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OPINION

Preconceptional genetic carrier testing and the commercial offer directly-to-consumers

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ABSTRACT: Recently, a number of commercial companies are offering preconceptional carrier tests directly-to-consumers. This offer raises a number of concerns and issues above and beyond those encountered with preconceptional tests offered within the traditional health care setting. In order to bring some of these issues to light and to initiate dialogue on this topic, this article discusses the following issues: the current offer of preconceptional carrier tests (until the end of 2010) through online commercial companies; the implications for the informed consent procedure and the need for good information; the need for medical supervision and follow-up; and the appropriate use of existing resources. The article concludes with some reflections about the potential sustainability of the offer of preconceptional carrier tests directly-to-consumers.

Key words: preconception care / carrier testing / direct-to-consumer

Introduction

Identifying carriers of autosomal recessive or X-linked disorders before pregnancy has the potential to benefit prospective parents. Couples can become aware of the possible genetic risks to future offspring and of the reproductive options available. These options include not only prenatal diagnosis followed (or not) by termination of the pregnancy in case of an affected fetus or by coming to terms with the risk, but also the choices of using preimplantation genetic diagnosis, using donor sperm or oocytes, seeking adoption or refraining from having children. In some culturally related marriage practices, it could also result in choosing a different partner.

There are two approaches to the identification of carriers: carrier screening and carrier testing. Carrier screening is defined as the detection of carrier status in persons who do not have an a priori increased risk for having a child with a certain disease, whereas with carrier testing, the persons do have a higher a priori risk based on their or their partners' personal or family history (Castellani *et al.*, 2010). Carrier screening can be offered on an individual basis, but also as an organized screening programme, either during or before pregnancy. While most screening programmes in health care aim to prevent, treat and alleviate disease, above and beyond these aims, the particular goal of preconceptional carrier screening is to strengthen reproductive autonomy and informed decision-making. If offered preconceptionally, this can mean less time constraints, less pressure and less emotional stress than when a test is performed during pregnancy (Bombard *et al.*, 2010)

Internationally, the potential of preconceptional carrier screening has been studied extensively for cystic fibrosis (CF) (Bekker *et al.*, 1993; Tambor *et al.*, 1994; Axworthy *et al.*, 1996; Honnor *et al.*, 2000; Henneman *et al.*, 2001; Lakeman *et al.*, 2009) and haemoglobinopathies (HbPs) (Modell *et al.*, 1998; Keskin *et al.*, 2000; Lakeman *et al.*, 2009). These studies have repeatedly revealed positive attitudes towards CF carrier screening from health care providers (Poppelaars *et al.*, 2004a; McClaren *et al.*, 2008), patients and their relatives (Poppelaars *et al.*, 2003) and from the general public (Poppelaars *et al.*, 2004c). Furthermore, preconceptional carrier screening for CF for couples with no family history of CF was recommended a decade ago by the National Institutes of Health (NIH) (National Institutes of Health, 1999), the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynaecologists (ACOG) (Grody *et al.*, 2001). Despite this, screening is not currently offered in most countries. Carrier testing for disorders such as CF is still usually restricted to families and partners of CF patients and carriers.

Apart from some specific regions (e.g. Thalassemia carrier screening in Cyprus and Sardinia) and specific communities (e.g. carrier screening for Ashkenazi Jews), traditional healthcare systems have hesitated to implement carrier screening programmes for the entire population of couples planning a pregnancy. Various concerns underlie this stance, including the psychological impact (Axworthy *et al.*, 1996) and risk of stigmatization/discrimination of being a carrier (McQueen, 2002), impairment of the freedom of choice because of the undue pressure on individual choice (Godard *et al.*, 2003), medicalization (Poppelaars *et al.*, 2004c), the fact that couples are difficult to reach before conception (Lakeman *et al.*, 2009), and provider-related barriers such as a lack of familiarity with genetics and selection criteria for offering screening (Morgan *et al.*, 2004).

Recently, commercial companies have been offering preconceptional carrier tests directly-to-consumers. These direct-to-consumer (DTC) tests provide information about monogenic diseases and the risk of having affected offspring. DTC genetic testing is often defined as the offer and/or marketing of genetic tests directly to the public without the intermediary of a health care professional from the traditional health care system. As has been suggested by the Human Genetics Commission, however, we also include in this discussion 'tests that are commissioned by the consumer' from a commercial company outside the traditional health care system 'but where a medical practitioner or a health professional is involved in the provision of the service' (Human Genetics Commission, 2010). The availability of DTC genetic testing services in general has created a huge debate about the desirability of these activities (Howard and Borry, 2008; Hunter *et al.*, 2008; Kaye, 2008). However, until now, these discussions have mainly focused on the commercial DTC offer of genome-wide-testing; a service which offers individual risk assessments for common disorders (Janssens *et al.*, 2008; Melzer *et al.*, 2008) with limited or no medical or health benefits to the individual user. Various concerns were raised with regard to this DTC offer of genetic tests, including, among others, concerns related to the validity and utility of tests offered, the absence of individualized medical supervision, the lack of an adequate consent procedure, the absence and/or quality of pre- and post-test genetic counselling, the inappropriate testing of minors, the respect for privacy and the potential burden on public health resources.

Because of the great heterogeneity in types of DTC genetic tests, and the fact that the consequences of their results vary widely, a one-size-fits-all approach is not appropriate for all DTC genetic tests. Since preconception carrier screening has been accepted by various medical associations, DTC testing for these tests may be regarded differently when compared with the DTC tests for common disorders that have been criticized because of, for example, the lack of clinical utility (i.e. how likely the test is to significantly improve patient outcomes) and analytical validity (i.e. how accurately and reliably the test measures the genotype of interest). Therefore, the aim of this article is to discuss various ethical issues raised by the DTC offer of preconceptional carrier tests for autosomal recessive disorders from commercial companies that are not embedded in regular health care.

In the following order, this article will present and discuss: (i) the current offer of preconceptional carrier tests through online providers; (ii) the implications for the informed consent procedure and the possible consequences for the provision of information; (iii) the need for medical supervision and follow-up and (iv) the current offer in relation to the appropriate use of existing resources.

The offer

Various commercial companies presently offer DTC carrier tests for recessive genetic disorders. The details of the offer from each company, however, vary greatly. In May 2010, the company *DNA Direct* (www.dnadirect.com) advertised one individual carrier test (for CF) and one carrier testing panel (for Ashkenazi Jews). On its website the company underscored that 'professional medical groups including the NIH (...) and ACOG recommend that CF carrier screening be offered to all couples who are planning a pregnancy or are currently pregnant' (https://www.dnadirect.com/web/article/testing-for-genetic-disorders/cystic-fibrosis/30/who-should-consider-testing accessed 19/01/2011). The company *DNATraits* says that they are 'committed to making all medically validated tests available to consumers rapidly, inexpensively and understandably' (www.dnatraits.com/compare accessed 03/05/2010) and is selling a limited number of individual tests (e.g. for Alpha-1-Antitrypsin Deficiency) as well as panels of disorders (e.g. an Ashkenazi Jewish Genetic Disease Panel or a sickle cell/beta-thalassaemia panel). Along with risk assessment information for other disorders, *Pathway Genomics* (www.pathway.com) and *23andMe* (www.23andme.com) include in their full genome testing report the carrier status for 37 and 24 different single-gene conditions, respectively. Finally, in February 2010 the company *Counsyl* (www.counsyl.com) launched their offer of a pre-pregnancy 'Universal Carrier Test' which tests an individual or couple for over 100, mostly autosomal recessive, genetic diseases. *Counsyl* considers these activities as 'a cause, a campaign to finally end the needless suffering of preventable genetic disease' (https://www.counsyl.com/about/counsyl/ accessed 19/01/2011).

These abovementioned DTC genetic tests providers do not make a distinction between screening individuals with an a priori low population risk or testing individuals with a high a priori probability of having an affected child. Because of this increasing possibility for determining an individuals' risk of transmitting a condition to his or her offspring and the potential opportunities and threats generated by these results to individual citizens and society as a whole, the Health Council of the Netherlands (2008), for example, emphasized the need for criteria for a responsible offer of genetic DTC screening as well. In this specific report, the original genetic screening criteria, as outlined by the WHO (Wilson and Jungner, 1968), which relate to the prerequisites for starting community-wide screening, are extended with a much larger view on screening. Not only are 'specific individuals being invited to undergo a medical test' included in the definition of a genetic carrier screening programme, but also a wider population is included by 'highlighting the opportunity to be tested in brochures or in the press, via advertising or promotion by commercial providers'. Screening can take the form of large-scale programmes for which all pregnant women, all newborn babies or all men or women in a particular age group are eligible. But it can also entail 'people responding to an advertisement or a website offer for a health check with a clinic or a health organization' (Health Council of the Netherlands, 2008). The large number of monogenic disorders included in the DTC genetic testing companies' services is in clear contrast with the selected number of disorders that is usually considered for inclusion

in preconception carrier screening programmes in the traditional health care system. On the basis of generally accepted genetic screening guidelines (Health Council of the Netherlands, 2008; European Society of Human Genetics, 2003; UK National Screening Committee, 2003; Nuffield Council on Bioethics, 2006), carrier testing for a larger number of disorders challenges at least two established specifications that have been followed in this field until now: (i) the condition should be an important health problem, and (ii) there should be a suitable test with known predictive value. Moreover, testing should lead to a favourable ratio of advantages to disadvantages, in which the voluntary character of consent, the information provision, the embedding in medical supervision and the appropriate use of existing resources are guaranteed (see below).

First, an important criterion that should be fulfilled before a screening programme is initiated is that the condition should be an 'important health problem' (European Society of Human Genetics, 2003; UK National Screening Committee, 2003) or a 'significant health problem' (Health Council of the Netherlands, 2008). It has been emphasized that 'importance' or 'significance' does not necessarily relate to the number of people affected; it also addresses the severity of a health problem even if a condition is rare (European Society of Human Genetics, 2003; Health Council of the Netherlands, 2008). The Universal Carrier Test offered by *Counsyl*, however, includes over 100 diseases. The salient question, therefore, is whether DTC carrier testing should be seen as an activity for which these screening criteria are applicable. It is then debatable whether every condition included could fulfil these genetic screening criteria. A disorder such as Gaucher Disease, for example, was already a matter of debate with regard to its integration in a panel for Ashkenazi Jews, since the most common Gaucher Disease mutation in this population leads to a highly variable but usually milder phenotype (Zimran *et al.*, 1997; Zuckerman *et al.*, 2007). This then raises the question of whether it is acceptable to systematically identify carrier couples for disorders that are less severe (Borry *et al.*, 2008). Severity judgments are complex and a particularly challenging base on which to make reproductive choices. Providing severe and possibly less severe disorders within the same panel undermines the consistency of that panel.

Secondly, it has been emphasized that screening should be based on a 'simple, safe, precise and validated test' (UK National Screening Committee, 2003) 'with known predictive value' (European Society of Human Genetics, 2003). Although the analytical validity of the test for each mutation included in panels offered by DTC genetic testing companies has likely been validated, the clinical validity (i.e. how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest) of the panel of mutations may be far from 100%. Moreover, the clinical utility of testing for some disorders is debatable as some homozygotes, because of low penetrance, may never develop overt disease and/or the expression may be variable (Levenson, 2010). For example, this is the case for hereditary haemochromatosis, which is also included in the *Counsyl* test panel. In addition, companies offering large panels of disorders may base their inclusion criteria on technical and economic aspects rather than on policy considerations, which take into account, among other things, carrier frequency, severity of the disorder and feasibility of testing in a particular population. It also raises doubts about the individual disorders included in these large testing panels, and questions whether 'more is really better' (Leib *et al.*, 2005). Moreover, the question is raised of whether good information and informed decision-making is still possible when the test panel contains such a heterogeneous group of disorders, for which test sensitivity and specificity are variable.

The need for good information

To ensure informed decision-making, it is crucial that individuals receive the necessary information about the purpose of the test, the reproductive choices resulting from the test, the reliability and limitations of the test, the possible psychological impact and the potential consequences of the test for the individual and his/her family members (McQueen, 2002). Privacy and confidentiality of the results, as well as possible consequences related to their disclosure to third parties, such as insurance companies and employers, should also be discussed. Moreover, the nature of the reproductive options makes it imperative to adopt a non-directive approach with potential users. Although some DTC genetic testing companies do include a lot of this information on their websites, the question is whether, while being commercially driven, the information presented is balanced enough to enable informed choice. Moreover, according to a recent study (Lachance *et al.*, 2010), many users would struggle to find and understand the important information on companies' websites needed to make an informed decision. Finally, although all companies selling DTC genetic tests require some form of consent from the consumer when ordering a test, the process of informed decision-making cannot be reduced to clicking a box to accept the terms of service or signing a document.

Educating people about carrier testing is complicated. The limited knowledge of genetics in the general population (Molster *et al.*, 2009), and the fact that carrier tests have a test sensitivity of $<100\%$ (causing a residual risk to people who are not found to be carriers) make the goal of transmitting information about these tests a non-trivial matter. Studies have shown that a significant proportion of participants who tested negative when undergoing preconceptional screening for CF or HbPs wrongly believed that they were definitively not carriers, while some carriers falsely believed that they were only likely to be carriers (Axworthy *et al.*, 1996; Honnor *et al.*, 2000; Henneman *et al.*, 2002). An offer of DTC testing is likely to face the same problems in educating people as has been demonstrated in these screening programmes. Multiple studies have also demonstrated that both carriers and non-carriers may experience negative feelings, such as anxiety and worry, when participating in genetic screening, although anxiety levels often decrease after a few months (Bekker *et al.*, 1994; Henneman *et al.*, 2002).

The DTC offer of genetic tests is worrisome in the light of these findings, where the practices of existing DTC genetic testing companies mainly only offer written information found on their website. As *DNA Direct* puts it: 'Pretest education is provided at no additional charge through in-depth, online materials for all tests' (www.dnadirect.com/web/consumers accessed 4/05/2010). Pre- or post-test counselling is often only possible at an additional cost ($250/hour for *DNA Direct*; $99/hour for *Pathway Genomics*), which may be a barrier for consumers to ask for it, although some insurance companies may reimburse it. In contrast, *DNATraits* offers a free optional consultation with their genetic counsellors before testing and a free mandatory consultation after to discuss the results (http://www.dnatraits.com/services accessed 04/05/2010). *23andMe* does not

offer pre- or post-test counselling and urges consumers 'to seek the advice of health professionals' if questions or concerns arise (https://www.23andme.com/about/consent/?version=1.3 accessed 19/01/2011). Similarly, *Counsyl* initially considered their test as an 'at-home carrier test, as a successor to the at-home pregnancy test' and did not consider offering any pre- or post-test counselling (http://precedings.nature.com/documents/4192/version/1 accessed 19/01/2011).

Medical supervision and follow-up

It has been suggested that general practitioners or midwives may be the most appropriate health care providers to offer carrier screening, since they can provide preconception care as part of ongoing primary care (Poppelaars *et al.*, 2004b). In addition, some carrier screening programmes are offered by gynaecologists or midwives in antenatal care. Embedding in a healthcare setting can ensure adequate information provision to increase informed choice, a more optimal informed consent procedure, a medical follow-up if necessary and psychosocial counselling.

An offer of carrier testing through the Internet by commercial companies runs the risk of disconnecting the service completely from its usual embedding in a medically supervised context. When these companies started to offer carrier tests, they referred consumers to seek medical supervision in the established health care system at the consumer's own discretion. *Pathway Genomics* suggested 'You should consult with a physician or other appropriate health care professional regarding the diagnosis, treatment and prevention of any disease or health condition' (http://www.pathway.com/more_info/terms_of_service accessed 04/05/2010). At the start of offering their service, *Counsyl* also sent out this message by underlying that people could order the test directly from their website to receive your kit immediately. 'Everyone has a prescription: the ACMG recommends that adults of reproductive age be offered carrier testing for CF and spinal muscular atrophy, two of the many conditions assayed by the Universal Genetic Test. Alternatively, you may get the test through your doctor' (https://www.counsyl.com/learn/easy/ accessed 04/05/2010). *Counsyl* recently changed its stance and since the beginning of May 2010, testing can only be requested through a physician, who can be found, among others, via the list offered on Counsyl's website. The company also sends the results directly to the physician for interpretation, thereby, technically no longer selling (but still advertising) tests directly to consumers. In October 2010, DNA Direct also changed its policy; one can find on their website that they 'are no longer offering testing services directly to consumers'; but are now focusing their 'efforts on providing comprehensive yet easy-to-understand information and tools to consumers, physicians, hospitals, employers and health plans' (http://www.dnadirect.com/web/consumers accessed 04/11/2010). Pathway Genomics has also, in the last few months, changed the way they offer tests; consumers must now obtain a physician prescription and the company offers consumers the opportunity to send an email to the treating physician of the consumer directly from the company site in order to request the prescription. The offer through physicians may eliminate some of the concerns that were raised about information provision, but does not solve the issue about the appropriateness of the test provided.

The absence of medical supervision for some DTC tests may compromise or fail to foster patient health especially in the case of carrier couples who may need intensive counselling regarding their reproductive choices, as well as concerning the risks for other family members.

The appropriate use of existing resources

As preconceptional carrier screening programmes have an impact on healthcare budgets, careful consideration should be given to whether the expenses for such a programme are justified within the realm of the healthcare system (Modell and Kuliev, 1991). Namely the option for and the cost of a specific screening programme might mean that other forms of screening cannot be carried out. Usually a balance should be made between the health gain obtained and the costs incurred. In the context of preconceptional carrier screening this has to be analysed carefully, as the primary goal of preconceptional carrier screening is enabling informed reproductive choice. Furthermore, the identification of a high number of carriers or false positives may create a higher number of visits to medical doctors for more information, and thus leading to higher costs in follow-up activities. Commercial companies underline that most users will pay for this test 'out of pocket' and therefore, the health care system will not be burdened. Since the need for follow-up information or tests is likely to happen in the traditional health care system, this is not completely true. It is foreseeable that companies testing for a whole list of disorders will create a higher number of patients visiting health services. For example, for the test panel offered by *Counsyl*, the company foresees that ~35% of the participating individuals would be carriers of at least one disease.

Furthermore, every mentioned company underlines the value of privacy and the possibility to perform the test outside the control of insurers or the healthcare system. They often play on people's fear that if testing is conducted within the traditional health care system, third parties could access their genetic information and that this might lead to discrimination. As expressed by *Counsyl*, 'no one will ever have access to your data without your express consent' (https://www.counsyl.com/about/privacy/ accessed 04/05/2010). *Pathway Genomics* states that 'Your DNA and results belong to you and no one else. Nobody should see your data or results unless you want them to' (http://www.pathway.com/more_info/dna_security accessed 04/05/2010). In contrast, *DNA Direct* and *Counsyl* want health insurers to be involved in their services. *DNA Direct* underlines that their services will be reimbursed by most insurers, although insurance companies may still ask for a letter of medical necessity which people with no *a priori* high risk may have. *Counsyl* advances that 'for many people the test will be entirely free [paid by the insurer]; for many others insurance will cover 70% or more of the cost'. In contrast, *DNATraits* refuses any reimbursement: '*DNATraits* does not accept reimbursement from insurance companies as this might limit our ability to ensure your privacy' (http://www.dnatraits.com/philosophy accessed 04/05/2010). As it is to be

expected that more companies will want their services to be reimbursed by insurance companies for their customers, it becomes crucial that carrier tests involve a required degree of usefulness, have a scientific basis and are voluntary in nature.

Conclusion

The implementation of a preconceptional carrier test should result in the optimization of the advantages whilst reducing as much as possible the risks or adverse effects of the offer. Therefore, it is crucial that the tests offered for important health problems are suitable and have a known predictive value. Furthermore, it is important to ensure quality pre- and post-test information and counselling that can lead to informed decision-making for the participants. All potential negative psychosocial impacts resulting from participation in a carrier test should be avoided or minimized and the testing process should lead to a correct understanding of the test result. In our opinion, a commercial offer of DTC genetic carrier testing through the Internet makes it difficult to meet all these criteria.

The purpose of carrier screening is to enlarge people's reproductive autonomy by enabling carrier couples to make informed reproductive decisions. In this paper, we have criticized DTC genetic testing companies that have included large numbers of disorders in the test panel, including less severe ones, as well as disorders for which only suboptimal tests are available according to the traditional screening criteria. It is, however, questionable whether commercial (preconceptional) carrier test providers can continue to exist using this business model as long as such genetic carrier tests are not integrated in larger, more comprehensive prenatal, or preferably in preconceptional, care settings (which are, admittedly, not really established in general healthcare yet). The company University Diagnostics Ltd (www.udlgenetics.com, only to be consulted on http://www.archive.org/), for example, started to offer a service to discover CF carrier status, but has ceased to exist (Advisory Committee on Genetic Testing, 1999). Furthermore, an analysis of the companies' activities in this field shows that various genetic tests that were marketed online in recent years are no longer available for purchase. Without the support of the healthcare system, it may be that only a relatively small percentage of the population will become aware of these services and will use them (Kolor *et al.*, 2009).

That being said, involving a physician in the DTC offer of genetic tests may not solve many of our concerns. If physicians are not well educated about which tests should be given based on specific criteria, they may simply become a pawn in the commercial companies attempt at increasing their market size. It will also be important to see how the regulatory frameworks will evolve. Various recent events have created the expectation that regulatory oversight will increase in the near future (Borry *et al.*, 2010). For example, the European Society of Human Genetics recently endorsed a statement in which it recommended to ensure, among other issues, the quality of the testing services, the provision of pretest information and genetic counselling, a face-to-face consultation and oversight of this industry (European Society of Human Genetics, 2010). As the government has a duty to protect citizens against the risks of unsound testing, the government can be expected to ensure that specific standards are being held and to promote the responsible provision and responsible use of specific genetic testing services to the public. If we agree that reproductive autonomy should be respected, carrier screening for various serious disorders should be available, but careful implementation is necessary in order to ensure optimization of the screening offer, counselling and follow-up.

Authors' roles

All authors provided a substantial contribution to the conception of the paper. P.B. elaborated a first draft of the paper. All other authors were involved in redrafting and revising of the paper and approved the final version of the manuscript for submission.

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