# How to approach direct-to-consumer genetic testing in primary care?

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**Abstract**

*Introduction*

Genetic testing has in recent years become more easily accessible through direct-to-consumer (DTC) genetic tests which can be ordered online. These tests have become increasingly affordable, resulting in an increase of people ordering a test kit. The patients' motives are mostly health related, though the entertainment value also plays an important role in the increasing popularity. Concerns around the clinical validity and ethical consequences of these test results have been expressed by multiple studies. Also, primary care physicians report a lack of knowledge to adequately advise their patients who want to undergo or have undergone such genetic testing. In this study, the patients' motives for ordering a direct-to-consumer genetic test is assessed through a study of currently available literature. Additionally, we assessed the opinion, experience and knowledge of the primary care physician by organising focus groups as well as studying available literature, in order to clarify how to approach DTC genetic testing in primary care.

*Material and methods*

This study is twofold. First, an extensive literature review concerning direct-to-consumer genetic testing was conducted. Secondly, a qualitative study was conducted by means of two consecutive focus groups, consisting of 12 Belgian primary care physicians. In the first focus group they were asked about their opinion, experience and knowledge as regards to direct-to-consumer genetic tests. Based on the results from this focus group, as well as results from our literature study, we developed a decision support tool to assist in advising patients wanting to undergo genetic testing and patients who already had undergone testing and needed help with the interpretation of the results. In the second focus group the decision support tool was presented to and discussed with the same 12 Belgian primary care physicians. Additionally, the decision support tool was demonstrated with a few clinical cases (see attachment 6).

*Results*

Focus groups and literature review have shown that patients' motives to undergo genetic testing include mainly curiosity and impulsivity. Also, the 'worried well' tend to order a DTC genetic test more often. The added value for the primary care physician is rather limited since clinical validity of test results is questionable. Also, primary care physicians report insufficient knowledge and experience. The role of the primary care physician according to them is mainly to provide information pre- and post-test, as well as make appropriate referrals and protect the patient from commercial motives. More educational support for the primary care physician in order to fulfil this role is much needed. Therefore, we developed a decision support tool for the primary care physician confronted with DTC genetic testing which is presented under the result section. Further

research for the refinement of the support tool is necessary as experience with the tool in daily practice increases. Also, more education for primary care physicians concerning genetics and genetic testing should be provided. Furthermore, primary care physicians ask for an enhancement of the cooperation between them and genetic specialists. In order for Europe to adequately prepare for the increase of DTC genetic testing, it is necessary to develop a universal legal framework.

*Discussion*

Ethical considerations are mainly related to patient privacy and data sharing, since several companies' disclosures do not comply with international guidelines and recommendations on DTC genetic testing. A clear legal framework around DTC genetic testing is still lacking to this day. The ethical duty to provide care for patients who ordered their genetic test on their own initiative creates a field of tension between the patient and the health care provider. It is important for companies providing DTC-genetic tests as well as health care providers to acknowledge the patient's right not to know. We describe several conditions that will need to be met in order for DTC-genetic testing to have an added value for the patient. The goal of our decision support tool is to help the patient and health care provider to be aware of the ethical considerations.

*Conclusion*

DTC genetic tests are on a rapid rise. Patients are mainly driven by curiosity or impulsivity to order one. This confronts them with potentially unwanted results and the urge to improve their health. The goal of this study is to help primary care physicians confronted with DTC genetic testing in their practice. In the focus groups the main concern was a lack of knowledge with primary care physicians and the questionable clinical validity of DTC genetic testing. This was confirmed in our literature review. In order to fill this gap we present the first detailed decision-support tools for primary care physicians, advising patients both before and after direct-to-consumer genetic testing.

**Abstract (Nederlands)**

*Introductie*

Genetische testen zijn de afgelopen jaren meer toegankelijk geworden door 'direct-to-consumer' (DTC) testen die online besteld kunnen worden. Deze testen worden steeds goedkoper en bijgevolg is er een toename in het aantal bestellingen van de testkits. Het motief van de patiënt is meestal gezondheid-gerelateerd, doch ook het entertainment gehalte van de testen is mede verantwoordelijk is voor de toenemende populariteit. Meerdere studies uiten bezorgdheden omtrent de klinische validiteit van de testen alsook de ethische consequenties. Verder rapporteren huisartsen een gebrek aan kennis om patiënten die dergelijke testen hebben ondergaan adequaat te kunnen adviseren. In deze studie werd de ervaring, kennis en mening van huisartsen onderzocht om na te gaan hoe direct-to-consumer genetische testen het best worden benaderd in de eerstelijns gezondheidszorg.

*Materialen en methoden*

Deze studie is tweeledig. Enerzijds werd een uitgebreide literatuurstudie uitgevoerd omtrent DTC genetische testen. Anderzijds werd een kwalitatieve studie opgezet waarbij twee opeenvolgende focusgroepen, bestaande uit 12 huisartsen, werden georganiseerd. In de eerste focusgroep werd hun mening, ervaring en kennis omtrent DTC genetische testen geëxploreerd. In de tweede focusgroep werd een beslissingshulp instrument gepresenteerd om hen te ondersteunen in het adviseren van patiënten die overwegen dergelijke test te bestellen, maar ook patiënten die reeds een test hebben ondergaan en advies vragen bij het interpreteren van de test resultaten. Deze beslissingshulp werd ontwikkeld op basis van zowel de literatuurstudie als de input en feedback uit de focusgroepen.

*Resultaten*

Het motief van patiënten wordt gedreven door nieuwsgierigheid en impulsiviteit. Verder bestellen 'the worried well' vaker DTC genetische testen. De toegevoegde waarde van de testen is eerder beperkt voor huisartsen gezien de klinische validiteit op heden onduidelijk is. Huisartsen rapporteren in de focusgroepen onvoldoende kennis en ervaring. De rol van de huisarts is volgens de deelnemers voornamelijk door informatie te verschaffen aan de patiënten zowel voor als na de test, alsook correcte verwijzingen maken en hen beschermen voor commerciële motieven. Om deze rol op zich te kunnen nemen is meer educatieve ondersteuning nodig. Om aan deze nood tegemoet te komen ontwikkelen wij in deze studie een beslissingshulp instrument die onder de resultatensectie gepresenteerd wordt.

*Discussie*

Ethische bezorgdheden zijn voornamelijk gerelateerd aan privacy van de patiënt en gegevens uitwisseling, gezien de algemene voorwaarden van meerdere commerciële bedrijven niet voldoen aan de richtlijnen uitgeschreven door de 'European Society of Human Genetics'. Een duidelijk wettelijk kader omtrent DTC genetische testen is tot op vandaag niet aanwezig, maar indien Europa zich correct wenst voor te bereiden op de opkomst van DTC genetische testen, zal een universeel wettelijk kader zich opdringen. Verder creëert de ethische verplichting om zorg te bieden aan patiënten die op eigen initiatief een genetische test bestelden een spanningsveld tussen patiënt en arts. Het is belangrijk dat zowel de bedrijven die genetische testen aanbieden, als artsen de patiënt correct informeren omtrent het 'recht om niet te weten'. Vervolgens beschrijven we enkele voorwaarden waaraan DTC genetische testen in de toekomst zullen moeten voldoen om te integreren als volwaardige speler in de gepersonaliseerde geneeskunde. Het beslissingshulp instrument kan mede een hulp zijn voor de huisarts om zich bewust te worden van bovenstaande ethische bezwaren en dit te bespreken met patiënten.

*Conclusie*

DTC genetische testen zijn aan een opmars bezig. Patiënten worden voornamelijk gedreven door nieuwsgierigheid en impulsiviteit bij het online bestellen van een test. Dit confronteert hen met potentieel ongewenste resultaten alsook mogelijke gezondheidsrisico's. Het doel van de studie is om huisartsen te ondersteunen wanneer zij in de dagelijkse praktijk geconfronteerd worden met DTC genetische testen. Zowel in de focusgroepen als de literatuurstudie is er voornamelijk bezorgdheid omtrent een gebrek aan kennis onder huisartsen alsook ontoereikende klinische validiteit van de testen. Om tegemoet te komen aan dit tekort hebben wij beslissingshulp instrument ontwikkeld en gepresenteerd in deze studie. Dit kan huisartsen ondersteunen in het adviseren van patiënten zowel voor als na het uitvoeren DTC genetische testen.

## Introduction

In the last decade companies have given people the opportunity to learn more about their DNA by offering the possibility to order a personal genome test without the involvement of a physician. Due to the rapid developments in genome technology and the growing interest in personalised medicine, the supply and use of these commercial tests is increasing rapidly, unlike the price which is continuously decreasing. These tests will among other things predict the likelihood of developing common diseases, predict medication-responses, trace genetic ancestry and search for single gene disorders (1–3). Most commonly these direct-to-consumer (DTC) genetic tests can be ordered via the internet without the intervention of a medical care professional, by providing a saliva sample using a saliva collection kit and sending it back to the company's lab, where it will be analysed.

The patient's motivation for ordering a DTC genetic test is mainly health related. The most common reasons include curiosity regarding ancestry, to assess the risk of developing a potentially hereditary disease, to make lifestyle changes, to support their own personal health management, as well to assist their physician to more adequately manage their health (4–6).

However, a few constraints of DTC genetic tests have emerged since they have been commercially available. There are serious ethical concerns about the way in which commercial companies are currently introducing genetic tests to the market outside of the scope of the traditional healthcare system. A general recommendation of the European Society of Human Genetics (ESHG) concerning DTC genetic testing goes as follows: in biomedical research, health care and marketing, relevant ethical principles should be respected, as well as international treaties and recommendations regarding genetic testing. Also, nationally approved guidelines considering all the above-mentioned aspects should be made and followed (7).

Specifically as regards privacy and confidentiality, the ESHG and the American College of Medical Genetics state that sensitive genetic information should be secured and the data safely guarded. Also, all claims regarding genetic tests should be transparent, advertisement should be unbiased and marketing of genetic tests should be fair (7,8). According to them, prior to testing, the patient should be informed as to who will have access to test results, how their results will be protected, what will happen to the DNA sample, and whether the test results may have any personal or family-related implications (7,8)

However there are multiple instances where disclosures do not comply with those guidelines. For example, DTC genetic testing companies do not have the necessary mechanisms in place to ensure that the biological sample provided for testing is obtained from the person claimed to be the sample provider (7). Moreover, most companies do not provide sufficient or clear information to patients about sharing data to third parties, also

some companies might have conducted research with consumer data without clear consent (9). This inadequate consent process through which customers are enrolled in such research can undermine the validity of the consent and raises serious concerns about privacy (9–11). Several studies therefore suggest the use of informed consent. DTC genetic testing companies still need to improve the transparency regarding handling of consumers' samples and data, including having an explicit and clear consent process for research activities (9).

Furthermore the validity and proven clinical utility of these tests is currently unclear (12). Therefore there often is an inability to determine the absolute disease risk for the patient, an absence of concrete health recommendations based on the results and a limited explanation of test results (13,14). The companies who supply these tests state that they will not provide medical advice and the results are not intended to be used for diagnosis or treatment (1,15). Since DTC genetic testing has become more common and since there is a limited availability of genetic counsellors, patients increasingly ask advice from their primary care physician on how to interpret their results and whether to follow up with additional testing (16–18). Primary care physicians are willing to help patients, although at this moment their knowledge, awareness and experience appears to be insufficient to adequately interpret the results and give proper advice (17,19,20).

Given the fact that there is a lack of knowledge among primary care physicians concerning DTC genetic testing, the objective of this study is to develop a decision support tool which they can use when confronted with patients asking for advice or dealing with results of those tests. On the one hand this decision support tool is based on the available literature concerning DTC genetic testing, with a focus on the obstacles and experiences primary care physicians are confronted with. On the other hand we organised two consecutive focus groups consisting of primary care physicians of whom we assessed their experience, ethical opinion and educational needs regarding DTC genetic testing and explored the practical use and feedback on the development of the decision support tool.

## Material and methods

In our study the knowledge, opinion and experience from primary care physicians, as well as the ethical consequences concerning direct-to-consumer genetic testing, is assessed by both a qualitative study as well as an extensive literature review.

In order to be able to have a better understanding of the point of view from the primary care physician in Belgium, we organised two consecutive focus groups with the same 12 primary care physicians, to assess their knowledge and experience with DTC-genetic tests and to present them the first draft of our decision support tool, designed to guide primary care physicians when they're confronted with DTC-genetic tests, before and after undergoing testing.

Qualitative study

A qualitative study (i.e. prospective observational) in which data were collected from licensed primary care physicians regarding their experience and knowledge of direct-to-consumer genetic testing was conducted with approval of the Research Ethics Committee of UZ Gent (see attachment 1). This was done by means of an initial focus group in which primary care physicians were asked about their current knowledge, experience and approach to direct-to-consumer genetic testing. Afterwards, data processing from this focus group in combination with a literature review resulted in the development of a decision support tool that can assist primary care physicians when confronted with direct-to-consumer genetic testing, helping the patient with the decision whether or not to undergo genetic testing, the interpretation of results and clinical decision-making. This decision support tool was presented to the same group of participants in a second focus group a few months later, where its practical usability and added value for practice was evaluated through specific clinical case presentations (see attachment 6 for the discussed case reports).

*Focus groups*

- *Recruitment of participants*

For this study, two consecutive focus groups were conducted on May the 27th 2021 and October the 7th 2021. Both focus groups were approximately 90 minutes long and were conducted in a local private conference room with a moderator and an assistant. With the help of chairmen of several local primary care physician associations, we reached out to primary care physicians in the area through email (see attachment 3). In the email our study goals were explained, as well as the course of both focus groups, by using an information letter and invitation about the subject and design of the study. Through this method we were able to recruit several groups of primary care physicians who were interested in participating in our study, from which we randomly chose one group to participate with, based on their availability.

- *Participant selection*

Participants were eligible if they were licensed primary care physicians in Belgium. There was no selection based on age nor gender. Neither was the organisation of the general practice a criterion for participation in the study, so primary care physicians from solo, duo, group and multidisciplinary practices were all eligible. In total, 12 primary care physicians were able to attend both focus groups. In the first focus group their knowledge and experience with DTC-genetic testing was assessed. In the second focus group we presented to them the first draft of a decision support tool and tested its practical usefulness with a number of clinical cases (see attachment 6). At the start of each focus group, all participants were asked to sign an informed consent form, again clarifying both the aim of the study and the course of the focus group.

- *Data collection and analysis*

The questions and discussions in the focus group were continued until it became clear that no more new data was obtained, i.e. until data saturation is reached. The focus groups were audio recorded and manually transcribed. Data was pseudonymized and treated with confidentiality. All of the obtained data was manually analysed according to thematic analysis in a qualitative study design based on methods described by Creswell (21). Firstly, data was organised and prepared for analysis. Then, all data was read through and coded with MAXQDA software. Since in qualitative research the goal is to aggregate data into a small number of themes, the coded data was used to distinguish 5 recurring main themes that were further used throughout our study. A thematic analysis was made by identifying recurring themes found in data obtained from the focus groups, checked by the available literature to assess their relevance. To minimise research bias, these data were analysed by two researchers. No pictures were taken. Additionally, audio recordings were only listened to and typed out by the researchers.

<u>Literature review</u>

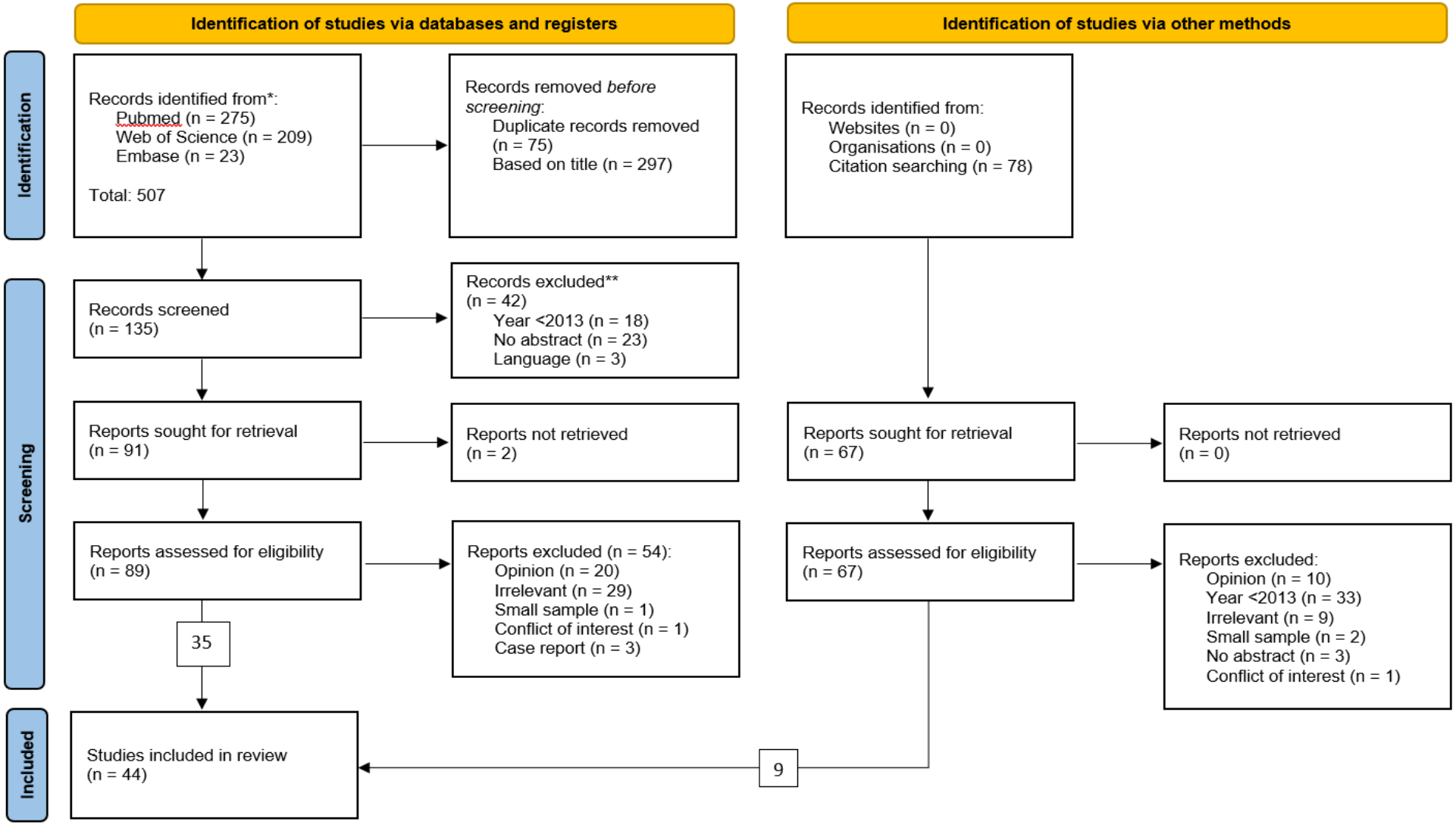
This literature review is based on database research using the keyword search technique. In some search terms, Medical Subject Headings (MESH) terms were used. Additional articles were sourced through citations and references of articles found through database searching. No articles older than 2013 were included in this study, except for one article from 2010 because it concerns the statement of the European Society of Human Genetics (ESHG) on direct-to-consumer testing. The decision to exclude articles older than 2013 was made based on the fact that starting from this year whole-genome sequencing became possible, also for commercial companies. Since then, prices have dropped and DTC-genetic testing became available to the general public. Also, companies could produce more extensive and detailed test results, appealing to the curiosity of the consumer. Before, tests were more expensive and less detailed, resulting in less sales and thus less data. Therefore, in order to assess experience and knowledge concerning DTC genetic tests as they are today, we chose not to include articles older than 2013. Also, a

language restriction was set so only articles written in English, Dutch or French were included. Opinion articles with only one author were rejected, as well as case reports since these are not relevant for our study.

The articles for this review were collected based on a number of searches in various internet databases including Pubmed, Web of Science and Embase. The search terms used in Pubmed include "("genetic testing"[MeSH Major Topic]) AND (Direct-To-Consumer Screening and Testing[MeSH Terms])", "(Direct-To-Consumer Screening and Testing[MeSH Terms]) AND (primary care[Title/Abstract])", "(genetic testing[MeSH Terms]) AND (physicians, primary care[MeSH Terms])", "(genetic testing[MeSH Major Topic]) AND (primary health care[MeSH Major Topic])", "((direct-to-consumer genetic test[Title/Abstract]) OR (direct-to-consumer genetic testing[Title/Abstract])) AND ((primary care[MeSH Terms]) OR (physician, primary care[MeSH Terms]))". In Web of Science, articles were sourced through certain topics, more specifically "TOPIC: (direct-to-consumer screening and testing) AND TOPIC: (genetic testing)", TOPIC: (direct-to-consumer screening and testing) AND TOPIC: (primary care)", "TOPIC: (direct-to-consumer genetic testing) AND TOPIC: (primary care physician)", "TOPIC: (direct-to-consumer genetic testing) AND TOPIC: (primary health care)", and "TOPIC: (direct-to-consumer genetic test) AND TOPIC: (primary care)". In Embase, search terms were as follows: "'genetic screening':ab,ti AND 'direct to consumer genetic testing':ab,ti", "'genetic screening':ab,ti AND 'primary health care':ab,ti" and "'genetic screening':ab,ti AND 'general practitioner':ab,ti".

The relevance of articles was assessed by means of a thorough review of abstracts (when available). If no decision could be made regarding whether or not to include the article in the study after reading the abstract, the entire article was reviewed. After screening all above mentioned databases, 507 records were identified. An additional 78 records were identified through 'similar articles' and via references of articles found through database screening. After duplicates and articles with an irrelevant title were removed, a total of 135 records sourced from database searches was screened for relevance, as well as 67 records sourced from citations. From the articles sourced from database searches, a total of 42 records could be excluded based on the absence of an abstract (n=23), year <2013 (n=18) and language restrictions (n=3). Eventually, 91 articles were sourced for retrieval, of which 89 full-text articles were assessed for eligibility since there was no full-text available for the other two. Of these full-text articles, 54 were excluded after thoroughly reviewing and assessing the full-text for relevance. Reasons for exclusion included small sample size (because of the risk data saturation is not obtained in qualitative research), conflicts of interest (since a substantial part of research regarding DTC genetic testing is sponsored by commercial companies) and study design (such as opinions and case reports). Database searches resulted in a total of 35 references. From the 67 records sourced from citations, 67 were also assessed for eligibility. After having applied the same exclusion criteria, another 9 articles were included for the literature review. For the Prisma flow chart, see attachment 2.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources




*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

## Results

The data from focus groups was analysed and grouped into various recurring themes from which we have distilled five main themes: patients' motives, ethical and legal considerations, interpretation of the test result and added value for the primary care physician, role of the primary care physician, support for the primary care physician. These topics have been checked against the relevant available literature to form a foundation for and clarify the relevance of our decision support tool that will be presented in the following section. Throughout the report of our study results consumers of DTC genetic tests will be referred to as patients since the study assesses the perspective of the primary care physician and the interaction between patient and primary care physician.

Patients' motives

*Curiosity*

In addition to well-known motivations we found during our literature review for patients to order a DTC genetic test such as interest in knowledge about risk of diseases, ancestry, help in planning a healthy lifestyle, exercise or diet decisions, (6,17,22,23) there was a recurring observation with primary care physicians that participated in our focus groups that curiosity might be a dominant cause for the success of DTC genetic testing (24).

> For example a participant states: "The companies respond to underlying curiosity by, for example, offering additional medical information in addition to ancestry testing, without the patient taking the outcome of these tests into account."(24, Pos. 353-362)

Judging by the current advertisements for DTC genetic testing, it is clear that marketing strategies benefit from this motive. Satisfying the curiosity of the customer as one of the main reasons for purchasing DTC genetic testing indicates that the entertainment value should receive considerable attention in justifying these tests (17).

*Impulsivity*

Besides curiosity, the participants of the focus groups agreed on the suspicion that the tests are often ordered as an impulsive decision without first contemplating the potential results and the associated consequences (24). This statement is clarified by the following statement from a primary care physician in the focus group:

> "Patients often buy the tests impulsively with the hope of reassurance. Once they get the test result, it is often too late to inform them correctly to create appropriate expectations about the test result."(24, Pos. 197-206)

Brothers et al. state "If there is a first rule of medicine, it is that physicians should never order a test unless there is a foreseeable benefit from ordering that test." (14). The expectation to be reassured and clearly informed by the test result is often overestimated, leading to increased concerns and lower satisfaction after receiving the test report (5).

These recurring concerns from participants in the focus groups are confirmed by the position statement of the American College of Medical Genetics in which they recommend that patients should be aware of the limitations of the tests. Furthermore they recommend interpreting test results by medical professionals such as primary care physicians (8,25).

'*Worried well*'

Literature shows that especially white people who are employed and have a relatively high income are more likely to order such tests, although the potential benefits of testing may be smaller (23,26). This finding is confirmed by the participants: for example, a primary care physician stated in the focus groups:

> Primary care physician 1: "A patient who is always worried and is concerned with his/her health will be more inclined to order such tests, while the potential benefit for such patients is rather limited."(24, Pos. 289-292)

The difficulty of these 'worried well' patients ordering DTC genetic tests, according to the primary care physicians of the focus groups as well as literature, is the fact that this might result in inappropriate use of the limited public health care resources and this may also further worsen inequality in society, as health and lifestyle are associated with socio-economic position (6,24,26).

*Implications for the patient*

These results highlight the ethical problems raised by the commercialization of DTC genetic testing. Problems that can mostly be related to effects of marketing and the involvement of profit motives such as tending to overemphasise the positive aspects of the product and the role of genes as a cause of disease. This creates a risk of misinformation and unrealistic expectations, driven by the curiosity and impulsivity of the patient as mentioned above (24,25). Furthermore the primary care physicians of the focus groups expressed serious concerns as it seems that 'the right not to know', which the patient is often only confronted with afterwards, is undermined (illustrated by the quote mentioned underneath)(24). This states the importance of pre-test considerations, as we will further describe in the presentation of the decision support tools.

> Primary care physician 2: "It is important that there is room for consultation before the test. Imagine you get to know that you have an increased risk of developing a serious disease for which there is no treatment. Would you and your family even want to know?" (24, Pos. 20)

<u>Ethical and legal considerations</u>

The focus groups as well as current literature show that one of the main concerns of primary care physicians and patients is the ethical aspect of DTC genetic tests. Concerns are raised in particular with regard to privacy matters and data sharing (6,23,27).

Participants of the focus groups have also been confronted with these ethical aspects. The uncertainty and the lack of transparency are considered a reason for restraint towards DTC genetic testing. Remarkably, throughout the two focus groups the participants indicated that they attach great importance to the ethical discussion raised by the topic and also feel responsible to inform their patients about it (24). This is demonstrated by the following citates:

> Primary care physician 3: "I wonder if there are any guarantees about what happens to your data when you order a test? Does Europe's current GDPR legislation apply to these companies? Surely it is important that the patient is aware of this before ordering a test and that we can inform them about this." (24, Pos. 243-248)
>
> Primary care physician 4: "Those companies will eventually have a lot of available data that can be sold to other companies to do research with. I think it is important to be aware of the fact that your data may be distributed. I think there are some patients who would not undergo a test if they knew this". (24, Pos. 122-130)

These concerns of the participants show that in the process of providing educational support to primary care physicians, in addition to the scientific component, the ethical discussion needs sufficient attention to facilitate the evaluation of DTC genetic testing.

<u>Interpretation of the test result and added value for the primary care physician</u>

Focus group participants experienced difficulties in interpreting DTC genetic testing applied to clinical use (24). Both clinical validity, the correct interpretation of the test result and a lack of experience and knowledge are perceived as struggles. Literature search confirms these difficulties when interpreting test results.

*Clinical validity*

To date, there is still much ambiguity about the clinical validity and transparency of DTC-genetic tests. It is associated with the risk of false negative and false positive results, which can lead to a false sense of reassurance or to unnecessary psychological stress (25). A recent study showed that up to 40% of genetic variants identified in DTC laboratories were not confirmed when retested by official techniques (14). In order to integrate DTC genetic testing into primary health care, the ESHG states it will be necessary to regulate laboratories to comply with accepted quality standards (22, 29). Without this regulatory supervision, there is only limited reliability of the test result.

*Insufficient knowledge and experience*

In addition to clinical validity, insufficient knowledge on how to interpret probabilistic data appears to be a common reason for misinterpretation of the test result (6, 29). Many results on test reports are displayed as percentages. However, some knowledge of statistics is required to be able to interpret these percentages and assess a correct risk

estimate. Specifically, patients may uncritically accept test results, may not appreciate drawbacks of increased choice, or may overestimate the potential for information to motivate behavioural change (29). Misinterpreting the test result may in turn lead to false reassurance, but also inaccurate perception of increase of disease risk and consequently unnecessary testing, overdiagnosis and medicalization (6, 18, 29). It is difficult for patients to put the percentages into perspective and assess their implications in a clinical situation. To dismiss these deficiencies DTC companies have to ensure that results are not only communicated to customers as raw test results but are also understood and will be acted on appropriately (30).

In response to difficult test interpretation, literature suggests that genetic counselling should be part of the process of DTC genetic testing (18,19, 29). This will lead to a rise in referrals to specialists, who will not be able to keep up with the increased demand (14). Thus, primary care physicians will likely be asked to interpret DTC genetic test results with increasing frequency, especially because it is necessary to have knowledge of the patient's medical and family history to contextualise a genetic finding (14,16). With the proper clinical skill and knowledge related to genetics, such information can be synthesised to guide a shared decision-making process. While primary care clinicians typically possess the necessary patient history and physical exam skills, it seems their knowledge and experience is not sufficient to interpret and assess risk conferred by individual genetic variants (14,19,20,31,32). Appropriate education of primary care providers imposes itself as DTC genetic testing is becoming more extensive (19,20,32).

*Input of the focus groups*

Although participants of the focus groups are open to learn more about DTC genetic testing, at present they do not encounter genetic information as an added value in clinical use. Mainly in multifactorial diseases where behavioural and environmental influences, family history, clinical symptoms and possibly blood results are taken into account, they experience percentage risk estimates of genetic testing not contributing to their evaluation of disease risk (13). After all, primary care physicians already use scientifically based guidelines on a daily basis to make these risk assessments based on the above mentioned risk factors, whereby the clinical utility of DTC genetic testing at present in primary care is restricted (20,34).

> Primary care physician 1: "I don't find it necessary at this time to have a genetic profile of all of my patients. The things you find on such a report I can also assess through thorough anamnesis. Moreover, for most conditions I can currently achieve the most with the optimization of lifestyle factors, rendering a genetic test redundant." (24, Pos. 171-180)

Recent literature confirms DTC genetic testing should not be treated as a substitute for a routine health assessment and clinical utility should be an essential criterion prior to offering a test to a patient (7,28). Furthermore, the focus group participants confirm the difficulty on correct interpretation of statistics and to make an estimation of the reliability

of the test results, even for medical professionals. Because of lack of knowledge, the participants of the focus groups confirm there is also a low level of comfort at present in advising patients (24,33).

> Primary care physician 5: "I find it not easy at this moment with all the information I have on a patient to make an accurate health risk assessment. If a genetic risk, from which I don't know if it is true, is added, it becomes even more difficult. In case of a low risk percentage on the other hand, you risk not following up the patient well enough. At this moment, I feel not confident at all to make a proper judgement" (24, Pos. 161-171)

> Primary care physician 6: "There is a patient who once told me that he had this kind of test done for prostate cancer. He was convinced that his test result was very reliable. His risk of disease percentage was 3 times the average. Alarm bells went off. I didn't know to what degree this was reliable or not. Do you have an idea, when a result like this comes in, you should take immediate action? (24, Pos. 48-49)

Despite the fact that there are a lot of concerns regarding interpretation of DTC genetic test results and their role in primary care, during the focus groups, the question arose whether the test result could be an additional motivator for lifestyle changes for the patient:

> Primary care physician 7: "Very often, as a primary care physician,, we encounter resistance when motivating people to change their lifestyle. I think that if the patient sees an increased risk percentage for himself and knows that the only thing he can do to reduce this risk is to change his lifestyle, this can be more motivating to take steps towards a more healthier lifestyle." (24, Pos. 283-288)

Literature conveys conflicting results. On the one hand some empirical studies have shown that risk information obtained via DTC genetic tests has little influence on changes in health-related behaviour. Such findings bolster worries about over-interpretation of health risk information but also lessen the hopes associated with preventive measures or lifestyle changes (35). By contrast other studies suggest test results allow patients to take preventive action, make lifestyle changes or seek earlier clinical intervention and follow-up (22,28). However, this positive influence in health behaviour change is only observed when guidance by a health professional is provided. (17,36)

Overall, participants of the focus groups are sceptical about DTC genetic testing at present and are reluctant to integrate it into clinical practice. However, they are aware of the possible added value in the future if these tests become more reliable. As there are serious doubts regarding clinical validity and the added value in clinical practice, it is important the decision support tool meets the demand to manage these difficulties.

<u>Role of the primary care physician</u>

To align the interests of the DTC market and those of medical health practitioners, DTC genetic testing should be guided by health professionals (30). The ESHG recommends advice from these health professionals before and after testing (e.g., in the form of genetic counselling) (7). This division will be adopted in the decision support tool as it requires a different approach, as pointed out below.

*Pre-test considerations*

In contrast to common medical practice, the patient and not the physician determines the need to order a test (28). Various companies take advantage of this by stating DTC genetic testing enhances an individual's autonomy and control over his or her future (7). ESHG underlines that this can occur only when patients are offered adequate pre-test information because the patient's interpretation of test results depends on what expectations they had beforehand (7).

Participants of the focus groups state the importance of providing information to address expectations, awareness concerning ethical considerations and preparedness for unexpected findings (4). They see their role mainly as a point of contact that provides information and make appropriate referrals and protects the patient from commercial motives (37).

> Primary care physician 2: "I think, what's very important is that you tell patients the whole story and warn them you will find out certain things and it's important that you think about what you're going to do with the test results at this point and what the implications could be. That's the counselling of: it's not just a piece of paper, what are you going to do with it? Have you thought about that yet? Some patients will be able to do this more easily than others, but I think it's our job to open up this discussion a little bit."
> Primary care physician 4:"Exactly, we're not really a counsellor to tell them what they have to do but I do think it's important to inform them so they know what consequences it can have. " (24, Pos. 218-227)

Ideally, there should be a contact with a health professional before ordering a DTC genetic test, improving pretest education to facilitate the kind of informed decision-making we would expect in a medical setting (4,30).

*Guidance after DTC genetic testing*

Due to difficult interpretation of a test result and in order to contextualise a genetic finding within the overall health of an individual, patients tend to contact their primary care physicians upon completing DTC genetic testing (17). The ESHG states genetic counselling appropriate to the type of test and disease should be offered; and for some tests psychosocial evaluation and follow-up should be available (7). In contrast Galior and Baumann conclude primary care should not make clinical decisions based on DTC genetic testing based on limited data availability and the concerns regarding the accuracy of the

tests (28). This creates a field of tension in which participants of the focus group feel responsible to give appropriate advice to their patients, but due to uncertainty concerning liability and lack of knowledge they tend to organise additional tests, follow-up or health screening to reassure their patients.

> Primary care physician 7: " Of course, it's kind of embarrassing that the patient comes to you for advice and he turns out to be three times more likely to have lung cancer and I as a primary care physician would judge that that risk increase is not increased enough to take further steps, but that patient does get lung cancer years later."
> Primary care physician 3: "But then what are you going to do? Refer him/her to radiology every year to avoid getting into that kind of situation?"
> Primary care physician 7: "I don't really know, if we don't do it the patient may accuse us of negligence afterwards. " (24, Pos. 260-265)

This leads eventually to unnecessarily burdening the health care system with estimated additional costs ranging from $40 to $20.604 (17). This demonstrates the urge for adequate and reliable information, on the part of primary care physicians, which they can apply in the shared decision-making process of specific clinical situations (14). The decision support tool is designed in order to meet this demand.

Support for the primary care physician

Finally, after discussing the themes in the focus groups as described above, participants were asked how they expect to be supported in the future. Ideally, for them this would be a combination of an increased accessibility of genetic specialists to discuss clinical cases as well as centralised, up-to-date scientific information (24).

*Genetics specialist*

On the one hand, primary care physicians express the need to be able to contact a specialist to discuss DTC genetic testing related results (24). A study of Evans et al. found that local specialists and the genetic service remain an important resource for advice and guidance for primary care physicians when confronted with the results of DTC genetic testing. Up to 41% of primary care physicians highlighted they would refer or liaise with their local specialist (38). Several studies highlight the need for closer ties with genetics specialists (19,38).

*Centralised information*

On the other hand, the participants of the focus group state a centralised online website is needed that enhances the correct interpretation of test results by providing relevant information, but is also continually updated with the latest insights (24). In the study conducted by primary care physicians in the UK by Evans et al. there was a mix of responses to the question where primary care physicians would search for information

concerning DTC genetic testing, with internet search engines being the most popular choice.

Referral pathways and local guidelines, through internet access, were also identified as valuable resources. Evans et al. state: “Pathways should ensure opportunities are utilised and maximised for disseminating information, for example, the design of test reports, the linking of laboratory results directly to pathways and resources held in places that primary care physicians are familiar with and accessible options for seeking specialist guidance” (38).

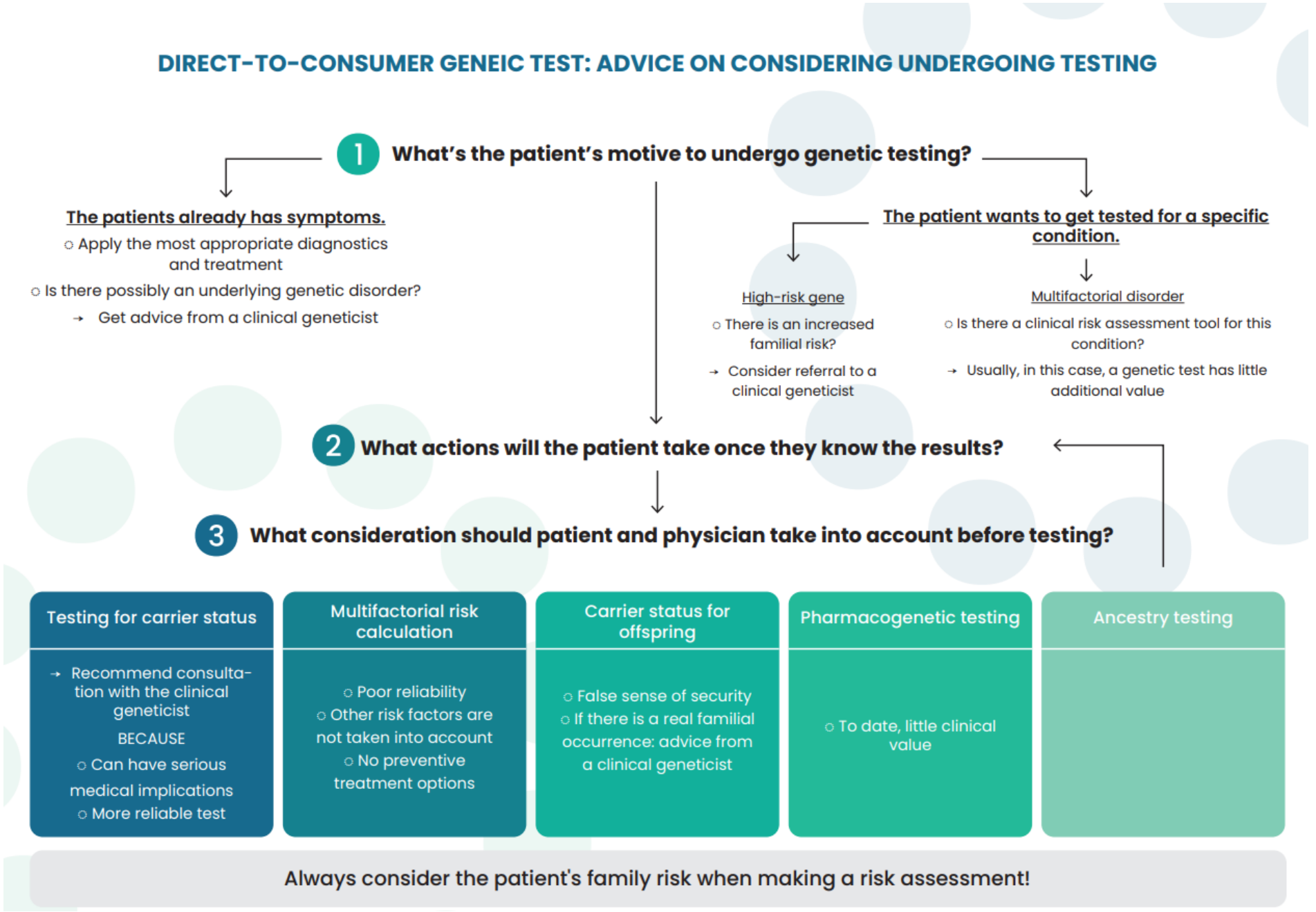
A recurring conclusion in several studies is the need for more educational resources that can be integrated into primary care practice, as well as clinical decision support tools to aid primary care physicians and patients (19,20,32,37–40). According to Wilkes et al., the next step in promoting active engagement between doctors and patients may be to put into place the tools and infrastructure that allow clinicians to easily access evidence-based information during the encounter, preparing physicians to engage in the joint discussions around genetic issues that patients need (39). It is essential that health professionals receive sufficient education and guidelines to equip them to help patients presenting with the results of these tests (19,20,32,40). The development of the decision support tools (as presented in the following section) is a first step in advancing this educational and supportive need for primary care physicians.

## Decision support tools

When starting the screening for literature for this study, it was soon clear that there were no practical guidelines, specifically aimed at primary care physicians that have to deal with DTC genetic testing. As mentioned above, many studies confirm this finding and highlight the need for education and provide a practical manual which can be used by primary care physicians (19,20,32,40). In order to fill this gap we tried to make a first attempt on making such a practical guideline in the form of a decision support tool.

The goal for this decision support tool is to assist primary care physicians when confronted with DTC genetic testing in both of the following scenarios, based on the input of the primary care physicians in the focus groups (cfr. Results - Role of the primary care physician): 1. a patient asks for advice concerning DTC genetic testing before they order a test, and 2. a patient comes and asks for advice interpreting the results of such a test. This distinction is important, since these are two very different scenarios. When confronted with a patient considering buying a test, a primary care physician can have an added value by creating correct expectations of the test result as well as reflecting about the ethical aspect s.a. privacy and the right not to know. On the other hand, when the patient has already undergone testing, a supportive tool was developed for primary care physicians on how to interpret results, or when to refer to a specialist. We also had the opportunity to present our decision support tools to a group of Belgian primary care physicians and assess their opinion, as well as discuss some specific cases using our decision support tool (see attachment 5) to optimise the clinical utility of the tool.

Pre-test decision support tool (see attachment 4)



*Current clinical situation*

Genetic testing in clinical validated laboratories is at present typically done for selected patients who, as a result of family history or clinical indications, are considered at risk of carrying genetic variations that are linked to a particular disease or disease predisposition. Mostly it concerns monogenetic (dominant or recessive) diseases such as BRCA mutations causing breast cancer, Hungtingtons disease, … On the other hand, since research of genetic mutations is evolving rapidly, recently it is possible to detect multiple genes involved in the onset of multifactorial diseases. Whether or not one develops a multifactorial disease (for example: diabetes mellitus type II, chronic kidney failure, cardiovascular diseases,...) depends in most cases on both lifestyle and genetic predisposition. DTC genetic tests currently available provide a wide range of health information based on mutations in genes. In the pre-test decision support tool we developed (see attachment 4), we tried to distinguish the most common tests provided on the commercial market.

We further specified the possible need for further testing by developing a decision support tool that comprises three questions/steps to advise on whether or not to consider a test as well as correctly inform the patient of ethical aspects and realistic expectations.

1. *First step: reason for the test*

The first step is to define the reason for the patient wanting a test. There are two motives that deserve extra attention.

> Firstly, if a patient presents with symptoms they are concerned about, assess, investigate and treat the symptoms in the same way that you would for any other patient (41).
>
> Secondly, if the symptoms might be caused by a genetic disease and there is a suggestive familial hereditary risk, refer the patient to a geneticist in a clinical validated laboratory for further assessment.

On the other hand, if a patient wants to be tested for a specific condition, it is important to verify whether it concerns a monogenetic disease or a multifactorial disease. In the focus groups we used the example of a healthy 60-year old man worried about his cardiovascular health (see attachment 6 for the full description of the case). He wanted to be tested to assess his risk for myocardial infarct. This is a multifactorial disorder, for which there exists already a good risk assessment tool that is very reliable and much more evidence based than the genetic tests currently available. After all, current knowledge to link specific identifiable genes to health conditions is insufficient to usefully predict multifactorial disease (20,41,42). As described in the result section (interpretation of the test result and added value for the primary care physician) participants of the focus group suggest in this case added genetic information is not valuable in a clinical setting (24). This is illustrated as well by a recent study, analyzing recommendations of primary care physicians after receiving test results from their patient, confirming these findings stating

that continuing current management was the most common advice from primary care physicians afterwards (34). This is why we conclude that genetic testing for multifactorial conditions will have little added value beyond what primary care physicians can estimate using risk assessment based on lifestyle factors and familial history. In contrast, in case of a monogenic disorder with a high risk of disease development, the primary care physician should also assess family history for this patient. If, based on family history, there's an elevated risk for developing the disease, or there are suggesting symptoms, it is advisable to have this verified by the clinical geneticist rather than by a commercial firm that supplies DTC genetic testing because of low validity of the test result (41,42).

2. *Second step: consequences of the test result*

The second step is aimed towards reflection: What will the patient do with the results? Does the patient have realistic expectations in doing so? After mapping out a full medical and familial history, it is possible that there is no need for further action. It is important to inform with the patient about why a DTC test is either not appropriate or may not be helpful. Instead, the focus should be shifted towards suggestions about what the patient can do in a preventive setting (42). It is important to engage in conversation about the patient's expectations and to relate those to what the patient would ideally do after he receives the results.

In the example of the 60-year-old man, we can ask what he would do if he were told that he was actually at increased risk based on genetic testing for myocardial infarct. Would he go to the cardiologist annually? Would he modify his lifestyle? Would he have more frequent blood tests? In shared decision making, the primary physician and patient should reflect on whether genetic testing is an adequate means to meet these expectations.

In this section it is also important to discuss the possible difficulties and consequences as mentioned above in the result sections ('motives of the patient' and 'interpretation of the test results') such as wrong expectations and clinical validity. The second step is important because often curiosity and impulsivity are at the basis of ordering such a test causing insufficient reflection beforehand on the possible consequences. As the primary care physicians suggested in the focus groups (result section - role of the primary care physician), they are both well placed and willing to guide the patient correctly in this process (24).

Furthermore it is possible to discuss the ethical aspect in this section. For example, a major concern of the physicians in the focus group was the possible undermining of the right not to know (result section - motives of the patient). This is because it often concerns disorders which are impossible to prevent (e.g. Alzheimer's disease). This affects not only the patient himself but also his immediate family. Finally, it is recommended to check if the patient is sufficiently aware of the disclosure regarding privacy and data protection, as well as the sharing of data with third parties (result section - ethical and legal aspects).

3. *The third step: inform the patient*

The third step contains guidelines on how to correctly inform the patient about the possible tests and their results. Moreover it gives the chance to link back to the expectations of the patient explored in steps one and two and engage the shared decision making process.

- *Monogenetic disorder*

If the patient wishes to be tested for a monogenetic disorder and the patient meets the criteria based on clinical information we advise referring the patient to a clinical geneticist. Testing for such disorders via DTC genetic testing is still very unreliable. On the one hand there is a questionable clinical validity, but on the other hand it can also provide a false sense of reassurance since DTC genetic testing may not cover all relevant genes and mutations in manifestation of the disorder. However, these are potentially serious conditions where the result of the test may have implications for treatment decisions (42).

- *Multifactorial disease*

DTC genetic testing for predicting multifactorial disease should be discouraged. The ability of the tests to predict actual disease is weak and there are inconsistencies in the various ways in which risk estimates are calculated across different commercial test providers. Furthermore, non-genetic risk factors are generally not taken into account although they tend to have a significant impact on predisposition of the disease. Possible treatment and preventive actions for multifactorial diseases are usually not affected by the test result (42).

- *Carrier testing*

If patients want to resort to DTC testing for carrier testing in the context of a desire to have children, it is advisable to view this in the context of reproductive medicine. There are currently many possibilities for prenatal diagnostics that are significantly more reliable and better framed. If there is no family history of a disorder, it may not be recommended to undergo prenatal screening because of renewed false reassurance or anxiety. In addition, testing is only done for a limited number of conditions that may be less relevant to the patient depending on the specific population to which they belong (e.g. cystic fibrosis mainly in Western population, sickle cell anemia in African and Middle East population) (42). Research further showed that patients' understanding of carrier status is poor and often causes confusion. To correctly interpret these results participants must grasp the distinction between carrier status and being affected by a condition. Since most patients are not familiar with the principle of recessive diseases, it seems difficult to correctly interpret the consequences (13,29). It might be useful to refer patients to a local centre for medical genetics for more information concerning carrier testing and to offer them appropriate guidance in this process.

- *Pharmacogenetic testing*

Pharmacogenetic testing is currently not very well substantiated in the majority of situations, although it is possible that it will become relevant and used more frequently in the future (42). So far, however, there is only limited proven value at current time and in literature patients have been found to adjust their medication on their own initiative in response to such testing (29).

- *Ancestry testing*

Ancestry testing does not belong to medical genetic testing but we still mention it in the decision support tool because harm could arise from the other (medical) tests included in the package ordered without proper pretest considerations.

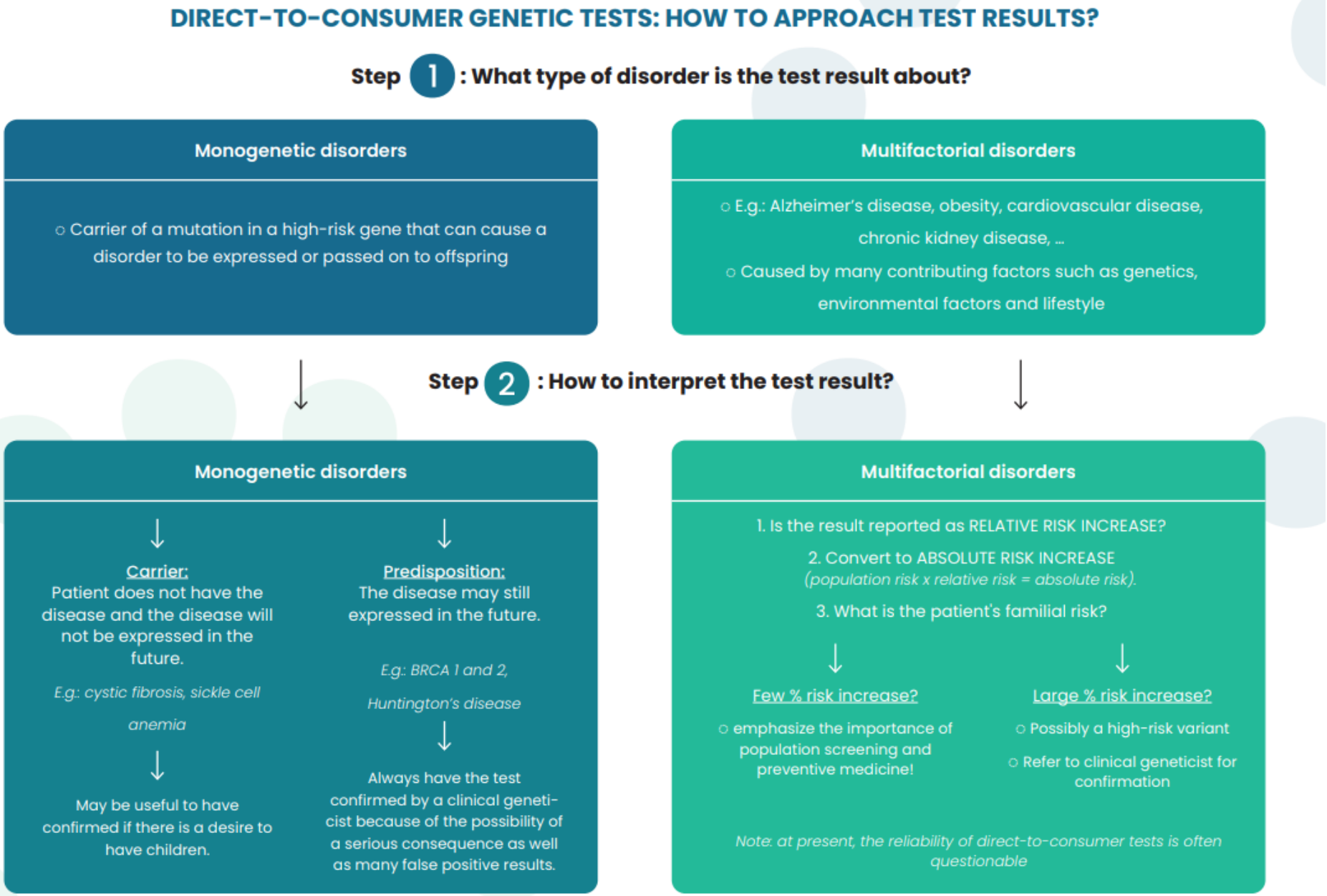
*Feedback from the focus groups (24)*

The primary care physicians in the focus group experienced this decision support tool as very clear and useful. All primary care physicians had a good intuitive sense of when a genetic test may or may not be useful, but confirmed that this flow chart provides them with a structured tool to engage in a discussion with the patient and to inform him/her correctly about the most common tests offered on the Internet, on the one hand, and when it is still important to refer the patient to the clinical geneticist, on the other. This is illustrated by the following citate:

> Primary care physician 8: "The decision support tool which you have developed, definitely gives something to hold on to. It shows what we all intuitively sensed but perhaps didn't dare to express for fear of overlooking something. I now feel more confident to give information to the patient and to bring a certain nuance to these tests." (24, Pos. 283-285)

They themselves suggested that this flowchart could also be useful for the patient during the process of shared decision making. However, the primary care physicians would find an additional patient leaflet with all the pitfalls and information, based on reliable sources, additionally helpful in providing information to the patient.

Post-test decision support tool (see attachment 5)



In our second, posttest decision support tool (see attachment 5), the goal is to guide primary care physicians to interpret the test result of DTC genetic testing correctly as well as to be able to assess if there should be any consequences to the test result. This was done by making a distinction between monogenetic and multifactorial disorders.

*Monogenetic diseases*

As mentioned above monogenetic diseases are caused by a mutation in a single gene. Within these mutations, we distinguish carriers and predispositions to develop the disease.

- *Carriers*

Carriers on the one hand are patients in which there's a mutation present in high-risk genes causing disease in their offspring when the specific affected gene is passed by both parents, but will not develop in the patient him/herself (f.e. mucoviscidose, sickle cell anaemia,..). Mostly, this concerns recessively transmitted diseases. If the carrier status result is considered reliable, it can be useful to confirm the test with a clinical geneticist, especially if there is a desire to have children.

- *Predisposition*

Predisposition on the other hand means that the disease can still be expressed in the future (e.g. BRCA and Huntington's disease). Follow-up of these potentially actionable DTC test results requires involvement of health care providers and confirmatory testing in a clinical laboratory (28). After all, the results obtained through DTC genetic tests are not yet reliable enough and there is a high level of false positive results described (14). Since the results of these tests can have serious consequences, it is important to be reassured that the result is correct in order to set treatment.

*Multifactorial diseases*

Whether or not developing multifactorial diseases (for example: diabetes mellitus type II, chronic kidney failure, cardiovascular diseases,...) depends on genetic predisposition as well as lifestyle factors. Consequently, DTC test results of multifactorial diseases will be presented as a percentage risk increase to develop the multifactorial disease, based on examining a selection of mutations in genes that are already known to play a role in the development of the disease. Presenting these test results using absolute versus relative risk estimates can influence individual interpretation, suggesting that the presentation or format of the test results influence customer understanding (13).

Consequently we recommend calculating the absolute risk increase, rather than the relative risk increase for a certain disease, as they present a less spectacular result and are easier to interpret, again referring to the underlying entertainment factor from the companies. The absolute risk can be calculated by multiplying the relative risk with the

prevalence of the disease in the general population (population risk). One common pitfall is to compare this result to a "zero risk," rather than population risk applied to the patient (41). Thus, it is very important to give proper attention to correctly interpret the given results from DTC-GT companies. For example, in the focus group we discussed the case of a 36 year old woman who has a 46 percent chance to develop colon cancer, according to the result of the DTC genetic testing (see attachment 6 for the full case description). This test result was presented as a relative risk increase. If this result is calculated to an absolute risk (assuming a population risk of 6.9 percent), she has a 10,1 percent lifetime risk to develop colon cancer. If this is compared to the population risk of 6.9 percent, she has 3.2 percent more change to develop the disease. The conversion of relative to absolute risk increase allows to assess percentages in a more intuitive way then the initially presented test results.

At this moment we weren't able to define a clear cut off value of the increase of percentage to develop the disease to decide whether or not it's necessary to refer the patient to a specialist. Consequence of this is that we made an arbitrary division between 'some percentages increase' and 'high percentages increase' in the decision support tool. If the absolute risk has increased by a few percentages then the cause will probably be a non-high risk mutation. The value of this risk increase is comparable to the impact of lifestyle factors in developing the condition. In this case it's responsible to not have any additional examinations done. Many DTC genetic test results relate to small risk changes for common diseases, which may be more appropriately interpreted as part of primary care and may not require a visit to a genetics specialist (16). Instead, those percentages can be used to start a conversation with the patient about preventive measures and set up a surveillance plan.

On the other hand, when there's a high risk increase, it's possible there's a high risk mutation present, not further specified by the DTC test company, for which it is then advisable to have it checked by an accredited clinical genetic specialist. Depending on a deviating medical en familial history of the patient, seriousness of the condition and medical treatment available, the primary care physicians of the focus groups experienced a small percentage difference as more relevant (24). Articulating the precise motive for this feeling proved difficult, although the entire group was in agreement. Most likely, this is due to the experience of primary care physicians and the strength of this profession to detect alarm signals and thus distinguish banal and serious diseases. Furthermore, primary care physicians are also more willing to provide guidance in case of well-known disorders, as opposed to test results regarding rare disorders (24). This may be because primary care physicians are trained to apply multifactorial clinical risk factors to patient decision making and use clinical information such as allergies and renal function to inform medication use. This is in contrast to the rare genetic disease scenario where non-genetic providers are less likely to have extensive experience (16). Lastly, when assessing genetic risk estimates, always take the family history into account, since this may contain relevant and valuable information.

*Feedback of the focus groups (24)*

Because the decision-support tools presented in the focus groups are simplified to ease the decision making process, the primary care physicians think they are helpful and applicable in specific patient cases. As cited below it can protect them from overdiagnosis and overtreatment since they state that a lack of knowledge and uncertainty may lead to the low-threshold request for additional examinations.

> Primary care physician 9: "The decision support tools are well constructed. I have the feeling that when I have to interpret a result I know how to distinguish and if necessary I can also reassure the patient with more confidence. This will avoid a lot of unnecessary additional investigations." (24, Pos. 301-305)

In addition the question arose of the availability of a list or summary of all currently available genetic tests and their correct interpretation. However, in creating the decision support tools, we deliberately chose not to specify genetic testing as in the short term it will be extremely difficult for most primary care physicians to develop an adequate understanding of genetics to counsel their patients appropriately. This is not only because requests of this sort are still relatively uncommon, but also because the science behind genetic testing results develops and changes rapidly (14). We believe it is important for primary care physicians to be able to consider their own insight and experience when reviewing test results , with support from the decision support tools as a guide. In this way, the flowcharts remain broadly applicable and will continue to apply, despite the rapid evolution within genetics.

## Discussion

How to approach DTC genetic testing in primary care?

DTC genetic testing is becoming more widespread since the price of these tests keep decreasing and they are easily accessible via the internet. In addition to the entertainment factor of ancestry testing, these reports often contain medical information, the patient did or did not want to know. Since primary care physicians are aware of patients' medical history and family history, they are usually the first point of contact for advice on DTC testing. Furthermore, on the test reports it is often advised to contact your primary care physician with any further questions. Given the fact that there is a lack of knowledge and experience among primary care physicians concerning DTC genetic testing, the objective of this study was to develop a decision support tool to meet the need for educational support. The decision support tool is a simplified guide allowing the primary care physician to assess the test result and make the correct estimation without detailed knowledge of the current evolution in genetics. They can use it when confronted with patients asking for advice (pre-test) or dealing with results of those tests (post-test).

Legal framework

However, we would like to emphasise that DTC genetic testing must be approached with thoughtful considerations. After all, the ethical discussion cannot be contained in a decision support tool, which presents a summarised and simplified approach to DTC genetic testing. The primary care physicians who participated in the focus groups indicated that they consider the ethical discussion to be a very important topic when discussing DTC genetic testing. Current ethical considerations are mainly related to patient privacy and data sharing, since several companies' disclosures do not comply with the guidelines published by the European Society of Human Genetics (ESHG) (7).

These disclosures show the need for a clear legislative framework. Although DTC genetic testing has been available for several years now, regulation across different countries is present in varying degrees. Despite a restrictive legal framework in Europe it is possible for patients to order genetic tests from companies located in other countries (30). In Greece for example, DTC genetic tests are available over the counter in pharmacies across the country (10). France, Germany, Portugal, and Switzerland have specific legislation that requires genetic tests to be carried out by a medical doctor, provided that the patient was given sufficient information and appropriate genetic counselling (10). In Belgium and the United Kingdom the commercial provision of DTC genetic testing is allowed (10). Italy on the other hand has no specific law concerning DTC genetic testing (10). To this date there is a lack of overarching laws for all member states to regulate DTC genetic testing. This unveils another challenge Europe has to deal with, since regulatory and control mechanisms for DTC genetic testing vary across different member states. This, in turn, leads to marketing of tests online with no regulation about quality or safety. In general, jurisdictions have very little regulatory control over DTC genetic testing in most European

countries and the United States. Analysis of current regulations shows a largely fragmented legislation and, in several member states, a lack of regulation in the European countries (10) . In 2013 the food and drug administration (FDA) tightened its control over DTC genetic testing in the USA (11). Only in 2017 the FDA authorised the first DTC test as an approved medical device (28). In Australia, DTC genetic tests are not regulated, but the National Health and Medical Research Council of Australia has warned consumers to be cautious on DTC genetic testing (11). Allyse et al. suggest that companies will have to embrace a hybrid approach in which modified protectionist strategies are used in partnership with licensed medical professionals (28).

Ethical obligation to provide care?

Another challenge for primary care physicians confronted with DTC genetic testing is the ethical obligation to provide care although they did not recommend their patient to order a test. Even though the quality and clinical validity of DTC genetic testing are still being questioned, it is the physician's duty to respond to questions from patients about these tests in a respectful way, in order to guide the patient in the decision(35). This creates a field of tension between the obligation for the physician to help the patient on the one hand, and the autonomy of the patient to order such a test on the other (14). Physicians might consider disavowing an obligation to discuss the results for the fear of liability of their advice. Because of liability and because physicians feel like they don't have enough knowledge regarding the results of DTC genetic tests, they might also want to meet the demands of the patient, which could potentially lead to overconsumption of medical care and undermine appropriate patient care. Participants (patients) in a study conducted by Schaper et al. in Germany expressed high expectations of physicians' abilities to interpret information obtained via DTC genetic testing companies and expected the physician to provide adequate counselling (30)**.** However, in general, primary care clinicians have significant leeway in deciding which types of care they want to take responsibility for and which they will refer to specialists.

Right not to know

In order to make an informed and deliberate decision on whether to undergo genetic testing or not, patients need to be well-informed and made aware of the possible consequences of knowing their test results. In clinical genetics this so-called right not-to-know is very important and should always be respected, especially in the case of receiving information about disease(s) that cannot be treated or prevented(28) . For DTC-genetic tests patients also need to be protected against unwanted and potentially harmful information. That's why it is important to implement informed consent for every patient wanting to undergo genetic testing (7). Only when they are informed about the content of the test, what the possible test results may be and what the implications of certain test results will be, can these tests have an added value to the autonomy of the patient (28). That's why suppliers of DTC-genetic tests should be more committed to informing and

educating their users, and give them the time to assess and weigh advantages and disadvantages before having to buy a test.

How is DTC genetic testing going to evolve?

When approaching DTC genetic testing in primary care, there are many considerations (as described above) to be made such as ethical concerns, the lack of an overarching legal framework, low reliability of the clinical validity, unrealistic expectations of patients regarding the test result and a lack of knowledge of health providers (as mentioned in the results section). In addition to offering a decision support tool as a guide, encouraging discussion in society, among physicians and policy makers will also be important as the knowledge of genetics is evolving rapidly (10,30).

If DTC genetic testing aims to have an additional value in personalised medicine in the future, they will have to comply with some conditions in order to provide a responsible supply of DTC testing options. The first condition is technical approval. This means that tests will need a certain clinical validity, as well as approval from federal agencies (e.g. FDA in the U.S.A.) about which tests will be carried out to make an assessment about a certain disease (8,10,30). Standards for the quality of scientific evidence should be applied, with an emphasis on outcomes of the tests. The second condition is a greater separation between health and entertainment. This means there will be a need for more regulation concerning marketing strategies (35,43,44). The health purpose of these tests should be the main reason why patients would consider undergoing testing, instead of being drawn to genetic testing by some sort of fun factor. The third condition for genetic testing to have an added value in personalised medicine is the implementation of more support by health providers, before and after testing. As mentioned above, it is important to properly inform and guide the patient in the decision whether or not to undergo genetic testing. Also, after getting their test results, patients should be able to call on a health professional to help them by interpreting their test results and guiding them in what to do after getting their results. Companies could choose to closely work together with health care providers who are specialised in clinical genetics or there should be committed to educating primary care physicians about genetic testing, so that the patient can be referred to their trusted physician, which can have an added value when confronted with difficult decisions (30). A fourth condition is to raise the social debate around DTC-genetic testing in order to create awareness around the considerations that need to be made before ordering a test, as well as the possible implications of test results (30,35). Also, people need to be educated about genetic information and about the fact that genetic information should be considered in the broader context of health, environment, and behaviours (30).

Awaiting the implementation of these conditions, we anticipate that the use of our decision support tool will enable primary care physicians to adequately discuss DTC genetic testing with their patients, which creates the opportunity to implement all aforementioned ethical considerations. This will turn out to be essential, since it will

equip them with enough knowledge to help patients generate realistic expectations of these tests and avoid creating a sense of false reassurance and overconsumption of technical examinations. We hope to meet this need with our study, in which a decision support tool is developed for the first time and to provide an initial guidance, to facilitate approaching DTC genetic testing for the primary care physician.

Limitations

A limitation of our study could be that the presented flowcharts haven't been able to be tested out on multiple groups of primary care physicians, coming from different regions and thus working with different types of populations. Nor did we have the chance to thoroughly assess the usefulness of the flowcharts in multiple different specific clinical cases. However, this limitation is inherent to qualitative, exploratory research with focus groups.

At this point, the demand for advice concerning how to handle DTC genetic testing in first line practices in Europe is rather limited, since DTC genetic testing hasn't reached the same popularity as in the USA. This limitation is twofold, since this also implies that most studies assessing user motivation for ordering DTC genetic testing used in our literature review originate from the USA, where public healthcare is differently organised. Most importantly, one of the biggest differences compared to Europe is the accessibility of health care, which is higher in Europe. This may lead to patients from the USA being more eager to buy a DTC genetic test before consulting a primary care physician, as well as being more reluctant to seek advice with a primary care physician to help with the interpretation of results.

The assistant moderator observed the interaction between the participants. All participants had opportunities to give their opinion, and everyone agreed on the summary. However, member checking was not used, which is a potential threat to data credibility.

Strengths

Already a lot of studies on experiences of patients and physicians on DTC genetic testing are available. Because of this, it is mostly clear where the pitfalls for DTC genetic testing are situated, given the extensive literature to draw on, even though they are still not overwhelmingly commonly used in Europe at the moment. However, it does not appear that an overarching legal framing will appear in the near future to restrict possibilities. It will therefore continue to be freely available and it is predicted that they will also become increasingly common in Europe, which will lead to more primary care physicians being faced with patients having questions about them.

In contrast to the existing literature, we tried to not only assess the known pitfalls, but also tried to make a decision support tool for primary care physicians to rely on when confronted with questions concerning DTC genetic testing. Only one other article included in this study has included a guideline prior to testing (42), but during the focus groups

conducted in this study it became clear that primary care physicians mainly anticipate having to give advice after the patient has received test results and also feel uncertain about giving advice on this topic, since education on the topic is lacking. We were the first to attempt to construct a decision-support tool and to test its usefulness, based on case reports from primary care practices (see attachment 6 for the discussed case reports in the focus groups) . Given the fact data was obtained through two consecutive focus groups, with the same participants, it enhances the continuum in data where a clear link could be made between the difficulties participants specified and how this could be addressed in the decision support tool. The decision support tool was developed based on the input of the participants and afterwards presented to the same participants in a second focus group to be able to optimise the decision support tool based on their feedback. The presented decision support tool was found to be very clear and primary care physicians clearly felt more confident to give advice to patients, despite lacking the detailed knowledge on how DTC genetic testing works.

Future

Based on a literature study and experiences and opinions from primary care physicians in Belgium about DTC genetic testing, we made an attempt to create a first rudimental version of decision support tool that can assist primary care physicians when being confronted with a patient before and after they underwent genetic testing through a DTC genetic testing. Afterwards we also presented this decision support tool to the same group of primary care physicians, and discussed its practicality and usability using specific clinical cases that other primary care physicians have been confronted with. In the future this decision support tool will likely have to be modified and refined in order to augment its practical usability in daily primary healthcare. Therefore, further research in experiences with this decision support tool is necessary, as well as more general research to find out the specific needs primary care physicians experience as more patients consult with questions about DTC genetic testing.

Also, more education concerning genetics and genetic testing for primary care physicians is needed, be it by providing a central website or through specific training for primary care physicians, since this is an often recurring request by primary care physicians. Today, primary care physicians experience a lack of knowledge concerning DTC genetic testing due to limited educational opportunities concerning the topic.

Another frequently mentioned sore point is the lack of availability of genetic counsellors. In order to gain more confidence giving advice to patients concerning DTC genetic testing, primary care physicians express the need of being able to discuss specific cases with their colleagues specialised in genetics. At the moment there are not many genetic specialists and the threshold for primary care physicians to contact them is rather high. In the future, more genetic specialists will be needed in order to meet the increased demand for genetic counselling because of anomalous DTC genetic testing results.

In order for Europe to adequately prepare for a possible increase of DTC genetic testing, it is necessary to develop a legal framework that's universal for all member states, since this will stimulate the correct use of DTC genetic testing and will result in patients being better informed before carelessly ordering such a test, protecting them from any potential unnecessary harm.

## Conclusion

DTC genetic tests are on a rapid rise. Patients are mainly driven by curiosity or impulsivity to order one. This confronts them with potentially unwanted results and the urge to improve their health. The goal of this study is to help primary care physicians confronted with DTC genetic testing in their practice. In the focus groups the main concerns from primary care physicians were a lack of knowledge and the questionable clinical validity of DTC genetic tests. In our literature review the same concerns were found, mainly expressed by primary health care providers. In order to help primary care physicians with their blind spot concerning knowledge about genetics and genetic testing, we presented the first detailed decision-support tools for primary care physicians, to help with advising patients both before and after undergoing genetic testing. The tool may act as a starting point for the future, for further guidelines and ethical reflection, and further refinement of the tool. We hope this tool will contribute to the known educational needs of primary care physicians and consequently enable health professionals to discuss DTC genetic testing appropriately with patients and generate realistic expectations for their test results.

## References


1. 23andMe. Health and Traits. List of Conditions. [Internet]. [cited 2021 Oct 21]. Available from: https://www.23andme.com/health/all/
2. MapMyGene. Inborn Talent Genetic Test [Internet]. [cited 2021 Oct 21]. Available from: http://www.mapmygene.com/inborn.htm
3. 23andMe. Genetic Testing for Ancestry (Home Page). [Internet]. [cited 2021 Oct 21]. Available from: https://www.23andme.com
4. Fleming J, Terrill B, Dziadek M, Kirk EP, Roscioli T, Barlow-Stewart K. Personal genomic screening: how best to facilitate preparedness of future clients. Eur J Med Genet. 2019;62(5):397–404.
5. Wang C, Cahill TJ, Parlato A, Wertz B, Zhong Q, Cunningham TN, et al. Consumer use and response to online third-party raw DNA interpretation services. Mol Genet Genomic Med. 2018;6(1):35–43.
6. Gerdes AM, Nicolaisen L, Husum E, Andersen JB, Gantzhorn MD, Roos L, et al. Direct to consumer genetic testing in Denmark-public knowledge, use, and attitudes. Eur J Hum Genet EJHG. 2021 May;29(5):851–60.
7. European Society of Human Genetics. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. Eur J Hum Genet EJHG. 2010 Dec;18(12):1271–3.
8. Directors AB of. Direct-to-consumer genetic testing: a revised position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016;18(2):207–8.
9. Badalato L, Kalokairinou L, Borry P. Third party interpretation of raw genetic data: an ethical exploration. Eur J Hum Genet. 2017;25(11):1189–94.
10. Rafiq M, Ianuale C, Ricciardi W, Boccia S. Direct-to-consumer genetic testing: a systematic review of European guidelines, recommendations, and position statements. Genet Test Mol Biomark. 2015;19(10):535–47.
11. 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 Health Care Philos. 2019 Mar;22(1):31–40.
12. Covolo L, Rubinelli S, Ceretti E, Gelatti U. Internet-Based Direct-to-Consumer Genetic Testing: A Systematic Review. J Med Internet Res. 2015 Dec 14;17(12):e279.
13. 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. Public Health Genomics. 2015;18(4):216–24.
14. Brothers KB, Knapp EE. How should primary care physicians respond to direct-to-consumer genetic test results? AMA J Ethics. 2018;20(9):812–8.
15. Myriad. Terms of Use. [Internet]. [cited 2021 Oct 21]. Available from: https://myriad.com/privacy/terms-of-use/
16. 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):1–12.
17. Stewart KFJ, Wesselius A, Schreurs MAC, Schols AMWJ, 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 Jan;9(1):1–18.
18. Gollust SE, Gray SW, Carere DA, Koenig BA, Lehmann LS, McGUIRE AL, et al. Consumer perspectives on access to direct-to-consumer genetic testing: role of demographic factors and the testing experience. Milbank Q. 2017;95(2):291–318.
19. Carroll JC, Makuwaza T, Manca DP, Sopcak N, Permaul JA, O'Brien MA, et al. Primary care providers' experiences with and perceptions of personalized genomic medicine. Can Fam Physician. 2016;62(10):e626–35.
20. Mainous AG, Johnson SP, Chirina S, Baker R. Academic family physicians' perception of genetic

testing and integration into practice: a CERA study. Fam Med. 2013 Apr;45(4):257–62.
21. Creswell JW. Research design: qualitative, quantitative, and mixed methods approaches. 4th ed. Thousand Oaks: SAGE Publications; 2014. 273 p.
22. Wasson K, Sanders TN, Hogan NS, Cherny S, Helzlsouer KJ. Primary care patients' views and decisions about, experience of and reactions to direct-to-consumer genetic testing: a longitudinal study. J Community Genet. 2013 Oct;4(4):495–505.
23. Roberts JS, Gornick MC, Carere DA, Uhlmann WR, Ruffin MT, Green RC. Direct-to-Consumer Genetic Testing: User Motivations, Decision Making, and Perceived Utility of Results. Public Health Genomics. 2017;20(1):36–45.
24. Vandeveire J, Haegeman L. Transcript focusgroep 1 en 2. 2021.
25. Isbell TS. Direct-to-Consumer Tests on the Market Today: Identifying Valuable Tests from Those with Limited Utility. Clin Lab Med. 2020 Mar;40(1):13–23.
26. Stewart KFJ, Wesselius A, Schols AMWJ, Zeegers MP. Stages of behavioural change after direct-to-consumer disease risk profiling: study protocol of two integrated controlled pragmatic trials. Trials. 2018 Apr 19;19(1):240.
27. Ruhl GL, Hazel JW, Clayton EW, Malin BA. Public attitudes toward direct to consumer genetic testing. In: AMIA Annual Symposium Proceedings. American Medical Informatics Association; 2019. p. 774.
28. Galior KD, Baumann NA. Challenges with At-home and Mail-in Direct-to-Consumer Testing: Preanalytical Error, Reporting Results, and Result Interpretation. Clin Lab Med. 2020 Mar;40(1):25–36.
29. SA M, AJ N. From Expectations to Experiences: Consumer Autonomy and Choice in Personal Genomic Testing.
30. Allyse MA, Robinson DH, Ferber MJ, Sharp RR. Direct-to-Consumer Testing 2.0: Emerging Models of Direct-to-Consumer Genetic Testing. Mayo Clin Proc. 2018 Jan;93(1):113–20.
31. Hsieh V, Braid T, Gordon E, Hercher L. Direct-to-consumer genetic testing companies tell their customers to 'see a genetic counselor'. How do genetic counselors feel about direct-to-consumer genetic testing? J Genet Couns. 2021 Feb;30(1):191–7.
32. Bernhardt BA, Zayac C, Gordon ES, Wawak L, Pyeritz RE, Gollust SE. Incorporating direct-to-consumer genomic information into patient care: attitudes and experiences of primary care physicians. Pers Med. 2012 Sep;9(7):683–92.
33. Heck PR, Meyer MN. Population whole exome screening: primary care provider attitudes about preparedness, information avoidance, and nudging. Med Clin. 2019;103(6):1077–92.
34. Vassy JL, Davis JK, Kirby C, Richardson IJ, Green RC, McGuire AL, et al. How primary care providers talk to patients about genome sequencing results: Risk, rationale, and recommendation. J Gen Intern Med. 2018;33(6):877–85.
35. Schaper M, Schicktanz S. Medicine, market and communication: ethical considerations in regard to persuasive communication in direct-to-consumer genetic testing services. BMC Med Ethics. 2018 Jun 5;19(1):56.
36. Hayashi M, Watanabe A, Muramatsu M, Yamashita N. Effectiveness of personal genomic testing for disease-prevention behavior when combined with careful consultation with a physician: a preliminary study. BMC Res Notes. 2018;11(1):1–6.
37. Carroll JC, Allanson J, Morrison S, Miller FA, Wilson BJ, Permaul JA, et al. Informing Integration of Genomic Medicine Into Primary Care: An Assessment of Current Practice, Attitudes, and Desired Resources. Front Genet. 2019 Nov 21;10:1189.
38. Evans WRH, Tranter J, Rafi I, Hayward J, Qureshi N. How genomic information is accessed in clinical practice: an electronic survey of UK general practitioners. J Community Genet. 2020 Jul;11(3):377–86.
39. Wilkes MS, Day FC, Fancher TL, McDermott H, Lehman E, Bell RA, et al. Increasing confidence and changing behaviors in primary care providers engaged in genetic counselling. BMC Med Educ. 2017;17(1):1–12.
40. Goldsmith L. Direct-to-consumer genetic testing from the perspective of the health professional:

a systematic review of the literature. 2013;
41. Horton R. Direct-to-consumer genetic testing. 2019 Oct;
42. Jackson L, Goldsmith L, Skirton H. Guidance for patients considering direct-to-consumer genetic testing and health professionals involved in their care: development of a practical decision tool. Fam Pract. 2014;31(3):341–8.
43. Niemiec E, Howard H. Ethical issues in consumer genome sequencing: Use of consumers' sample and data. Appl Transl Genom. 2016;8:23-30.
44. Whitley K, Tueller J, Weber K. Genomics education in the era of personal genomics: Acadamic, professional and public considerations. Int J Mol Sci. 2020;21(3):768

## Attachments

Attachment 1: Approval of the Research Ethics Committee of UZ Gent



Afz.: Commissie voor Medische Ethiek

Prof. Dr. Ignaas Devisch
VG Volksgezondheid en Eerstelijnszorg - GE39
ALHIER

| contact | telefoon | e-mail | |
|---|---|---|---|
| Commissie voor medische Ethiek | +32 (0)9 332 41 81 | Ethisch.comite@uzgent.be | |
| Ons kenmerk | Uw kenmerk | datum | pagina |
| BC-09042 | NVT | 18/12/2020 | 1/2 |

**Betreft** : Advies voor monocentrische studie met als titel:

"HOW TO APPROACH DIRECT-TO-CONSUMER GENETIC TESTING IN PRIMARY CARE? - MaNaMa: LISA HAEGEMAN"

**B.U.N.:** B6702020001067

* Adviesaanvraagformulier Versie 1 dd 20/11/2020 (Volledig ontvangen dd 25/11/2020)
* Begeleidende brief dd 24/11/2020
* Protocol: Onderzoeksprotocol
* Patiënteninformatie- en toestemmingsformulier (Ontvangen dd 25/11/2020)

**Advies werd gevraagd door:** Prof. Dr. Ignaas Devisch

**BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD. ER WERD EEN POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 16/12/2020 INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 16/12/2021, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.**
**Vooraleer het onderzoek te starten dient contact te worden genomen met HIRUZ CTU (09/332 05 00).**

**THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.A POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON 16/12/2020 IN CASE THIS STUDY IS NOT STARTED BY 16/12/2021, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.**
**Before initiating the study, please contact HIRUZ CTU (09/332 05 00).**

**DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 19/01/2021.**
**THIS ADVICE WILL APPEAR IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 19/01/2021.**

° *Het Ethisch Comité werkt volgens 'ICH Good Clinical Practice' - regels*
° *Het Ethisch Comité beklemtoont dat een gunstig advies niet betekent dat het Comité de verantwoordelijkheid voor het onderzoek op zich neemt. Bovendien dient U er over te waken dat Uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.*
° *In het kader van 'Good Clinical Practice' moet de mogelijkheid bestaan dat het farmaceutisch bedrijf en de autoriteiten inzage krijgen van de originele data. In dit verband dienen de onderzoekers erover te waken dat dit gebeurt zonder schending van de privacy van de proefpersonen.*
° *Het Ethisch Comité benadrukt dat het de promotor is die garant dient te staan voor de conformiteit van de anderstalige informatie- en toestemmingsformulieren met de nederlandstalige documenten.*
° *Geen enkele onderzoeker betrokken bij deze studie is lid van het Ethisch Comité.*
° *Alle leden van het Ethisch Comité hebben dit project beoordeeld. (De ledenlijst is bijgevoegd)*
° *The Ethics Committee is organized and operates according to the 'ICH Good Clinical Practice' rules.*
° *The Ethics Committee stresses that approval of a study does not mean that the Committee accepts responsibility for it. Moreover, please keep in mind that your opinion as investigator is*



*presented in the publications, reports to the government, etc., that are a result of this research.*
° *In the framework of 'Good Clinical Practice', the pharmaceutical company and the authorities have the right to inspect the original data. The investigators have to assure that the privacy of the subjects is respected.*
° *The Ethics Committee stresses that it is the responsibility of the promotor to guarantee the conformity of the non-dutch informed consent forms with the dutch documents.*
° *None of the investigators involved in this study is a member of the Ethics Committee.*
° *All members of the Ethics Committee have reviewed this project. (The list of the members is enclosed)*

**Namens het Ethisch Comité / On behalf of the Ethics Committee**

**Prof. dr. P. Deron**
**Voorzitter / Chairman**

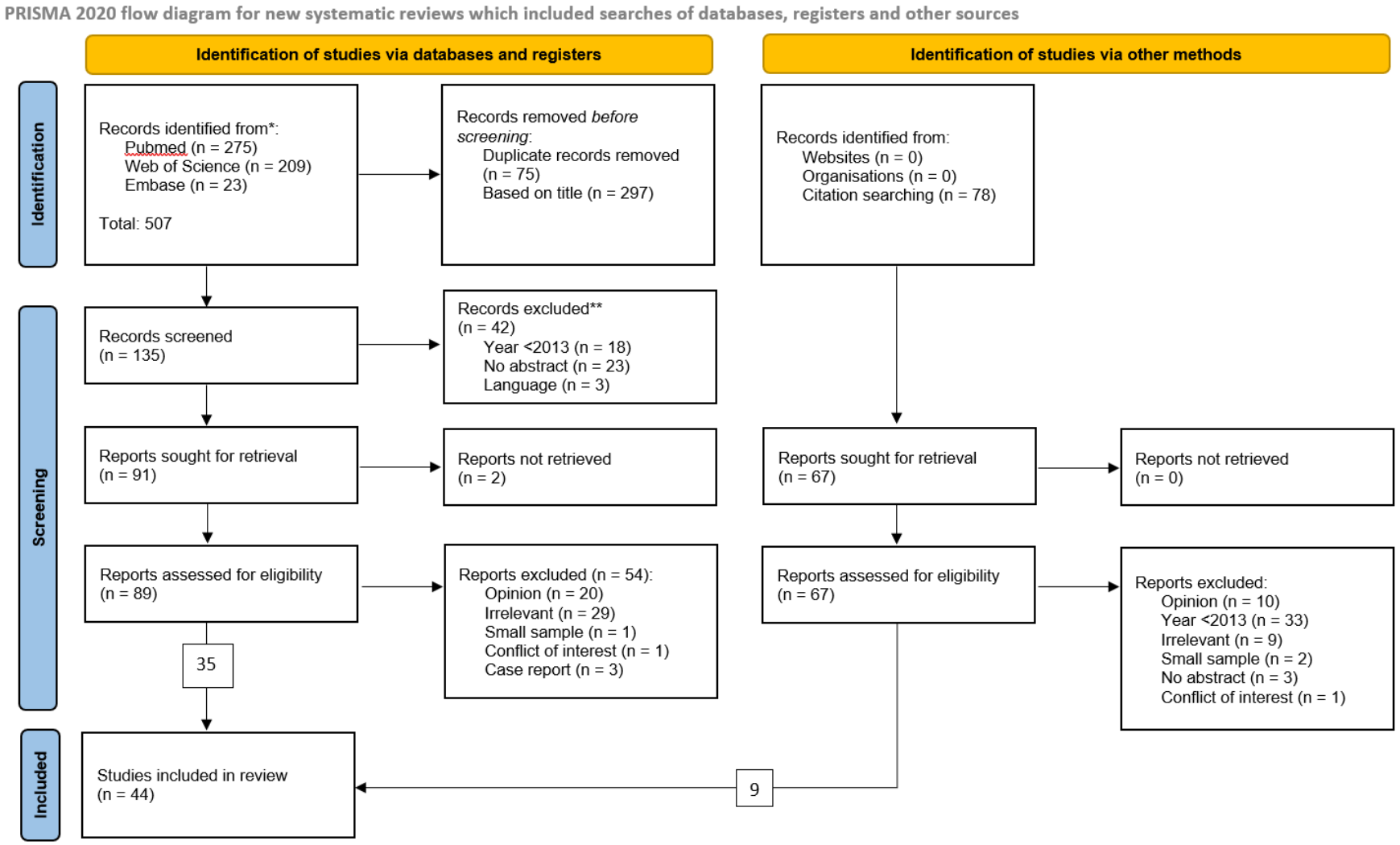
CC: UZ Gent – HIRUZ CTU
FAGG - Research & Development; Victor Hortaplein 40, postbus 40 1060 Brussel

**Ledenlijst 2019-2023:**

Voorzitter: Prof.dr. P. DERON (UZG – chirurg, ♂)
Secretaris: Prof.dr. R. PELEMAN (UZG –internist, ♂)

Leden:
Prof.dr. mr. T. BALTHAZAR (UG - jurist, ♂)
Dhr. K. BENHADDOU (menswetenschapper, ♂)
Prof.dr. W. CEELEN (UZG – chirurg, ♂)
Prof.dr. J. DECRUYENAERE (UZG – internist, ♂)
Dhr. C. DEMEESTERE (UZG – verpleegkundige, lic. Medisch sociale wetenschappen, ♂)
Prof. dr. K. DHONDT (UZG – (kinder)psychiater, ♀)
Prof.dr. D. DE BACQUER (UG - statisticus, ♂)
Dr. K. DE GROOTE (UZG – kindercardioloog, ♀)
Prof.dr. M. De MUYNCK (UZG – fysiotherapeute, ♀)
Dhr. G. DE SMET (UZG – verpleegkundige, - lic. Medisch sociale wetenschappen ♂)
Mevr. M. FOUQUET (UZG – verpleegkundige, ♀)
Dr. L. GOOSSENS (UZG – neonatoloog, ♀)
Dr. S. JANSSENS (UZG – geneticus, ♀)
Mevr. K. KINT (UZG – apotheker, ♀)
Prof.dr. F. MORTIER (UG – moraalfilosoof, ♂)
Prof.dr. W. NOTEBAERT (UG – psycholoog, ♂)
Dr. N. PETERS (UZG – fertiliteitsarts, ♀)
Prof.dr. R. PIERS (UZG - geriater, ♀)
Prof.dr. R. RUBENS (UZG – endocrinoloog, ♂)
Prof.dr. P. SCHELSTRAETE (UZG – kinderpneumoloog/infectioloog, ♀)
Prof.dr. S. STERCKX (moraalfilosoof, ♀)
Mevr. C. VANCAENEGHEM (patiëntvertegenwoordiger)
Dhr. B. VANDERHAEGEN (UZG - moraaltheoloog, ♂)
Prof.dr. W. VAN BIESEN (UZG – nefroloog, ♂)
Dr. J. VAN ELSEN (huisarts, ♂)
Dr. G. VAN LANCKER (UZG – klinisch farmacoloog, ♀)
Prof.dr. K. VAN LIERDE (UG – logopediste, ♀)
Prof.dr. H. VERSTRAELEN (UZG – Vulva-arts, ♂)

Attachment 2: Prisma flowchart




*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Attachment 3: Invitation of the focus group sent by email

# UITNODIGING

**Hoe omgaan met commerciële genetische testen in de huisartspraktijk?**

## LOK-VERGADERING VOOR HUISARTSEN

In de evolutie naar gepersonaliseerde geneeskunde zijn de 'direct-to-consumer' genetische testen aan een opmars bezig. Deze steeds goedkoper wordende commercieel verkrijgbare testen zullen in de toekomst een uitdaging vormen voor de huisarts, bij wie patiënten met de verkregen resultaten zullen aankloppen voor meer duiding en advies.

## PROGRAMMA

Twee interactieve LOK-sessies:

- Deel I: Discussie en verkenning van het onderwerp, kritische vraagstelling, valkuilen, ervaringen, ...
- Deel II: Praktijkgerichte casussen zullen worden voorgesteld en besproken. Een handleiding opgesteld op basis van literatuuronderzoek en de input van deel I zal dienen als leidraad.



## MEER WETEN OVER ONZE LOK-VERGADERING?

Deze LOK groep vergaderingen maken deel uit van een masterproef binnen de opleiding Master-na-Master Huisartsgeneeskunde, met als titel 'How to approach direct-to-consumer genetic testing in primary care?', onder leiding van prof. Dr. Ignaas Devisch – medisch filosoof UZ Gent.

Het doel van deze kwalitatieve studie is om aan de hand van de beschikbare literatuur over direct-to-consumer (DTC) genetische testen, aangevuld door het het peilen naar de huidige kennis en ervaringen van huisartsen met deze testen, de uitdagingen voor de toekomst in kaart te brengen. Hieruit volgend zal de praktische bruikbaarheid alsook de additieve waarde van een informatieve handleiding voorgesteld en getoetst worden. Deze handleiding heeft als doel een leidraad te vormen voor de huisarts om resultaten te interpreteren en adequate informatie aan de patient te kunnen verschaffen.

Praktisch zal dit gebeuren aan de hand van twee opeenvolgende focusgroepen na overleg met de voorzitter van de lokale overlegkring. Bij het begin van de focusgroep zal aan de deelnemers gevraagd worden een geinformeerde toestemming te ondertekenen waarbij informatie wordt gegeven omtrent de doelstelling van het onderzoek. Alle data zullen tijdens het onderzoek anoniem geanalyseerd worden en met vertrouwelijkheid behandeld.

Dit onderzoek zal mede dankzij uw deelname nuttige gegevens opleveren in het kader van een kwaliteitsverbeterend project. Deze resultaten kunnen mogelijks in de nabije toekomst een voordeel bieden om de aanzet te geven tot het maken van een richtlijn die de huisarts kan ondersteunen als hij/zij geconfronteerd zal worden met direct-to-consumer genetische testen.

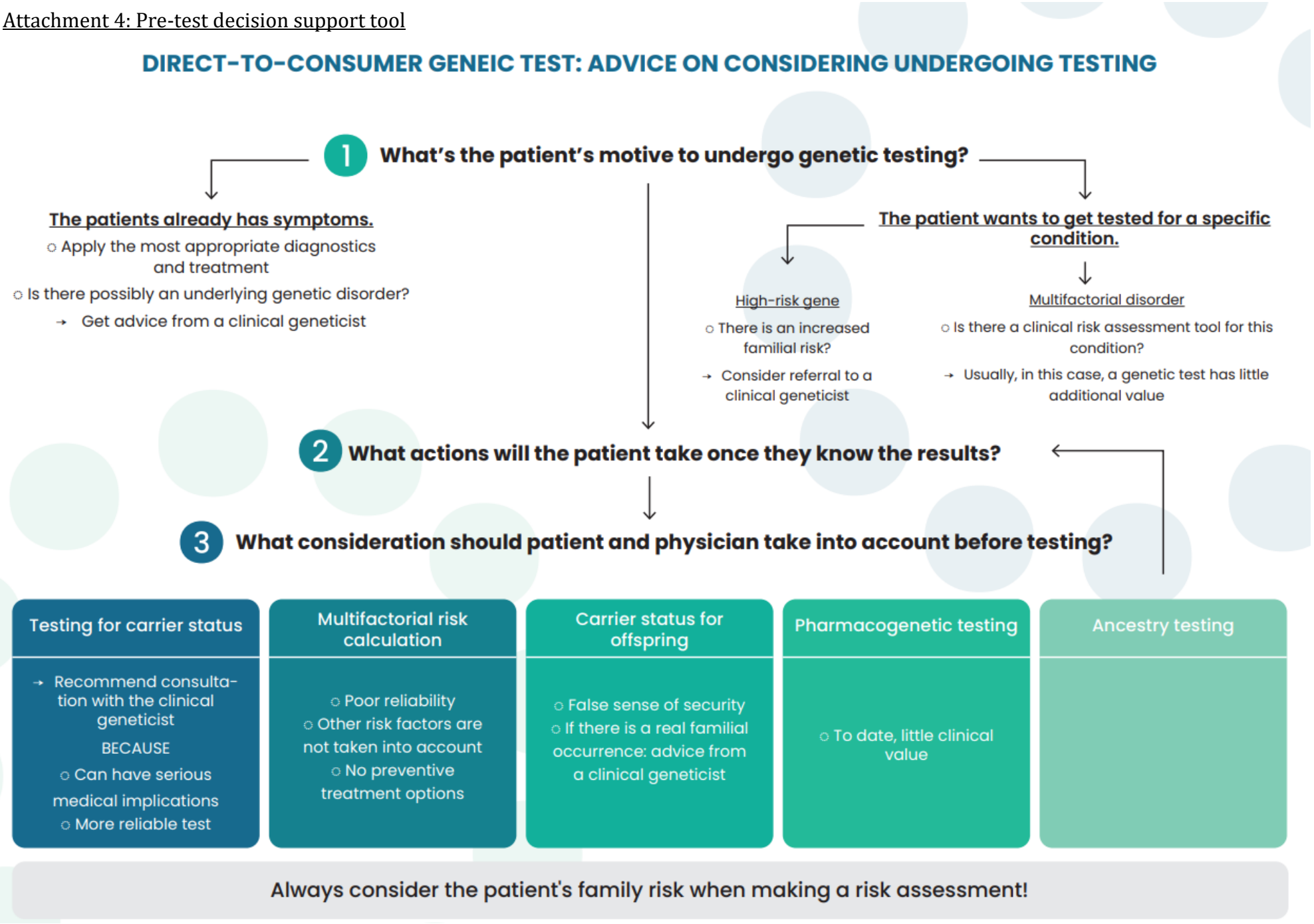
**ACCREDITERING**
zal aangevraagd worden

**DATUM EN LOCATIE**
te plannen tussen mei en september 2021

**VOOR MEER INFORMATIE CONTACTEER**
lisa.haegeman@student.kuleuven.be
jakobarnout.vandeveire@ugent.be



Attachment 4: Pre-test decision support tool



Attachment 5: Post-test decision support tool

# DIRECT-TO-CONSUMER GENETIC TESTS: HOW TO APPROACH TEST RESULTS?

## Step 1 : What type of disorder is the test result about?

### Monogenetic disorders

- Carrier of a mutation in a high-risk gene that can cause a disorder to be expressed or passed on to offspring

### Multifactorial disorders

- E.g.: Alzheimer's disease, obesity, cardiovascular disease, chronic kidney disease, ...
- Caused by many contributing factors such as genetics, environmental factors and lifestyle

## Step 2 : How to interpret the test result?

### Monogenetic disorders

**Carrier:**
Patient does not have the disease and the disease will not be expressed in the future.

*E.g.: cystic fibrosis, sickle cell anemia*

↓

May be useful to have confirmed if there is a desire to have children.

**Predisposition:**
The disease may still expressed in the future.

*E.g.: BRCA 1 and 2, Huntington's disease*

↓

Always have the test confirmed by a clinical geneticist because of the possibility of a serious consequence as well as many false positive results.

### Multifactorial disorders

1. Is the result reported as RELATIVE RISK INCREASE?
2. Convert to ABSOLUTE RISK INCREASE
   *(population risk x relative risk = absolute risk).*
3. What is the patient's familial risk?

**Few % risk increase?**

- emphasize the importance of population screening and preventive medicine!

**Large % risk increase?**

- Possibly a high-risk variant
- Refer to clinical geneticist for confirmation

*Note: at present, the reliability of direct-to-consumer tests is often questionable*

Attachment 6: Discussed case reports in the focus groups

*Pre-test considerations regarding a multifactorial disease*

Koen, 60 years old, doesn't normally come to the practice very often. You followed him for a while last year for a meniscus tear after he followed a program to start running. Today he seems a bit concerned. Yesterday, one of his colleague was taken to the hospital because of a myocardial infarct. Now he wants to know what his risk of getting a myocardial infarct is and he has heard that he can order a genetic test online to assess his disease risk. Koen does not take any medication, in his family there are no people with cardiovascular disease.

*Post-test interpretations regarding a monogenetic disease*

Julie, 20 years old, got a genetic test from her aunt via 23andme for Christmas, accompanied by the message "Find out what your DNA says about you and your family". She immediately sent her saliva sample back to the company. Her report states that she has the disease-causing BRCA 1 mutation and therefore an increased risk of breast and ovarian cancer. In her family, her father's sister had breast cancer at the age of 54; there are no other known cases. She asked for a consultation with her primary care physician to refer her to the surgeon for a preventive mastectomy. She was soon able to obtain a consultation with the surgeon, who scheduled a date for the surgery to happen. However, her primary care physician also sent her to the clinical geneticist where genetic testing was repeated. The mutation in the BRCA 1 gene was not present. The surgery was cancelled, but Julie still feels anxious about her cancer risk.

*Post-test interpretations regarding a multifactorial disease, though with an elevated family risk.*

A 36-year-old woman visited her primary care physician with the results of a commercial DNA test she ordered online. After receiving the results by mail, she was referred to her primary care physician for any further questions, including questions about the cancer risk described in the report. The patient is shocked to learn that she has a 46% increased risk of colon cancer, even more so because her father died of colon cancer. She is now seeing her primary care physician for advice and possible preventive measures.

*Post-test interpretations regarding carrier testing*

A 34-year-old woman, Sofie, visits her primary care physician to discuss the results of her direct-to-consumer genetic test that she commissioned through an online firm. She sent in a saliva sample, after which she was sent an online report three weeks later that she now wants to discuss with her primary care physician. The report describes that Sofie is carrier of the pathogenic variant of the PKHD1 gene, which is associated with the autosomal recessive form of polycystic kidney disease (ARPKD). She has many questions regarding this information. She is concerned because she is a carrier of the PKHD1 variant. Even though her first child (2 years old) was born with no evidence of polycystic kidney disease, she wonders if she is at risk of passing on the disease if she were to have a second child.

Persoonlijke reflectie over het verloop van het groepswerk

## Verloop van het groepsproces

In totaal hebben we met twee studenten master-na-master huisartsgeneeskunde samengewerkt om dit project tot een goed einde te brengen. Beiden hadden we interesse in ethiek en genetica, waardoor we ons samen hebben aangeboden voor een eerste gesprek met promotor en copromotoren. In het algemeen kan gesteld worden dat het groepsproces gedurende de hele periode heel vlot verlopen is. Initieel dachten we onderzoek te gaan doen naar de waarde van een eventuele uitbreiding van de NIPT-test voor de huisarts en hoe deze daar tegenover staat. Nadat we samen een zaalshow van Lieven Scheire gingen bezoeken over DNA, viel ons oog op de direct-to-consumer genetische testen. Hierover is al veel te doen in de Verenigde Staten, en komt stilaan ook op in Europa. Om die reden leek het ons wel interessant om hierover te polsen naar de ervaringen en kennis omtrent deze genetische testen bij de huisartsen in Vlaanderen. Om dit te kunnen doen werd al snel de idee geopperd om een focusgroep te organiseren. Hieruit konden we dan, in combinatie met onze literatuurstudie, proberen om een eerste aanzet te geven tot een handleiding of leidraad om de huisarts bij te staan wanneer hij/zij geconfronteerd wordt met vragen over een direct-to-consumer genetische test of de resultaten ervan. Eens duidelijk was hoe we ons onderzoek gingen uitvoeren, is alles zeer vlot verlopen. Dit ook mede dankzij een goed contact met promotor en copromotoren. We organiseerden twee opeenvolgende focus groepen, waarbij we overeen kwamen om elk één focus groep te modereren. Voor de transcriptie van de focusgroepen deelden we ze telkens op in twee stukken, waardoor we elk de helft voor onze rekening namen. Tussenin beide focusgroepen deden we onze literatuurstudie, waarbij we op regelmatige tijdstippen hebben samen gezeten om telkens 'live' met elkaar te kunnen overleggen. We legden een soort database aan van gekozen artikels en de reden waarom we ze wel/of niet zouden includeren. Ook hier hebben we snel beslissingen kunnen nemen en zaten we heel snel op dezelfde golflengte. Na het organiseren van de 2de focusgroep en het afronden van de aansluitende transcriptie, hebben we ons volledig toegelegd op het uitschrijven van onze masterthesis. Hierbij hebben we de verschillende onderdelen (inleiding, methoden, resultaten, discussie en conclusie) stuk voor stuk aangepakt en opgedeeld. Na het schrijven van een bepaald item door de ene werd dit ook telkens nagelezen door de ander. Om te vermijden dat er in offline documenten wijzigingen zouden worden aangebracht en dat er verschillende versies zouden ontstaan, werkten we in een online document dat continu werd opgeslaan in de 'cloud'. Wat betreft communicatie naar promotor en copromotoren, kozen we er steeds voor om eerst onderling overleg te plegen om dan een gemeenschappelijke e-mail te kunnen opstellen, dit om de communicatie te bevorderen en mogelijks miscommunicatie te vermijden.

## Persoonlijke aandeel

Deze masterproef leende zich er vlot toe om al het werk evenwichtig te verdelen tussen beide studenten. Dankzij het onderlinge vlotte contact konden we de literatuurstudie

simultaan volbrengen. Hierbij toetsten we zoveel mogelijk live bij elkaar af hoe de ander evolueerde in dit proces. Op deze manier werd onze visie stelselmatig op elkaar afgesteld en groeide ook het vervolg van de masterproef met de nadrukken die we graag wilden leggen op een erg organische manier. Verder vullen onze sterktes elkaar goed aan. Ik ben erg sterk in het planmatige en organisatorische betreffende het uitwerken van de onderzoeksvraag alsook steeds overzicht behouden en even terug koppelen naar de essentie. Jakob daarentegen is heel sterk in het helder rapporteren van de onderzoeksresultaten en deze op een opbouwende logische manier verwoorden tot een geheel. Ik heb het gevoel dat we door deze samenwerking in staat waren om ons niveau te optimaliseren. Ik heb doorheen het hele proces genoten van deze samenwerking en van het opstellen van de masterproef. Het heeft mij voldoening gegeven om naast het klinische werk in de opleiding ook een wetenschappelijke stimulans te ervaren.

**Persoonlijke visie op wat het werk betekent voor het werkveld**

Het onderwerp van deze masterproef is ontstaan vanuit onze gemeenschappelijke interesse voor genetica en de onderzoeksvraag is op een erg natuurlijke manier kunnen groeien. Naar mijn aanvoelen is het onderwerp daardoor erg relevant en is het me ook doorheen het hele proces blijven boeien. Regelmatig spraken wij over onze onderzoeksvraag met collega huisartsen, maar ook met kennissen zonder medische achtergrond en telkens was de respons erg enthousiast en nieuwsgierig. Voor mij toont dit aan dat het een onderwerp is die enerzijds tot de verbeelding spreekt maar anderzijds toch wel steeds meer aanwezig zal zijn in de maatschappij. Tijdens de uitvoering van de studie in de focusgroepen en de literatuurstudie werd dit gevoel beaamd. Wij kregen bovendien meermaals de vraag van LOK-groepen die niet geselecteerd waren binnen de studie of we een LOK-vergadering omtrent het onderwerp konden leiden omwille van de grote interesse. Wij hopen dan ook met deze studie een overzicht te kunnen bieden omtrent het onderwerp voor alle geïnteresseerde zorgverleners alsook een eerste aanzet geven tot een educatief ondersteunend stappenplan. Hopelijk kan deze in de toekomst uitgroeien tot een volwaardig hulpmiddel voor huisartsen die in de praktijk worden geconfronteerd met direct-to-consumer genetische testen.