European Journal of Human Genetics (2021) 29:851–860
https://doi.org/10.1038/s41431-021-00810-3

ARTICLE

Direct to consumer genetic testing in Denmark—public knowledge, use, and attitudes

Anne-Marie Gerdes[1] · Line Nicolaisen[1] · Egil Husum[2] · Janne Bayer Andersen[1] · Martin Dræbye Gantzhorn[2] · Laura Roos[1] · Birgitte Rode Diness[1]

Received: 14 October 2020 / Revised: 7 January 2021 / Accepted: 7 January 2021 / Published online: 1 March 2021

Abstract

Direct to consumer genetic testing (DTC-GT) is offered by commercial companies, but the use in the general population has only been sparsely investigated. A questionnaire was sent to 2013 representative Danish citizens asking about their awareness and use of DTC-GT. Individuals who had undergone a genetic test were interviewed to determine if the results had been understood correctly. A pilot study with 2469 questionnaires was performed before this study. In total, 45.4% of the individuals ($n = 913/2013$) had knowledge about DTC-GT and 2.5% ($n = (18 + 5)/913$) previously had a genetic test by a private company and 5.8% through the public health care system ($n = (48 + 5)/913$). Curiosity about own genetic information was the most frequent motivation (40.9%, $n = 9/22$) as well as knowledge of ancestry (36.4%, $n = 8/22$) and advice about lifestyle, exercise, or diet (36.4%, $n = 8/22$). Test of own disease risk was given as a reason in 27.3% ($n = 6/22$) and seeking possible explanation of specific symptoms in 13.6% ($n = 3/22$). 50% ($n = 11/22$) answered that they had become concerned after the test, and 17.4% ($n = 4/23$) had consulted their GP. Interviews in a subset of respondents from the pilot study revealed problems with understanding the results. One problem was how to interpret the genetic test results with respect to individual risk for a disease. For example, the difference between disease causing genetic variants in monogenetic diseases versus statistical risks by SNPs in multifactorial diseases was not understood by the respondents.

Introduction

Genetic testing is an integrated element in human health-related strategies, in particular in the diagnostic setting regarding genetic diseases. Traditionally, genetic tests are applied for monogenic disorders in a clinical setting with focus on testing the patient in the context of their family. Commercial genetic testing (Direct To Consumer Genetic Testing, DTC-GT) is increasingly used where individuals can order a genetic test online without involvement of a health care professional and receive the results by e-mail. Many professionals find DTC-GT controversial for various reasons [1–3]. One of the major concerns is that the companies mainly offer testing of Single Nucleotide Polymorphisms (SNPs) associated with multifactorial disorders instead of analyzing validated disease causing variants in known disease related genes [1, 2]. SNPs are important tools for research aimed at finding genetic etiologies for many kinds of diseases. SNP studies are population dependent and usually applied in association studies, but not very useful for disease prediction in healthy individuals.

Commercial genetic testing companies are also offering carrier testing for autosomal recessive disorders, which is relevant when planning pregnancy. One example is cystic fibrosis in the Danish population, due to the high carrier frequency. Not all diseases occur with a frequency that supports testing of these rare conditions in all populations, and not all the diseases found in testing batteries are clinically relevant in a reproductive setting. Furthermore, many companies do not perform full sequencing of the genes of interest, but only analysis of founder variations, where relevance varies between populations.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-021-00810-3.

✉ Anne-Marie Gerdes
Anne-Marie.Gerdes@regionh.dk

[1] Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[2] Bech-Bruun Law Firm P/S, Copenhagen, Denmark

Another concern is the lack of professional counseling and help with interpretation of the results, resulting in an increased risk of misinterpretation of the complex data [3]. A normal test result may give a false sense of security whilst the individual is unaware of the limitations of the test. On the other hand, increased worry may be the result when a risk SNP is detected if this is perceived as carrying a high risk of disease, which may not be the case in multifactorial diseases [3].

Denmark has a national health care system with general practitioners (GP) serving as gate keepers for hospitals and other specialists. GP and hospital consultations do not require payment and genetic testing deemed medically relevant is offered to patients free of charge through the departments of Clinical Genetics. Still, DTC-GT outside the national system could be a positive element in patient empowerment and an important aspect of personalized medicine. It is also relevant for the genetic departments to be prepared for an increasing need for professional genetic counseling of individuals who have difficulties with interpretation of the results from DTC-GT. Several studies have explored the public interest and awareness of DTC-GT with focus on specific groups [4–7], but to our knowledge only one study has explored the actual use of DTC-GT, this was done in a subpopulation in Australia [8]. Therefore, we sent out a questionnaire to a representative group of Danish individuals to determine if the general population was aware of DTC-GT and if they used this service. Furthermore, we investigated whether Danish users of DTC-GT interpreted the medical implications of their test results correctly.

Methods

A questionnaire was created and introduced in a pilot study consisting of two groups: first, a small group of 28 participants at the annual "open hospital" event at Copenhagen University Hospital on the 12th of October 2018. This is a large event where the hospital is open to the population without prior appointment, so the number of visitors is unknown, but exceeds 500 people. Second, participants were recruited from the DR's (Danish Broadcasting Corporation) website via an article about genetic testing with a link to the online survey. The survey was launched on www.dr.dk on the 14th November 2018 and 2441 people responded. In total 2469 persons participated in the pilot study.

A few questions were subsequently added to the questionnaire. The questionnaire survey was conducted by the polling institute "Epinon". Epinion has an established panel of responders, invited to the panel according to the principle of equal sample-extraction probability. Thirty percent ($n =$ 2016 individuals) of invited panelists accepted to join the panel. It is not possible to self-invite. Panelists received a digital invitation and a hyperlink to active questionnaires by e-mail in January and February 2019. Panelists were taken to our survey unless sufficient responses from their subsegments in the underlying sample-matrix (gender, age, and region) had already replied. This ensured a representative distribution based on the latest statistics from the relevant National Bureau of Census. The global completion rate by the panelists was 88%. The questionnaire was administered in Danish and it is available as supplementary material. For the purpose of this report relevant items from the questionnaire have been translated (Tables 1 and 2). The translation is not validated or adapted. The original questionnaire in Danish is available on request.

Participants were asked to provide background information regarding gender, age, educational level, region of residence and self-perceived health. In total, 2013 persons answered the questionnaire (Table 3). They were then asked about their knowledge of and attitudes toward genetic testing and previous experience with genetic testing, both DTC-GT and through the public health system. Those who had undergone DTC-GT were asked about motivation and concern and contact with their general practitioner afterwards. They were also asked if they could be contacted regarding the test results. If they agreed to be contacted, they were invited to an interview with the first author (AMG, who is a medical specialist in Clinical Genetics) of this publication to discuss the results of their tests with a semistructure interview guide containing key elements in understanding DTC-GT. Only participants from the pilot study agreed to be interviewed. The interview was performed as a genetic counseling session, but the participants were also asked questions about the results and the interpretation. All medically relevant abnormal results were discussed with each participant, such as results showing increased risk of disease. The results and genetic framework were explained to the participants with special focus on the differences between risk markers from association studies versus disease causing variants in genes known to be related to monogenic disorders. All participants in the study participated voluntarily and without payment.

Results

Participant flow is shown in Fig. 1.

Pilot study

The questionnaire was answered by 2469 individuals in the pilot study. In total, 66.0% ($n = 1629/2469$) had knowledge of DTC-GT and 12.2% ($n = 200/1629$) had undergone a genetic testing; 8.5% through a hospital ($n = 138/1629$),

Table 1 Respondents who had a DTC-GT.

A. Which of the following statements are important for you when you consider having a genetic test performed online? (You may select more than one answer)

	Pilot study	Study cohort
I am curious about my genes	72.4% ($n = 42$)	40.9% ($n = 9$)
I want more knowledge about my family	58.6% ($n = 34$)	36.4% ($n = 8$)
The genetic test will help me in making decisions about lifestyle, exercise or diet	29.3% ($n = 17$)	36.4% ($n = 8$)
There are diseases in my family, and I want to know my risk	29.3% ($n = 17$)	27.3% ($n = 6$)
I have specific symptoms and I want to have an explanation	3.4% ($n = 2$)	13.6% ($n = 3$)
Others have encouraged me to have a test	6.9% ($n = 4$)	4.5% ($n = 1$)
The test result will not be part om my medical record but will be confidential to my GP and others	8.6% ($n = 5$)	4.5% ($n = 1$)
It is easily accessible/quick, and I do not have to see my GP	19.0% ($n = 11$)	9.1% ($n = 2$)
Other	19.0% ($n = 11$)	4.5% ($n = 1$)

B. Were you more worried after receiving the test results?

	Pilot study	Study cohort
Yes, but only for a short period of time	7.0% ($n = 4$)	4.5% ($n = 1$)
Yes, and I am still worried	1.8% ($n = 1$)	45.5% ($n = 10$)
No, I was relieved	14.0% ($n = 8$)	13.6% ($n = 4$)
No, I did not get worried	77.2% ($n = 44$)	36.4% ($n = 8$)

C. Did the test results influence your decision to see your GP? (You may select more than one answer)

	Pilot study	Study cohort
Yes, I saw my GP because of a risk shown by the test	5.2% ($n = 3$)	17.4% ($n = 4$)
Yes, I have changed my lifestyle due to the test results	5.2% ($n = 3$)	39.1% ($n = 9$)
No	84.5% ($n = 49$)	43.5% ($n = 10$)
Yes, I have avoided seeing my GP due to the test results	0% ($n = 0$)	0% ($n = 0$)
Other	8.6% ($n = 5$)	0% ($n = 0$)

3.6% online ($n = 59/1629$) and 0.2% ($n = 3/1629$) had both online and hospital based testing. In total, 3.8% ($59 + 3/1629$) of the respondents from the pilot study previously had DTC-GT. See Fig. 1 and Tables 1 and 2 for further details.

Study population and knowledge of DTC-GT

The questionnaire was answered by 2013 individuals. The cohort was evenly distributed according to age, gender and region of residence, but with an overrepresentation of individuals with a high school or vocational education. Demographic characteristics of the study population and the participants in the pilot study are reported in Table 3. Of the respondents 45.4% ($n = 913/2013$) had knowledge about DTC-GT.

Experience with genetic testing

The 913 individuals who had knowledge about DTC-GT were asked if they had undergone genetic testing, and 907 responded to this question, and 7.8% ($n = (48 + 18 + 5)/907$) answered positively to this question. In total, 18 respondents had undergone DTC-GT online, 5 had undergone genetic testing both online and at a hospital, 48 had undergone genetic testing through the public health care system (Fig. 1). Thus, in total 2.5% of the respondents had previously undergone DTC-GT ($n = (18 + 5)/907$).

Motivation for DTC-GT

Individuals who had undergone DTC-GT were presented with a number of statements and asked to indicate which of the statements were important for their choice of having DTC-GT. It was possible to select multiple statements. Curiosity about own genetic information was the most frequent motivation (40.9%, $n = 9/22$) as well as knowledge of ancestry (36.4%, $n = 8/22$) and advice pertaining to lifestyle, exercise, or diet (36.4%, $n = 8/22$). Test of own risk for a disease was an explanation for 27.3% ($n = 6/22$) or a possible explanation of specific symptoms in 13.6% ($n = 3/22$).

Table 2 General attitudes toward genetic tests regarding cancer, NIPT (Non Invasive Prenatal Test) and future pregnancies.

A. Would you be interested in buying a genetic test online to examine your risk of a genetic predisposition to cancer?		
	Pilot study	Study cohort
Yes	52.8% ($n = 1145$)	13.9% ($n = 279$)
No	47.2% ($n = 1025$)	63.8% ($n = 1285$)
Do not know	0% ($n = 0$)	22.4% ($n = 450$)

B. Which of the following statements do you agree to?		
	Pilot study	Study cohort
Available and free for all, via GP or public hospital	26.2% ($n = 569$)	23.3% ($n = 470$)
Available and free for all when it is medical relevant, and otherwise with self-payment for other indications	53.2% ($n = 1154$)	46.3% ($n = 933$)
Available and free for all when it is medical relevant, and not available for other indications	18.5% ($n = 401$)	0% ($n = 0$)
Available with self-payment for all	10.8% ($n = 234$)	9.6% ($n = 194$)
Prohibited	0.5% ($n = 10$)	0% ($n = 0$)
Do not know	3.5% ($n = 76$)	20.7% ($n = 416$)

C. A blood sample from pregnant women can with high precision calculate the risk of Down's syndrome and other relatively frequent chromosomal abnormalities in the fetus. If you and your partner were pregnant, would you be interested in such a test? (NIPT: Non Invasive Prenatal Test)		
	Pilot study	Study cohort
Yes	81.8% ($n = 1775$)	56.4% ($n = 1136$)
No	8.4% ($n = 183$)	19.6% ($n = 394$)
Do not know	9.8% ($n = 212$)	24.0% ($n = 483$)

D. Which of the following statements about NIPT do you agree to?		
	Pilot study	Study cohort
Available and free for all, via GP or public hospital	60.7% ($n = 1318$)	42.1% ($n = 847$)
Available and free for all when it is medical relevant, and otherwise with self-payment for other indications	26.5% ($n = 575$)	33.8% ($n = 680$)
Available and free for all when it is medical relevant, and not available for other indications	11.4% ($n = 247$)	0% ($n = 0$)
Available with self-payment for all	3.8% ($n = 82$)	6.0% ($n = 120$)
Prohibited	0.7% ($n = 15$)	0% ($n = 0$)
Do not know	3.0% ($n = 65$)	18.2% ($n = 367$)

E. A blood sample from couples who are planning a pregnancy can with high precision reveal genetic defects that may result in a number of serious genetic diseases in the coming child. If you and your partner were planning a pregnancy, would you then be interested in such a test?		
	Pilot study	Study cohort
Yes	62.8% ($n = 1363$)	40.5% ($n = 815$)
No	20.0% ($n = 433$)	30.0% ($n = 604$)
Do not know	17.2% ($n = 374$)	29.5% ($n = 594$)

F. Which of the following statements about this blood sample do you agree to?		
	Pilot study	Study cohort
Available and free for all, via GP or public hospital	40.3% ($n = 874$)	31.5% ($n = 634$)
Available and free for all when it is medical relevant, and otherwise with self-payment for other indications	36.6% ($n = 795$)	39.6% ($n = 797$)
Available and free for all when it is medical relevant, and not available for other indications	16.8% ($n = 365$)	0% ($n = 0$)
Available with self-payment for all	6.9% ($n = 150$)	9.6% ($n = 194$)
Prohibited	0.9% ($n = 20$)	0% ($n = 0$)
Do not know	5.6% ($n = 122$)	19.3% ($n = 389$)

Table 3 Demographic data from the study cohort and the pilot study.

	Study cohort	Pilot study
Sex		
Male	50.6% ($n = 1018$)	32.5% ($n = 803$)
Female	49.4% ($n = 995$)	67.5% ($n = 1666$)
Age (years)		
<18	0	0.7% ($n = 17$)
18–25	13.4% ($n = 269$)	11.5% ($n = 285$)
26–35	16.4% ($n = 331$)	27.0% ($n = 667$)
36–45	19.3% ($n = 389$)	21.4% ($n = 528$)
46–55	20.3% ($n = 408$)	18.4% ($n = 454$)
56–65	17.3% ($n = 348$)	12.5% ($n = 308$)
66–75	13.3% ($n = 268$)	7.5% ($n = 186$)
>75	0	1.0% ($n = 24$)
Education		
Preschool	1.5% ($n = 31$)	0.2 ($n = 4$)
Primary school up to 6th grade	0.8% ($n = 16$)	0.3 ($n = 8$)
Primary school 7th-10th grade	11.7% ($n = 235$)	4.2 ($n = 104$)
Secondary school (high school)	32.5% ($n = 655$)	14.1 ($n = 348$)
Associate degree	15.8% ($n = 318$)	10.4 ($n = 257$)
Bachelor's degree	22.8% ($n = 458$)	34.3 ($n = 848$)
Master's degree	11.5% ($n = 231$)	30.2 ($n = 746$)
Doctoral degree	1.0% ($n = 20$)	5.3 ($n = 131$)
Do not wish to inform	2.4% ($n = 49$)	0.9 ($n = 23$)
Residence		
Capital Region	28.6% ($n = 576$)	53.4% ($n = 1319$)
Region Zealand	16.6% ($n = 334$)	11.9% ($n = 295$)
Region Southern Denmark	22.1% ($n = 445$)	12.8% ($n = 317$)
Central Denmark Region	10.6% ($n = 214$)	16.4% ($n = 404$)
Region Northern Denmark	22.1% ($n = 444$)	5.4% ($n = 134$)

Concern and contact with GP after the test

All participants who had undergone DTC-GT answered questionnaire items regarding health behavior after receiving the test result. 22 out of 23 individuals (95.7%) answered questionnaire items regarding whether it led to relief or worry (Table 1). Of the 22 individuals answering the question about worries, 11 (50%) had become worried and 4 of these consulted their GP because of the test and 7 made lifestyle changes. The 11 responders that were not worried did not consult their GP and only 2 made lifestyle changes.

Attitude to genetic testing for specific health related risks

All participants were asked if they would be interested in a genetic test that could reveal information on specific health-related risks. All participants answered these questions, results are shown in Table 2. 118/801 responders (15%) quoted concerns regarding data protection as a reason for not having DTC-GT. In the pilot study 354/1065 (33%) quoted this reason.

All participants were asked about interest in carrier screening of couples planning pregnancy (typically autosomal recessive and X-linked disorders) and 2013 individuals responded to this question: 40.5% ($n = 815/2013$) replied that they were interested in this kind of genetic test, 30.5% ($n = 604/2,013$) were not interested, and 29.5% ($n = 594/2013$) had not decided (Table 2). Respondents of the reproductive age, for whom pregnancy is more relevant, were generally more positive toward carrier screening (45% in the age range of 18–25 years old vs. 37% in those above 55 years, data not shown).

Follow-up appointments

None of the 23 DTC users in the study group allowed us to contact them for evaluating their results from the genetic tests performed via internet-based companies. In total, 6 of these 23 responders answered that their motivation was interest in knowledge about a disease running in the family, and 3 individuals responded that they were seeking information about specific symptoms. From the pilot study 34 persons with experience with DTC allowed us to contact them. One of these 34 individuals was a colleague to the authors and was excluded from the interview.

Thirteen (13) individuals did not reply when they were contacted twice, 9 cases had a genetic test done due to non-health related issues (exercise, diets, etc.) and 11 cases were related to a potential genetic predisposition to disease. An appointment was established in 6 of these 11 cases (the remaining 5 cases had not confirmed a date for appointment after at least 6 months since the last contact). The 6 appointments were performed face-to-face at the hospital clinic in 4 cases, by telephone in one case, and by Skype video in the last case. Two (2) cases had used 23AndMe, 2 cases had used Ancestry and uploaded the results into Livewello and Promethase respectively, and the last 2 cases had their genetic test done by other companies not revealed to the interviewer.

The reason for choosing genetic tests by private internet-based companies was curiosity in 3 cases, 1 case was due to ethnicity, but the individual also uploaded raw data for own interpretation concerning disease risks, 1 case was due to neurodegenerative diseases in the family, and the last case was not clearly stated, but included concerns regarding symptoms in an offspring.

Four interviewees had not understood how to interpret the majority of the genetic test results with respect to individual risk of a disease. For example, they did not know the difference between disease causing genetic variants in monogenetic diseases versus statistical risks by SNPs in multifactorial diseases. In one of these 4 cases a risk factor (apoE4) was detected and the individual did understand this result correctly. Two cases (where the interviews were done

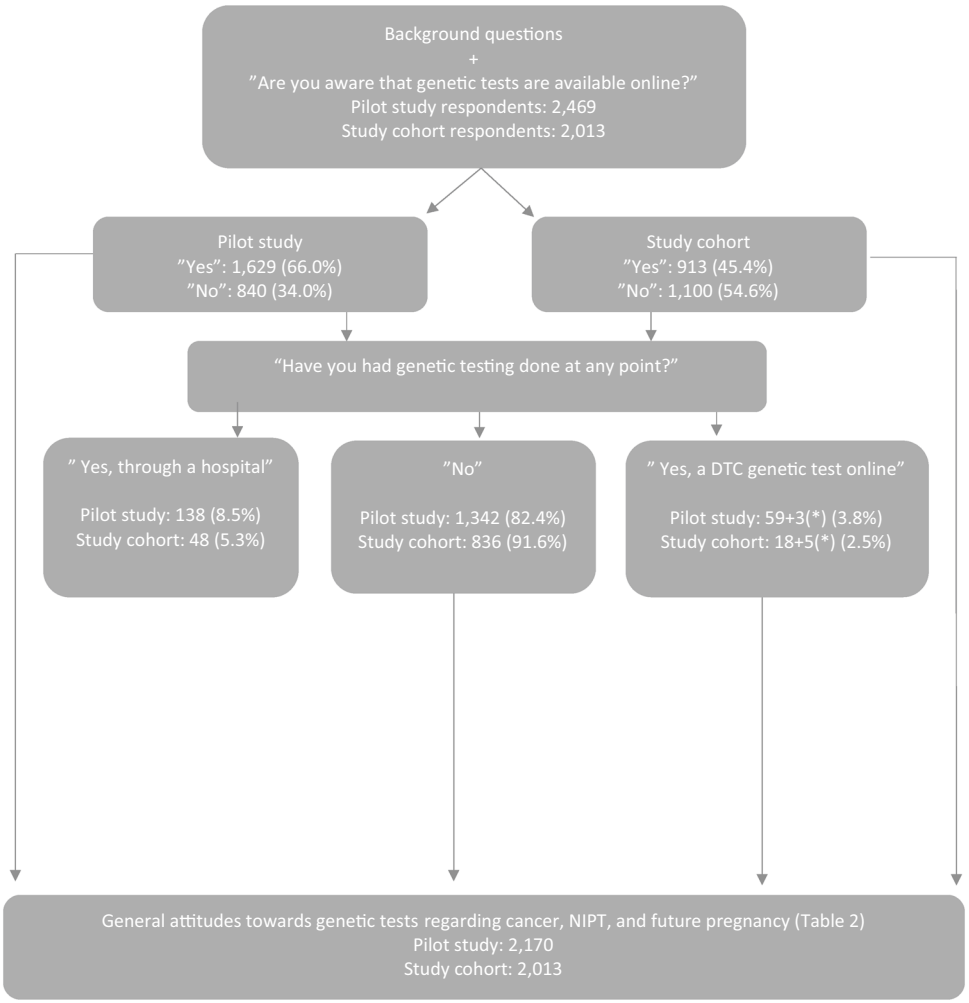

Fig. 1 Flow diagram of the study. Main questions and number of respondents. (*) this includes both people who only had a DTC-GT and people who had both a DTC-GT and a genetic test through a Public Hospital. DTC-GT: Direct To Consumer Genetic Test.

by telephone or Skype) said they had understood the results, but the individual results were not discussed in detail with the interviewer. In 3 of the 6 interviewed cases, a risk of age-related macular degeneration was detected, but in one of these cases this was not reported as a risk factor by the company.

Discussion

The public interest in DTC-GT has been studied in different countries but most of the studies only inquired into the intent to use this commercial approach to genetic testing [4, 5, 7, 9]. We investigated a representative group of 2,013 individuals and asked them about their awareness of and experience with DTC-GT. In total, 45% of the responders expressed knowledge about DTC-GT and 2.5% had undergone DTC-GT and 5.8% had genetic testing through the public health care system. The motivations for genetic testing were primarily interest in knowledge about risk of diseases and/or curiosity, but ancestry and help in planning a healthy lifestyle, exercise or diet decisions were also important.

An Australian study asked a selected group of participants from the multi-stage Genioz study about their awareness of, attitudes toward and experiences with genetic testing, seeking help with interpretation of tests, privacy and third-party access to genomic data among other issues [8]. Recruitment also used social media, and a survey marketing company was used toward the end of recruitment to increase under-represented areas. 571 out of 2841 (20.1%) had undergone genetic testing of any type. In total, 322 out of 2841 (11.3%) respondents reported having been tested by a personal genomic test (DTC-GT) which is much higher than our cohort of 2.5%. The Australian study showed that 82.9% reported ancestry and/or genealogy as the reason for testing, 31.4% for carrier testing, 31.4% for serious and preventable diseases, 20.2% for nutrition and/or wellness, and 5.9% for fitness related causes. The present study does not allow conclusions as to why this difference between Denmark and Australia is so pronounced. We speculate that the relative homogeneity of the Danish population explains

the lower curiosity regarding ancestry, but differences in the public health system and the non-randomly selection of participants in the Australian study may also contribute and prevent conclusions regarding true differences.

DTC-GT in the form of reproductive carrier screening is increasingly used to identify individuals whose children may be at high risk of developing recessive or X-linked diseases [10]. Screening can provide couples with the ability to make choices regarding reproductive planning. Attitudes toward screening and the expected uptake rate are highly dependent on the population's general knowledge of genetic diseases, perception of risk, financial framework, and ethical and religious believes [11, 12]. The variability in uptake rates found in different populations reflect this: In a recent literature review, van Steijvoort et al. included 12 studies surveying the respondent's attitudes toward reproductive carrier screening. Between 32% and 76% of the respondents were interested in a hypothetical carrier screening, while the studies investigating the actual uptake of a carrier screening found rates to be lower, between 8 and 50%. In general, a higher uptake rate was found among pregnant woman, compared to respondents in the pre-conception period, suggesting that the respondents have a higher interest in carrier screening when it is immediately relevant [13]. In our study, 40.5% ($n = 813/2013$) of the respondents were positive concerning carrier screening and, not surprisingly, that respondents of the reproductive age were more positive. Of the 41% of respondents interested in extended carrier, 31.5% ($n = 634/2013$) thought it should be accessible and free to everyone through the public health care system. The only other study of attitudes toward reproductive carrier screening in the Danish population is a pilot study in 1990–1992, where cystic fibrosis carrier screening was offered to pregnant women. A very high uptake rate of 89% was found [14]. A Swedish study conducted a study among pregnant women and their partners and found that approximately one-third of the respondents would consider carrier screening [15], and similar results, with 31% of respondents expressing interest, were found in a Dutch study including respondents in the reproductive age, but not necessarily planning a pregnancy [16]. Although our study does not allow an in-depth analysis of the motives for requesting carrier screening or potential concerns, our result does indicate a high level of interest in the Danish population compared to neighboring countries. Further studies are needed to understand the public perception of carrier screening and thereby optimize the possible clinical use of reproductive carrier screening.

An increase in the use of DTC-GT is to be expected, as the awareness of the possibilities of online genetic testing in the population is increasing in combination with the empowerment of patients and citizens as part of the strategy for personalized medicine. Genetic knowledge may be perceived as increasingly relevant for many people, but one concern is the product delivered by many DTC-GT companies does not support the necessary tools for clarification. Even for professionals, interpretation of complex genetic results can be difficult [17]. One aspect is insufficient help with the interpretation of complex results from genetic testing, thereby risking delivering an insufficient or even false answer to the question motivating the test. This is in accordance with the results from interviews of 4 participants in this study where the overall conclusion was that the interviewed persons did not understand the results of the genetic test performed by the internet-based company. In contrast to our findings Ostergren et. al. found a high degree of comprehension when DTC users were presented with hypothetical scenarios [18] but research in the area is conflicting [3, 18, 19].

Another issue is incorrect interpretation of gene variants by the company or the software used by the individual. This can result in false positive results where the individual interprets benign gene variants as disease-causing variants or to inaccurate estimation of risk [20]. The authors of this study have encountered several examples from the clinic in which patients could not differentiate between benign gene variants and disease-causing variants in the *BRCA1/2*-genes. Sometimes the individual uploaded the raw data into a software program using databases which were not sufficiently updated, resulting in wrong conclusions. False positive results and overestimation of risk can create a demand for professional help and request for genetic counseling, which is problematic, because most genetic departments do not have the resources to accomplish this task [2, 3, 21]. False positive results can also create opportunistic screening, that is the tested person's request for screening even though there is no medical indication. False negative results may also be problematic because they can give the individual a false sense of security, so they may not be aware of symptoms of a disease, thereby delaying a diagnosis and relevant treatment. In this study we interviewed 4 individuals about their DTC-GT results. The overall conclusion was that they did not understand the reported medical implications of the genetic test performed by the internet-based company. Several of the interviewed persons expressed frustration about having received results that were not explained sufficiently to them by the company.

The Australian study showed that up to a third of participants sought medical advice after receiving the results [8]. Our study showed that 50% of the respondents had become concerned after receiving the results from the DTC-GT. In total, 17% had consulted their GP because of a disease risk revealed by the test and 40% remained concerned even after discussing the test result with their GP. These results must be interpreted with caution because of small numbers, but

the trend is worrying. It is in agreement with other studies of health care behavior after DTC, showing that a high percentage of consumers contact health care professionals after having received the results [19, 22]. In Denmark 70 clinical geneticist are currently registered by the health authorities, but far from all are clinically active in the public health system. Our study showed that 23 participants had DTC-GT while 48 had genetic testing through a hospital. This shows that a substantial fraction of the genetic testing activity is performed outside the public health care system despite the publicly funded approach. Plöthner et al. reflect over the implications in a publicly financed health-care system and speculate that results of DTC may influence expenditure in other parts of the health care system [23]. As usage of DTC-GT increases, the potential risk of skewing the distribution of use of health-care resources also grows, risking increased inequality in the society.

In 2018 we conducted a pilot study among GPs in the Capital Region to see if they had been contacted by patients after DTC-GT and appr. 30% had experienced patient requests (unpublished data). 67 GPs responded and only 4 GPs felt sufficiently educated to handle this kind of requests, 16 felt moderately educated, 15 felt educated to a minor degree, and 31 felt not prepared at all. Fifty-two out of the 67 GPs suggested proper updating and an online tool/website for this. This indicates that there is a need to involve and educate GPs to handle such questions from their patients.

A third aspect is the insufficient quality-control of the technical parts of the analyses. Tandy-Connor (2018) showed that 40% of variants in a variety of genes in DTC-GT raw data were false positives [24]. This is in accordance with the experience by the authors of this study where we repeated the analysis from DTC-GT in several cases from the clinic with a suspicion of a disease causing variant in *BRCA1/2*-genes and were only able to confirm one case (unpublished data). The American Association for Molecular Pathology Position Statement about DTC-GT from June 2019 states that they support DTC-GT for clinically meaningful tests, which may benefit consumers especially when health related tests have well-established clinical validity and the data and analytical methodology should always be present for the consumer [25]. Furthermore, referral for genetic counseling services are recommended as well as the importance of information to relatives. The results from the present study do not indicate that these guidelines are followed by private DTC-GT companies. Furthermore, there are varying degrees of regulation across different countries which is furthermore complicated when individuals live in one country and the company is located in another country [26, 27]. This problem can only be solved by an international agreement.

A specific challenge is genetic testing of children when the parents choose DTC-GT for late-onset-disorders such as hereditary breast-ovarian cancer or for disorders where the clinical validity is insufficient [24, 28]. In clinical genetics it is customary to adhere to the European Convention on Human Rights and Biomedicine, that discourages genetic testing of minors unless it is in their direct interest. Therefore, testing children for late-onset disorders have been postponed until adulthood in respect of the child's autonomy. The increasing use of whole genome sequencing (WGS) challenges this, but in Denmark WGS is only an option in the health care system after informed consent from the parents where issues such as reporting secondary findings are discussed before the genetic test is performed. There is a concern that information of late-onset disorders could harm the child and result in discrimination and/or stigmatization.

Data protection and privacy are also major concerns. The reason is that DTC-GT involves genetic data and the results will often be considered as data concerning health. Both genetic data and data concerning health are considered as special categories of personal data pursuant to the GDPR. There is a general prohibition in the GDPR on processing special categories personal data unless one of the exceptions apply.

In the context of a private companies' processing of genetic data and data concerning health as part of DTC-GT, an explicit opt-in consent, which complies with the strict requirements in the GDPR, will normally be required as legal basis.

There is also a risk that the companies will disclose customers' data with third-party collaborators [1]. In this study 15% of responders worried about data security, and more than twice as many from the self-recruited cohort (the pilot study) had this concern.

It must be assumed that disclosure of genetic data and data concerning health from a DTC-GT test, as a minimum will result in substantial demands on the information to be provided to customers for the purposes of transparency and the legal basis of consent. Given the very different purpose of the disclosure than the test itself, even consent as legal basis may not be sufficient to legally disclose such data to third parties depending on the purpose and the circumstances of the disclosure.

There are limitations of this study. Even though the cohort was statistically representative for age, region and sex non-participants may have a different awareness and attitude to DTC-GT from participants. The study design aimed to reduce bias by ensuring responses distributed over sex, region, and age, but residual bias is possible. The number of individuals who had a DTC-GT for health-related issues was low which makes the results less reliable and only participants from the pilot study agreed to be

interviewed about their understanding of the results. The strength of this study is that it represents a large and likely representative sample of Danish individuals, whereby the results will represent the Danish population more accurately than the pilot study where participants were recruited by a website.

With the increasing involvement of the public in commercial genetic tests there is a need to address some of the concerns and pitfalls. There are technical challenges with the genetic analyses performed by the companies, but these will be overcome in the near future when the proper techniques will be implemented and when the prices will be reduced. But there will still be a need for tailored and evaluated information, interpretation, and counseling of the individuals. This study shows that the current information to the consumers is insufficient. Whether this should be solved by the DTC-GT providers or handled in the health care system is controversial. A more transparent consent form should be developed so the customers know to what they are consenting. Data protection and patient privacy are more relevant now than ever because of the large amounts of sensitive data that are stored by the private companies. It would be best to have a global regulation of online DTC-GT companies or at least the same regulation within EU where The European Society of Human Genetics has official recommendations [29].

In conclusion, the increasing use of DTC-GT with insufficient information and counseling provided by the DTC-GT companies to the consumers will cause an increased demand for genetic counseling provided by the public health care in Denmark. This will result in inappropriate use of the limited resources in the public health care and this will also increase inequality in the society. It should be possible to demand that the companies provide better and more professional information of the consumers. Improvement of genetic knowledge in the public and education of GPs should also be prioritized. Another important issue is lack of regulation and control of the techniques and laboratory methods used by the companies where regular and transparent quality assessment programs should be mandatory just like the certified hospital-based laboratories. But also, critical assessment of the clinical validity of the tests provided by the companies is highly needed.

Acknowledgements Dr. Thomas Saxild is greatly acknowledged for his contribution to the survey sent to GPs in the Capital Region. All participants in the study are acknowledged and especially the persons who shared their genetic test results during the interview. Dr. Sophia Hammer-Hansen is greatly acknowledged for excellent help with English editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Petersen LM, Lefferts JA. Lessons learned from direct-to-consumer genetic testing. Clin Lab Med. 2020;40:83–92.
2. Horton R, Crawford G, Freeman L, Fenwick A, Wright CF, Lucassen A. Direct-to-consumer genetic testing. BMJ. 2019;367:1–6.
3. Dinulos MBP, Vallee SE. The impact of direct-to-consumer genetic testing on patient and provider. Clin Lab Med. 2020;40:61–7.
4. Charbonneau J, Nicol D, Chalmers D, Kato K, Yamamoto N, Walshe J, et al. Public reactions to direct-to-consumer genetic health tests: a comparison across the US, UK, Japan and Australia. Eur J Hum Genet. 2020;28:339–48.
5. Critchley C, Nicol D, Otlowski M, Chalmers D. Public reaction to direct-to-consumer online genetic tests: Comparing attitudes, trust and intentions across commercial and conventional providers. Public Underst Sci. 2015;24:731–50.
6. Stewart KFJ, Wesselius A, Schreurs MAC, AMWJ Schols, Zeegers MP. Behavioural changes, sharing behaviour and psychological responses after receiving direct-to-consumer genetic test results: a systematic review and meta-analysis. J Community Genet. 2018;9:1–18.
7. Mavroidopoulou V, Xera E, Mollaki V. Awareness, attitudes and perspectives of direct-to-consumer genetic testing in Greece: a survey of potential consumers. J Hum Genet. 2015;60:515–23.
8. Metcalfe SA, Hickerton C, Savard J, Stackpoole E, Tytherleigh R, Tutty E, et al. Australians' perspectives on support around use of personal genomic testing: findings from the Genioz study. Eur J Med Genet. 2019;62:290–9.
9. Schaper M, Wöhlke S, Schicktanz S. "I would rather have it done by a doctor"—laypeople's perceptions of direct-to-consumer genetic testing (DTC GT) and its ethical implications. Med Heal Care Philos. 2019;22:31–40.
10. Henneman L, Borry P, Chokoshvili D, Cornel MC, El CG Van, Forzano F, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet. 2016;24:1–12.
11. Holtkamp KCA, Mathijssen IB, Lakeman P, Maarle MC Van, Dondorp WJ, Henneman L, et al. Factors for successful implementation of population-based expanded carrier screening: learning from existing initiatives. Eur J Public Health. 2017;27:372–7.
12. Shiroff JJ, Nemeth LS, Jefferson T. Public perceptions of recessive carrier prenatal periods. J Obstet Gynecol Neonatal Nurs. 2015;44:717–25.
13. Van Steijvoort E, Chokoshvili D, W Cannon J, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Hum Reprod Update. 2020;26:335–55.
14. Brandt NJ, Schwartz M, Skovby F. Screening for carriers of cystic fibrosis. Result of a pilot study among pregnant women. Ugeskr Laege. 1994;156:239–44.
15. Ragnar ME, Tydén T, Kihlbom U, Larsson M, Ekstrand M, Tydén T, et al. Swedish parents' interest in preconception genetic carrier screening. Ups J Med Sci. 2016;121:289–94.
16. Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. Mol Genet Metab. 2019;126:14–22.
17. McGrath SP, Walton N, Williams MS, Kim KK, Bastola K. Are providers prepared for genomic medicine: Interpretation of Direct-to-Consumer genetic testing (DTC-GT) results and genetic self-efficacy by medical professionals. BMC Health Serv Res. 2019;19:1–12.

18. Ostergren JE, Gornick MC, Carere DA, Kalia SS, Uhlmann WR, Ruffin MT, et al. How Well Do Customers of Direct-to-Consumer Personal Genomic Testing Services Comprehend Genetic Test Results? Findings from the Impact of Personal Genomics Study for the PGen Study Group. Public Health Genom. 2015;18:216–24.
19. Kaufman DJ, Bollinger JM, Dvoskin RL, Scott JA. Risky business: risk perception and the use of medical services among customers of DTC personal genetic testing. J Genet Couns. 2012; 21:413–22.
20. Roberts JS, Ostergren J. Direct-to-consumer genetic testing and personal genomics services: a review of recent empirical studies. Curr Genet Med Rep. 2013;1:182–200.
21. Jonas MC, Suwannarat P, Burnett-Hartman A, Carroll N, Turner M, Janes K, et al. Physician experience with direct-to-consumer genetic testing in Kaiser permanente. J Pers Med. 2019;9:47.
22. Millward M, Tiller J, Bogwitz M, Kincaid H, Taylor S, Trainer AH, et al. Impact of direct-to-consumer genetic testing on Australian clinical genetics services. Eur J Med Genet. 2020;63:103968.
23. Plöthner M, Klora M, Rudolph D. Health-related genetic direct-to-consumer tests in the German setting: the available offer and the potential implications for a solidarily financed health-care system. Public Health Genom. 2017;20:203–17.
24. Tandy-Connor S, Guiltinan J, Krempely K, LaDuca H, Reineke P, Gutierrez S, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med. 2018;20: 1515–21.
25. Association for Molecular Pathology. Association for Molecular Pathology Position Statement: Consumer Genomic Testing. 2019. https://www.amp.org/AMP/assets/File/position-statements/2019/AMP_Position_Statement_Consumer_Genomics_FINAL.pdf?pass=73 (accessed 29 Sep2020).
26. Hoxhaj I, Stojanovic J, Sassano M, Acampora A, Boccia S. A review of the legislation of direct-to-consumer genetic testing in EU member states. Eur J Med Genet. 2020;63:103841.
27. Borry P, Van Hellemondt RE, Sprumont D, Jales CFD, Rial-Sebbag E, Spranger TM, et al. Legislation on direct-to-consumer genetic testing in seven European countries. Eur J Hum Genet. 2012;20:715–21.
28. Clayton EW. Be ready to talk with parents about direct-to-consumer genetic testing. JAMA Pediatr. 2020;174:117–8.
29. Borry P. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. Eur J Hum Genet. 2010;18: 1271–3.