy to verify that the fetus had not inherited the disorder?	Female respondent	Yes	63/125	50.4	41.3–59.5
		No	57/125	45.6	36.7–54.8
		Do not know	5/125	4.0	1.3–9.1
	Male respondent	Yes	44/78	56.4	44.7–67.6
		No	31/78	39.7	28.8–51.5
		Do not know	3/78	3.9	0.8–10.8
	Total	Yes	107/203	52.7	45.6–59.7
		No	88/203	43.4	36.4–50.5
		Yes	63/125	50.4	41.3–59.5
Were you concerned during your pregnancy that the fetus had inherited the disorder despite PGT?	Female respondent	Yes	50/125	40.0	31.3–49.1
		No	71/125	56.8	47.6–65.6
		Do not know	4/125	3.2	0.9–8.0
	Male respondent	Yes	28/78	35.9	25.3–47.6
		No	48/78	61.5	49.8–72.3
		Do not know	2/78	2.6	0.3–9.0
	Total	Yes	78/203	38.4	31.7–45.5
		No	119/203	58.6	51.5–65.5
		Do not know	6/203	3.0	1.1–6.3
Was it your experience that your partner shared your concern?	Female respondent	Yes	29/50	58.0	43.2–71.8
		No	14/50	28.0	16.2–42.5
		Do not know	7/50	14.0	5.8–26.7
	Male respondent	Yes	23/28	82.1	63.1–93.9
		No	4/28	14.3	4.0–32.7
		Do not know	1/28	3.6	0.1–18.35
	Total	Yes	52/78	66.7	55.1–76.9
		No	18/78	23.1	14.3–34.0
		Do not know	8/78	10.3	4.5–19.2

[4/34] of female and male respondents, respectively). None of these patients were referred to PGT based on indications that would be detectable on the nuchal translucency scan. Twenty percent of respondents reported other reasons (19/95), with the most reported reasons being that the risk of miscarriage associated with CVS was comparable to the risk of misdiagnosis of PGT, that they did not progress far enough into the pregnancy for CVS to be an option, that they found the risk of misdiagnosis associated with PGT sufficiently low or that they had chosen non-invasive alternatives. Noteworthy, 18.2% (37/203) of respondents reported that they were not aware of the fact that the nuchal translucency scan only rarely gives information on whether the fetus has inherited the disorder (15.2 [19/125] and 23.1 [18/78] for female and male respondents, respectively; Table 3). Of those respondents not aware of this and who did not opt for CVS ( $n = 18$ ), three would have opted for CVS had they been aware (16.7%).

Patients' experience from the preclinical consultation about CVS are shown in Table 4. Most respondents (93.6%, 190/203) recalled that they had been informed of the option of CVS to investigate whether the fetus had inherited the disorder (95.2 [119/125] and 91.0 [71/78] of female and male respondents, respectively). Of those who recalled having been informed about the possibility of CVS, 54.2% (103/190) answered that they recalled that the clinic recommended CVS in case of pregnancy following PGT (59.7 [71/119] and 45.1% (32/71) of female and male respondents, respectively), 1.6% (3/190) that the clinic did not recommend CVS (1.7 [2/119] and 1.4% [1/71] of female and male respondents, respectively), and 35.3% (67/190) that the clinic had no recommendation neither for nor against CVS (33.6 [40/199] and 38.0% [27/71] of female and male respondents, respectively). The majority (86.3%, 164/190) of respondents recalled being informed on risk(s) associated with CVS (86.3 [103/119] and 85.9% [61/71] of female and male respondents, respectively), with 93.3% (153/164) of

TABLE 2 Choice of CVS

			N	Percentage	CI <sub>95</sub>	
Did you opt for CVS in any of your pregnancies following PGT?	Female respondent	Yes	46/108	42.6	33.1-52.5	
		No	61/108	56.5	46.6-66.0	
		In some	1/108	0.9	0.0-5.1	
	Male respondent	Yes	29/64	45.3	32.8-58.3	
		No	34/64	53.1	40.2-65.7	
		In some	1/64	1.6	0.0-8.4	
	Total	Yes	75/172	43.6	36.1-51.4	
		No	95/172	55.2	47.5-62.8	
		In some	2/172	1.2	0.1-4.1	
Was it your experience that you and your partner agreed with respect to your choice of CVS?	Female respondent	Yes	119/125	95.2	89.9-98.2	
		No	4/125	3.2	0.9-8.0	
		Do not know	2/125	1.6	0.2-5.7	
	Male respondent	Yes	74/78	94.9	87.4-98.6	
		No	3/78	3.9	0.8-10.8	
		Do not know	1/78	1.2	0.0-6.9	
	Total	Yes	193/203	95.1	91.1-97.6	
		No	7/203	3.5	1.4-7.0	
		Do not know	3/203	1.5	0.3-4.3	
Relation between desire for verification and choice of CVS	Desired verification	Female respondent	CVS	43/56	76.8	63.6-87.0
			No CVS	13/56	23.2	13.0-36.4
		Male respondent	CVS	23/33	69.7	51.3-84.4
			No CVS	10/33	30.3	15.6-48.7
		Total	CVS	66/89	74.2	63.8-82.9
			No CVS	23/89	25.8	17.1-36.2
	No desire for verification	Female respondent	CVS	2/46	4.4	0.5-14.8
			No CVS	44/46	95.7	85.2-99.5
		Male respondent	CVS	5/27	18.5	6.3-38.1
			No CVS	22/27	81.5	62.9-93.7
		Total	CVS	7/73	9.6	3.9-18.8
			No CVS	66/73	90.4	81.2-96.0
Why did you opt for CVS? (Multiple reasons can be selected)	Female respondent	Because we wanted a termination of pregnancy in case of an affected fetus	32/46	69.6	54.3-82.3	
		Due to recommendations from the clinic	31/46	67.4	52.0-80.5	
		Due to an abnormal result on the nuchal translucency scan	2/46	4.4	0.5-14.8	
		To be prepared in case the fetus had inherited the disorder because termination of pregnancy was not an option	4/46	8.7	2.4-20.8	

TABLE 2 (Continued)

		N	Percentage	CI <sub>95</sub>
	Male respondent			
	Do not know	0/46	0	0.0–7.7
	Other reason	5/46	10.9	3.6–23.6
	Because we wanted a termination of pregnancy in case of an affected fetus	20/29	69.0	49.2–84.7
	Due to recommendations from the clinic	11/29	37.9	20.7–57.7
	Due to an abnormal result on the nuchal translucency scan	0/29	0	0.0–11.9
	To be prepared in case the fetus had inherited the disorder because termination of pregnancy was not an option	6/29	20.7	8.0–39.7
	Total			
	Do not know	0/29	0	0.0–11.9
	Other reason	1/29	3.5	0.1–17.8
	Because we wanted a termination of pregnancy in case of an affected fetus	52/75	69.3	57.6–79.5
	Due to recommendations from the clinic	42/75	56.0	44.1–67.5
	Due to an abnormal result on the nuchal translucency scan	2/75	2.7	0.3–9.3
	To be prepared in case the fetus had inherited the disorder because termination of pregnancy was not an option	10/75	13.3	6.6–23.2
	Do not know	0/75	0	0.0–4.8
	Other reason	7/75	9.3	3.8–18.3
Why did you not opt for CVS? (Multiple reasons can be selected)	Female respondent			
	Termination of pregnancy would not be an option no matter the result	20/61	32.8	21.3–46.0
	Because of the associated risk of miscarriage	43/61	70.5	57.4–81.5
	I was not aware that CVS was an option	1/61	1.6	0.0–8.8
	I was convinced that a normal result following the nuchal translucency scan was sufficient	14/61	23.0	13.2–35.5
	Do not know	0/61	0	0.0–5.9
	Other reasons	14/61	23.0	13.2–35.5

(Continues)

TABLE 2 (Continued)

		N	Percentage	CI <sub>95</sub>
Male respondent	Termination of pregnancy would not be an option no matter the result	11/34	32.4	17.4–50.5
	Because of the associated risk of miscarriage	23/34	67.7	49.5–82.6
	I was not aware that CVS was an option	0/34	0	0.0–10.3
	I was convinced that a normal result following the nuchal translucency scan was sufficient	4/34	11.8	3.3–27.5
	Do not know	3/34	8.8	1.9–23.7
	Other reasons	5/34	14.7	5.0–31.1
	Total	Termination of pregnancy would not be an option no matter the result	31/95	32.6
	Because of the associated risk of miscarriage	66/95	69.5	59.2–78.5
	I was not aware that CVS was an option	1/95	1.1	0.0–5.7
	I was convinced that a normal result following the nuchal translucency scan was sufficient	18/95	19.0	11.6–28.3
	Do not know	3/95	3.2	0.7–9.0
	Other reasons	19/95	20.0	12.5–29.5

Abbreviations: CVS, chorionic villous sampling; PGT, preimplantation genetic testing.

those answering that there was a risk of miscarriage associated with the procedure (96.1 [153/164] and 88.5% [54/61] of female and male respondents, respectively). Other risks mentioned were infections and possible harm to the fetus without mentioning miscarriage explicitly. The majority of the respondents (87.7%, 178/203) felt that they had received sufficient information regarding CVS (88.0 [110/125] and 87.2% [68/78] of female and male respondents, respectively). Additional information on patients' responses with respect to oral and written information about CVS and time of receiving the information are detailed in Table S4.

Respondents' opinions with respect to non-invasive alternatives are shown in Table 5. When asked about non-invasive alternatives to CVS, 89.2% (181/203) of respondents reported that they would have opted for non-invasive prenatal testing had it been offered (89.6 [112/125] and 88.5% [69/78] of female and male respondents, respectively). The major arguments for choosing the non-invasive test were that it would not be associated with a risk of miscarriage (93.4 [169/181], 94.6 [106/112], and 91.3% [63/69] for all, female and male respondents, respectively), and the procedure would not be as unpleasant as invasive testing (51.4 [93/181], 48.2 [54/112], and 56.5% [39/69] for all, female and male respondents respectively). In

the small group of respondents who would not opt for non-invasive testing, most would decline the test because they did not consider termination of pregnancy as an option (76.9 [10/12], 75.0 [6/8], and 80.0% [4/5] of all, female and male respondents, respectively).

#### 4 | DISCUSSION

Prenatal testing following PGT to verify that pregnancy has been achieved with an unaffected fetus is important to identify the rare cases of misdiagnosis and to ease the minds of women and their partners during pregnancy.

In this study, we examined the choices, preferences, and opinions regarding prenatal testing of female and male respondents who had achieved pregnancy following PGT. In line with what had been experienced by our health care professionals but never quantified or qualified, approximately half of the respondents did not opt for CVS, despite clinical recommendations (Table 2). While most respondents reported having been informed about CVS including the associated risk of miscarriage during preclinical consultation, almost half of them did not recall that the clinic recommended CVS (Table 4). It is



TABLE 3 Nuchal translucency scan

			N	Percentage	CI <sub>95</sub>
Were you aware that the nuchal translucency scan only rarely gives information on whether the fetus has inherited the disorder?	Female respondent	Yes	103/125	82.4	74.6–88.6
		No	19/125	15.2	9.4–22.7
		Do not know	3/125	2.4	0.5–6.9
	Male respondent	Yes	49/78	62.4	51.1–73.5
		No	18/78	23.1	14.3–32.0
		Do not know	11/78	14.1	7.3–23.8
	Total	Yes	152/203	74.9	68.3–80.7
		No	37/203	18.2	13.2–24.2
		Do not know	14/203	6.9	3.8–11.3
If you had been aware of this fact, would you then have chosen CVS?	Female respondent	Yes	7/19	36.8	16.3–61.6
		No	10/19	52.6	28.9–75.6
		Do not know	2/19	10.6	1.3–33.1
	Male respondent	Yes	8/18	44.4	21.5–69.2
		No	6/18	33.3	13.3–59.0
		Do not know	4/18	22.2	6.4–47.6
	Total	Yes	15/37	40.5	24.8–57.9
		No	16/37	43.2	27.1–60.5
		Do not know	6/37	16.2	6.2–32.0

Abbreviation: CVS, chorionic villous sampling.

possible that the recommendation of CVS was provided but not recalled by some patients or, that the recommendation had not been properly communicated. Nonetheless, this indicates that more emphasis may be put on ensuring that the recommendations are understood by patients during preclinical counseling.

Surprisingly, despite PGT, a noteworthy proportion of patients reported being concerned that the fetus had inherited the disorder or having a desire for prenatal verification of a pregnancy with an unaffected fetus (Table 1). Interestingly, despite a desire for prenatal verification, approximately one in four patients still rejected invasive testing. While this might be simply due to the disagreement between partners, this was not the case as almost all respondents reported that they agreed on their choice (Table 2). Hence, it appears that despite a wish to obtain the information that the CVS-procedure can provide, it is rejected by some patients.

The primary reason for declining CVS was the associated risk of miscarriage, while one third of respondents reported declining CVS because termination of pregnancy would not be an option for them no matter the test result (Table 2). Surprisingly, approximately 20% of respondents reported a normal result from the nuchal translucency scan as the reason for declining CVS (Table 2). This might indicate that some patients might find it difficult to distinguish between the type of information obtained from the two procedures. In support of this, almost one in five respondents reported that they were not aware that the nuchal translucency scan only rarely provides information on whether the fetus has inherited the disorder for

which PGT was performed (Table 3). Hence, it might be that a normal result from the nuchal translucency scan has been misinterpreted as the fetus not having inherited the disorder by some patients. Misjudgment by patients of the purpose and capability of the nuchal translucency scan has previously been reported.<sup>19–21</sup> This suggests that better counseling regarding the different prenatal tests available might be required so that patients can make a more informed decision with respect to CVS following PGT. In fact, three of 18 respondents who declined CVS would have chosen otherwise, had they been aware of the limitations of the nuchal translucency scan.

In line with previous findings,<sup>22</sup> we show that the risk of miscarriage associated with invasive testing is a primary reason for patients to decline prenatal testing (Table 2). Hence, the need for the introduction of non-invasive alternatives is imminent, and previous studies have shown that patient decision making in relation to prenatal testing is greatly influenced by test safety.<sup>11,12</sup> We echo these findings showing that nine in 10 respondents would opt for non-invasive prenatal testing had it been offered to them, citing no risk of miscarriage as the primary reason (Table 5). Of those who would not opt for CVS nor non-invasive prenatal testing, the primary reason was that termination of pregnancy would not be an option for them no matter the test results. We recently published a proof-of-concept of the use of cell-based non-invasive prenatal testing (cbNIPT) following PGT for different types of monogenic disorders,<sup>15</sup> and the results presented here indicate that cbNIPT would be welcomed by patients and potentially lead to more couples accepting prenatal

TABLE 4 Patient experience from preclinical consultation about CVS

			N	Percentage	CI <sub>95</sub>
Were you informed of the option of CVS to investigate whether the fetus had inherited the disorder?	Female respondent	Yes	119/125	95.2	89.9–98.2
		No	5/125	4.0	1.3–9.1
		Do not know	1/125	0.8	0.0–4.4
	Male respondent	Yes	71/78	91.0	82.4–96.3
		No	2/78	2.6	0.3–9.0
		Do not know	5/78	6.4	2.1–14.3
	Total	Yes	190/203	93.6	89.3–96.6
		No	7/203	3.5	1.4–7.0
		Do not know	6/203	3.0	1.1–6.3
What was the clinic's recommendations with respect to CVS	Female respondent	The clinic recommended CVS	71/119	59.7	50.3–68.6
		The clinic didn't recommend CVS	2/119	1.7	0.2–5.9
		The clinic had no recommendations for or against CVS	40/199	33.6	25.2–42.9
		Do not know	6/199	5.0	1.9–10.7
	Male respondent	The clinic recommended CVS	32/71	45.1	33.2–57.3
		The clinic didn't recommend CVS	1/71	1.4	0.0–7.6
		The clinic had no recommendations for or against CVS	27/71	38.0	26.8–50.3
		Do not know	11/71	15.5	8.0–26.0
	Total	The clinic recommended CVS	103/190	54.2	46.9–61.4
		The clinic didn't recommend CVS	3/190	1.6	0.3–4.5
		The clinic had no recommendations for or against CVS	67/190	35.3	28.5–42.9
		Do not know	17/190	9.0	4.9–13.0
Were you informed on any risks associated with CVS	Female respondent	Yes	103/119	86.6	79.1–92.1
		No	6/119	5.0	1.9–10.7
		Do not know	10/119	8.4	4.1–14.9
	Male respondent	Yes	61/71	85.9	75.6–93.0
		No	2/71	2.8	0.3–9.8
		Do not know	8/71	11.3	5.0–21.0
	Total	Yes	164/190	86.3	80.6–90.9
		No	8/190	4.2	1.8–8.1
		Do not know	18/190	9.5	5.7–14.6
What risk(s) did you understand that the CVS entailed from the information you received from the clinic? (Free text answer)	Female respondent	Risk of miscarriage	99/103	96.1	90.4–98.9
		Other risk(s) or no answer	4/103	3.9	1.1–9.7
	Male respondent	Risk of miscarriage	54/61	88.5	77.8–95.3
		Other risk(s) or no answer	7/61	11.5	4.7–22.2
	Total	Risk of miscarriage	153/164	93.3	88.3–96.6
		Other risk(s) or no answer	11/164	6.7	3.4–11.7

TABLE 4 (Continued)

			N	Percentage	CI <sub>95</sub>
In your opinion, was the information provided regarding CVS sufficient?	Female respondent	Yes	110/125	88.0	81.0–93.1
		No	15/125	12.0	6.9–19.0
	Male respondent	Yes	68/78	87.2	77.7–93.7
		No	10/78	12.8	6.3–22.3
	Total	Yes	178/203	87.7	82.4–91.9
		No	25/203	12.3	8.1–17.6

Abbreviation: CVS, chorionic villous sampling.

testing following PGT. Practically, non-invasive testing should be more manageable compared to invasive testing, as blood sampling is less challenging and time-consuming compared to chorionic villus sampling and amniocentesis. NIPT has been around for 2 decades<sup>23</sup> and has been used clinically for the detection of unbalanced translocations,<sup>24</sup> subchromosomal deletions,<sup>24,25</sup> duplications,<sup>25</sup> copy number variations,<sup>26</sup> and monogenic disorders,<sup>15,27–29</sup> indicating its potential for prenatal testing. Despite the technology being available, implementation of NIPT is challenged by the cost of<sup>30,31</sup> and lack of education of health care professionals on the procedure.<sup>31</sup>

Non-invasive alternatives might differ from the current invasive methods by cost, accuracy, reliability, and the amount of genetic information obtained, and the time in pregnancy at which they can be performed. Importantly, the sensitivity and specificity as well as the risk of inconclusive results have to be properly evaluated prior to clinical implementation. In the case of cbNIPT using short tandem repeat marker analysis as detailed in our recent paper,<sup>15</sup> the accuracy is expected to be similar compared to CVS, as in both cases, intact cells stemming from the placenta are analyzed and informative DNA markers used to ensure that the origin of the DNA can be indisputably determined (or else called as inconclusive). A higher risk of inconclusive test results from non-invasive alternatives should not disqualify it from being used in clinical practice, as long as it can be performed sufficiently early to allow for invasive testing as a second-line option in case of an inconclusive test result. In such a setup, the majority of patients may still avoid invasive prenatal testing.

Importantly, since women have been shown to place much emphasis on test safety, thorough counseling on the pros and cons of available tests is important to facilitate informed decision making and to ensure, that patients think beyond the issue of safety. As detailed in the introduction, doctor-patient communication is challenging.<sup>4–6</sup> Communication may be further complicated by the fact that health care professionals and patients place emphasis on different attributes of NIPT, such as patients caring most about the test safety of the procedure while health care professionals emphasize test accuracy.<sup>13</sup> The task of adequately providing patients with information to enable them to make informed decision on prenatal testing will be further complicated as the number of tests and the amount of obtainable genetic information increases. A rethinking of current methods and the time available for counseling might be imminent. Providing written material that repeats what has been orally

communicated to patients might aid in ensuring that the majority of the patients can make an informed decision. Additionally, facilitating easy communication between the patients and clinic in case that additional questions or uncertainties present themselves may further aid patients in making an informed decision.

Spreading awareness of hereditary disorders is important to improve the chance that couples might become aware of potential hereditary disorders in their family during family planning. Solutions might be increased focus on the topic in schools, national awareness campaigns, or offering couples some form of pregnancy preparation counseling with their general practitioner. This is important so that couples at risk can be informed on the possible alternatives to spontaneous pregnancy during initial family planning, such as adoption, gamete donation, PGT, carrier screening, and prenatal testing, thereby facilitating them in making a properly informed decision. Interestingly, almost 50% of respondents were not aware that they were at risk of passing on a hereditary disorder when they attempted to achieve pregnancy prior to PGT, with almost one in five reporting having a child affected by the hereditary disorder (Table S1). There was a statistically significant difference between respondents being aware and not being aware of their risk of passing on the disorder and the percentage of them reporting having children affected by the disorders prior to initiating PGT (Table S2). This indicates that when aware of the risk, couples tend to choose measures to alleviate the risk. A more in-depth analysis of patients' preferences and opinions on invasive and non-invasive testing when presented with detailed test parameters for each procedure would be interesting to determine how patients rank different test attributes in their decision-making process. Such a study should include but not necessarily be limited to accuracy, reliability, time of pregnancy that the test can be performed, test safety, amount of genetic information obtained and cost. As has previously been performed in the context of NIPT for aneuploidies,<sup>11–13,31</sup> including the preferences of health care professionals would also be interesting.

#### 4.1 | Study limitations

We acknowledge that the number of respondents is small, especially for conditionally branched questions. The general application of

TABLE 5 Non-invasive alternative to CVS

			N	Percentage	CI <sub>95</sub>
Given that it was possible to test whether the fetus had inherited the disorder from a blood sample, would you have opted for this solution? (Assuming that the test is as good as the CVS)	Female respondent	Yes	112/125	89.6	82.9–94.4
		No	8/125	6.4	2.8–12.2
		Do not know	5/125	4.0	1.3–9.1
	Male respondent	Yes	69/78	88.5	79.2–94.6
		No	5/78	6.4	2.1–14.3
		Do not know	4/78	5.1	1.4–12.6
	Total	Yes	181/203	89.2	84.1–93.1
		No	13/203	6.4	3.5–10.7
		Do not know	9/203	4.4	2.1–8.3
Why would you choose the test? (More than one answer is possible)	Female respondent	The procedure is not as unpleasant as CVS	54/112	48.2	38.7–57.9
		No associated risk of miscarriage	106/112	94.6	88.7–98.0
		Other reasons	8/112	7.1	3.1–13.6
	Male respondent	The procedure is not as unpleasant as CVS	39/69	56.5	44.0–68.4
		No associated risk of miscarriage	63/69	91.3	82.0–96.7
		Other reasons	2/69	2.9	0.4–10.1
	Total	The procedure is not as unpleasant as CVS	93/181	51.4	43.9–58.9
		No associated risk of miscarriage	169/181	93.4	88.7–96.5
		Other reasons	10/181	5.5	2.7–9.9
Why would you not choose the test? (More than one answer is possible)	Female respondent	Termination of pregnancy was not an option	6/8	75.0	34.9–96.8
		Do not know	0/8	0	0.0–36.9
		Other reasons	2/8	25.0	3.2–65.1
	Male respondent	Termination of pregnancy was not an option	4/5	80.0	28.4–99.5
		Do not know	1/5	20	0.5–71.6
		Other reasons	0/5	0	0.0–52.2
	Total	Termination of pregnancy was not an option	10/12	76.9	46.2–95.0
		Do not know	1/12	7.7	0.2–36.0
		Other reasons	1/12	7.7	0.2–36.0

Abbreviation: CVS, chorionic villous sampling.

these findings might be limited as the study was performed at a single clinic. Additionally, we do not know if the participants reflect the entire PGT cohort as the approximately one third of invitees not participating might have different views. Lastly, we were not able to match responses where both partners completed the questions, which might have been interesting.

## 5 | CONCLUSION

Despite recommendations from the clinic, approximately half of the women and men achieving pregnancy following PGT declined CVS citing the risk of miscarriage as the primary reason. A substantial fraction of patients achieving pregnancy following PGT report being

concerned or having a desire for verification of the original PGT result, suggesting that measures to enhance uptake of prenatal testing, such as non-invasive alternatives, might provide patients with some ease of mind. The findings presented here suggest that some patients did not understand the limitations of the nuchal translucency scan, warranting better counseling to ensure that couples can make an informed decision on prenatal testing following PGT. Offering a non-invasive alternative to invasive prenatal testing will likely cause a larger fraction of patients to opt for a confirmatory prenatal test following PGT.

## ACKNOWLEDGEMENTS

We would like to thank all the respondents who completed the questionnaire and the personnel at the Department of Molecular Diagnostics, Aalborg University Hospital, the Department of Clinical Genetics, Aalborg University Hospital and the Fertility Unit, Aalborg University Hospital, who provided feedback on the questionnaire during its design. No external funding was obtained for this study.

## CONFLICT OF INTEREST

No authors have any conflicts of interest to declare. Please see the attached ICMJE Forms for Disclosure of Potential Conflicts of Interest.

## ETHICAL APPROVAL

Ethical approval was obtained from the Danish Patient Safety Authority (Reference: 31-1521-19) and the North Denmark Region (Reference: 2020-042859).

## DATA AVAILABILITY STATEMENT

Data acquired in this study is not available for sharing.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Toft CLF, Diemer T, Ingerslev HJ, Pedersen IS, Adrian SW, Kesmodel US. Patients' choices and opinions on chorionic villous sampling and non-invasive alternatives for prenatal testing following preimplantation genetic testing for hereditary disorders: a cross-sectional questionnaire study. *Prenat Diagn.* 2022;1-14. <https://doi.org/10.1002/pd.6088>