

Ethical challenges in offering expanded carrier screening in the context of third-party reproduction

Les enjeux éthiques liés au test de dépistage génétique dans le cadre de l'assistance médicale à la procréation avec un tiers donneur

Davit Chokoshvili
Eva Van Steijvoort
Pascal Borry

Centre for Biomedical Ethics and Law,
Department of Public Health and Primary
Care, University of Leuven, Belgium
<pascal.borry@kuleuven.be>

Abstract. The importance of screening gamete donors and recipients for genetic disorders in the context of third-party reproduction has been recognized for a long time. Recently, expanded carrier screening (ECS) for a large number of monogenic disorders has been made available. Although ECS offers considerable potential advantages, its widespread implementation is also associated with notable ethical challenges. This paper discusses some of the key ethical issues pertaining to ECS. The paper contrasts ECS in the context of third-party reproduction with ECS in the general population, highlighting several morally relevant differences between the two contexts. Owing to the unique characteristics of third-party reproduction, it is suggested that continued expansion of carrier screening to include mild disorders and variants of limited clinical significance could be less morally problematic when ECS is performed as part of third-party reproduction. However, the paper argues that this does not make ECS in third-party reproduction completely immune to ethical challenges, cautioning against several potential context-specific pitfalls. It is important that ethical issues pertaining to ECS in third-party reproduction receive adequate attention as we move towards establishing ECS as a new standard practice in this domain of reproductive medicine.

Key words: expanded carrier screening, third-party reproduction, ELSI genomics

Résumé. L'importance du dépistage génétique chez les donneurs et les receveurs de gamètes a été reconnue dans le cadre de l'assistance médicale à la procréation (AMP) avec un tiers donneur. Récemment, un test de portage pour un grand nombre de maladies héréditaires monogéniques a été mis à disposition. Bien que le dépistage génétique offre des avantages considérables, la mise en œuvre généralisée d'un tel test est également associée à de multiples défis éthiques. Dans cet article, certains des principaux enjeux éthiques liés au test de dépistage génétique dans le cadre de l'AMP avec un tiers donneur sont abordés. En faisant la comparaison d'offrir le test de dépistage génétique dans la population générale, plusieurs différences moralement pertinentes sont mis en évidence entre ces deux contextes. Il est suggéré que l'expansion du test de portage avec d'autres maladies moins sévères ou des variantes génétiques avec une signification clinique plus limitée pourrait être moins problématique du point de vue moral dans le cadre de l'AMP avec un tiers donneur. Cependant, l'article fait valoir que cela ne donne pas une immunité complète face aux défis éthiques en soulignant plusieurs pièges potentiels liés au contexte. Il est important que les enjeux éthiques liés au dépistage génétique de porteurs dans le cadre de l'AMP avec un tiers donneur fassent l'objet d'une attention suffisante comme nous avançons vers l'établissement du dépistage génétique de porteurs comme une pratique courante dans le domaine de la santé reproductive.

Mots clés : dépistage génétique de porteurs, procréation avec un tiers donneur, ELSI genomics

Médecine
de la **Reproduction**

Tirés à part : P. Borry

Over the past decades, the use of donor gametes has become an integral part of assisted reproduction. Donor gametes have been increasingly utilized to assist infertile heterosexual couples who cannot conceive using their own sperm or oocytes due, for example, to azoospermia of the male partner, or primary ovarian failure in the female partner [1, 2].

Simultaneously, in many countries, the use of donor gametes has grown among same-sex couples and single individuals seeking to reproduce. This includes lesbian couples and single women undergoing donor insemination [3], as well as men or same-sex male couples utilizing donor oocytes in conjunction with gestational surrogacy [4].

doi:10.1684/mte.2019.0722

The growing demand for donor gametes has given rise to the practice of collecting and preserving gametes for extended periods of time for their future use to achieve a pregnancy. Service providers specialized in this area, such as sperm and egg banks, maintain their gamete repositories by recruiting large numbers of donors on an ongoing basis. In order to determine donor eligibility, individuals willing to donate their gametes are subjected to a medical screening process, which typically includes the assessment of a prospective donor's risk of transmitting a genetic disease to his or her offspring. Genetic risk assessment in prospective donors may be carried out using several complementary methods, including: taking the individual's detailed family history, using karyotyping (in oocyte donors), and performing genetic testing for monogenic disorders [5, 6].

With respect to testing for monogenic disorders, of particular interest are recessive disorders, where donors can be healthy carriers, having no personal or family history for the disorder, but being at risk of conceiving an affected child. When both the gamete donor and the recipient are carriers of the same autosomal recessive disorder, 25% of the embryos created using the gametes from the donor-recipient pair will be affected by the disorder. In X-linked recessive disorders, where female donors can be healthy carriers, 25% of embryos (or, alternatively, 50% of male embryos) created using the carrier donor's oocytes will be affected [6].

The importance of performing carrier screening for recessive disorders has long been recognized. A 2010 survey of seventeen US-based sperm banks found that all but one bank screened all of their prospective donors for cystic fibrosis (CF), and most also routinely screened for haemoglobinopathies. Additionally, the majority of sperm banks had implemented ethnicity-based carrier screening for disorders relatively common within certain ethnic groups, most notably Tay-Sachs disease, which was screened for in all Jewish donors by thirteen sperm banks [7]. Similarly, a 2013 survey of seven commercial egg banks in the US found that carrier screening for recessive disorders in oocyte donors was a common practice. More specifically, all seven banks reported screening all prospective oocyte donors for CF and five additionally routinely performed screening for fragile X syndrome, the most common X-linked recessive disorder [8].

However, until more recently, strategies utilized to perform carrier screening in gamete donors remained limited in two ways. First, most carrier screening tests were focused on relatively common monogenic disorders, thus excluding a large number of less frequent disorders. Second, within the included disorders, carrier screening tests could only identify carriers of the mutations whose pathogenicity had been previously established, with some carriers of less known or novel pathogenic mutations remaining undetected. As a consequence, gametes of carrier donors had been routinely used to create poten-

tially at-risk embryos, occasionally resulting in the birth of affected children. For example, a retrospective review of outcome reports of a sperm bank in California revealed that during 2007-2015, at least 20 donor-conceived children were diagnosed with an autosomal recessive disorder [9]. Owing to the deficiencies of earlier carrier screening programs in gamete donors, authors had emphasized the need for more comprehensive screening efforts [9-11]. Nevertheless, because of traditionally high costs and limited sensitivity of multiplex genetic testing, implementing routine comprehensive screening of gamete donors for monogenic disorders had remained a challenge. However, recently this has changed, due largely to the emergence and growing availability of multi-disease carrier screening, known as expanded carrier screening (ECS). This paper discusses the advent of comprehensive genetic testing technologies, such as ECS, and their potential implications for the practice of third-party reproduction. The paper describes the emergence of ECS and highlights the advantages of ECS over traditional forms of carrier screening. Subsequently, it focuses on the ethical issues raised by expanded carrier screening in the context of third-party reproduction.

Expanded carrier screening in third-party reproduction

With the ongoing improvements in medical genetics and the continued diminishing costs of genetic testing, the scope of carrier screening has continued to evolve. Over the past few years, traditional carrier screening, which was limited to the most frequent pathogenic mutations associated with relatively common recessive disorders, has been gradually supplanted by more comprehensive approaches to carrier screening, commonly referred to as expanded carrier screening (ECS) [12]. ECS refers to carrier screening for a large number of monogenic disorders in a single genetic test. Compared to traditional carrier screening, the advantage of ECS is its ability to screen for both an array of genes associated with multiple monogenic disorders and to analyze a wider range of mutations within these genes. Since the cost of ECS does not exceed that of traditional carrier screening, this means that ECS identifies significantly more carriers in a cost-effective manner [13]. Currently, different ECS tests are available through various commercial genetic testing laboratories, and most of them screen for more than 100 disorders. While the majority of the disorders in a typical ECS panel are recessive, some ECS tests may also include mild or late-onset dominant disorders, where some affected individuals may not have been diagnosed and could therefore be unaware of their reproductive risks [14].

The development of ECS has been welcomed by various providers of third-party reproduction services, who

have become early adopters of this technology. Since 2015, a number of sperm and egg banks and fertility clinics have reported using ECS in their clinical practice [9, 15-17]. As of 2018, ECS has become a widespread practice in third-party reproduction, with many providers employing ECS to perform comprehensive genetic risk assessment of gamete donors [15].

The main rationale for using ECS in third-party reproduction is that ECS allows providers to further reduce the probability of creating affected embryos using donor gametes. This, in turn, means that fewer children with genetic diseases will be born to the recipients of donor gametes, sparing them from the emotional burden of having a diseased child.

However, despite considerable advantages of ECS, its widespread adoption in the context of third-party reproduction raises ethical questions, calling for a critical reflection on ECS. In the remainder of the paper, some of the key ethical issues pertaining to ECS are explored, with a particular emphasis on their implications for third-party reproduction.

Departure from traditional screening criteria

In general, one of the main criticisms of ECS has been the argument that ECS so significantly departs from the scope of traditional carrier screening that it may no longer meet the criteria commonly used to morally justify carrier screening. For example, traditional carrier screening initiatives, which have been available in some countries since as early as the 1970s, focused on childhood-onset life-limiting recessive disorders such as Tay-Sachs disease and hemoglobinopathies [18, 19]. By contrast, the modern-day ECS typically also includes mild disorders, such as HFE-related hemochromatosis or MTHFR deficiency, that have minimal impact on the affected individuals' health [14]. This gives rise to cases where couples at risk of having a child with a mild disorder need to make decisions about keeping the pregnancy or altering their reproductive plans, often through prenatal diagnosis and selective termination of an affected pregnancy. In the case of mild disorders, this obviously leads to more ethical tensions [20, 21]. Similarly, while traditional carrier screening was limited to a small number of known pathogenic mutations with well-established genotype-phenotype correlations, many currently available ECS tests include variants of uncertain or limited clinical significance. This leads to situations where some couples undergoing ECS receive indeterminate test results, creating ambiguity and raising couples' worries that they may be at risk, even though many of such couples are not true biological carriers [22]. Given these concerns, authors and professional medical societies recommend that in order to minimize poten-

tial harms arising from ECS, the development of ECS tests should be constrained through the application of clearly defined medical criteria. In particular, they suggest that ECS should be limited to childhood-onset disorders with significant impact on an affected individual's health, and to the mutations with well-established clinical significance [23-25].

However, when viewed specifically in the context of third-party reproduction, ECS may be less susceptible to the criticism discussed above. In third-party reproduction, the identification of a gamete donor-recipient pair who would be at risk of conceiving an embryo affected by a recessive disorder may lead to excluding the donor from being matched with the recipient. This decision differs from outcomes seen in reproducing couples in two morally relevant ways. First, most carrier couples wishing to reproduce using their own gametes but seeking to prevent the birth of an affected child will utilize one of the following two options: pursuing in vitro fertilization through pre-implantation genetic testing to select against affected embryos; or conceiving naturally and undergoing prenatal diagnosis with a view on terminating an affected pregnancy [26]. By contrast, in the context of third-party reproduction, preventing the birth of an affected child can be achieved by avoiding matching a carrier donor with a carrier recipient, obviating the need for discarding an embryo or terminating a pregnancy for that recessive disorder. Second, when the members of a reproducing couple are found to be at risk of having an affected child, this could have significant emotional consequences, potentially impacting the quality of their relationship [27]. By contrast, intended parents undergoing third-party reproduction are less likely to experience significant emotional distress over the fact that their risk of having an affected child with a given gamete donor is high. This is because intended parents typically do not seek to reproduce with a particular gamete donor. Instead, suitable donors are usually selected from a large pool of individuals who have donated their gametes, with recipients having no personal relationship with them [28]. Consequently, the decision not to reproduce using gametes of a particular donor due to an increased genetic risk is unlikely to be an emotionally challenging one.

Because of these reasons, it appears that the continued expansion of carrier screening, even when ECS includes mild disorders and/or variants of limited clinical significance, is less morally problematic in the context of third-party reproduction than it would otherwise be.

Maximizing clinical sensitivity of ECS in third-party reproduction

Departing from the premise that third-party reproduction using gamete donors is fundamentally different from

conceiving with one's partner, it is possible to argue that providers of third-party reproduction services should seek to adopt the most comprehensive ECS strategies to maximize the sensitivity of testing. Although many providers already employ ECS tests that include hundreds of recessive disorders, this approach is still deemed insufficient by some authors who argue that its sensitivity can be further increased [17]. In order to do so, it has been proposed that providers of third-party reproduction services could use genome-wide screening. In this approach, donors would have all of their genes associated with both dominant and recessive disorders fully sequenced. At the same time, recipients of gametes would undergo full sequencing for autosomal recessive genes to allow for identifying donor-recipient pairs where both the donor and the recipient harbor a potentially disease-causing mutation in the same autosomal recessive gene [17]. In this way, ECS would achieve a complete coverage of all known monogenic disorders, maximizing clinical sensitivity and minimizing residual risk following a negative ECS test result.

Given the current trends in genetic testing practices in the context of third-party reproduction, further expansion of carrier screening through genome-wide genetic testing is to be expected. In addition to being increasingly technically and economically feasible, this approach also appears to be in line with the predominant views regarding third-party reproduction. In particular, third-party reproduction is increasingly viewed as a service, where consumers expect high quality, including reasonable efforts by the provider to minimize any risks associated with the procedure. Owing to the wide publicity surrounding the cases where donor-conceived children are diagnosed with genetic disorders, many recipients of donor gametes become aware of this possibility, demanding more rigorous testing [28]. At the same time, the competitive nature of the third-party reproduction industry motivates many providers, such as gamete banks and assisted reproduction clinics, to adopt more extensive genetic screening strategies, in order to increase their appeal among prospective consumers. Such providers usually direct their marketing efforts at emphasizing their comprehensive screening strategies, which they may use to claim offering a superior service [6, 28].

One criticism traditionally raised with respect to genome-wide ECS in gamete donors is that by significantly lowering the risk threshold acceptable in gamete-conceived reproduction, this approach would result in the exclusion of most gamete donors, thus draining the pool of available gametes [6, 28, 29]. However, it has also been argued that there may be strategies to achieve comprehensive genome-wide screening without compromising the availability of donor gametes. For example, in autosomal dominant and X-linked disorders, genetic risk assessment of donors can be combined with

other methods, such as performing diagnostic testing and taking the donor's family history, in order to safeguard against cases where prospective donors are excluded based on false-positive genetic test results. In autosomal recessive disorders, it has been suggested that because virtually all individuals carry pathogenic mutations in one or more genes associated with autosomal recessive disorders, carrier donors need not be excluded. Instead, it would be prudent to perform screening in both the donor and the recipient to identify donor-recipient pairs at risk of conceiving an affected embryo [17]. While collectively these approaches would certainly render more prospective donors as being at a higher risk, it is likely that their impact on the availability of donor gametes will be less significant than initially feared.

Nevertheless, the goal of pursuing maximum sensitivity of genome-wide ECS tests in third-party reproduction is not free of potential ethical pitfalls. One important concern is that adopting a more comprehensive ECS in the context of third-party reproduction could place recipients of donor gametes at an advantage compared to other prospective parents. Because the more comprehensive ECS offered in third-party reproduction would additionally screen for disorders and mutations excluded from ECS in other contexts, this would make conception through donor gametes safer than reproducing with one's partner. The ethical question as to whether third-party reproduction should be made safer than human reproduction in general has been widely discussed [5, 6, 28]. One view is that, as a medical service, third-party reproduction should seek to prevent iatrogenesis, including births of affected children, which justifies the use of the most comprehensive ECS. On the other hand, it can also be argued that limiting the most comprehensive ECS to patients undergoing third-party reproduction may disadvantage couples who do not make use of this service and reproduce using their own gametes [6, 28]. Of note, this concern cannot be resolved by simply offering the same ECS test to all future parents because, as discussed previously, ECS in third-party reproduction differs from ECS in general in morally significant ways and, therefore, offering an identical ECS in both settings may not be appropriate.

Another important ethical issue arises from the fact that although genome-wide ECS may be the most comprehensive option currently available, it cannot fully eliminate the probability of creating an affected embryo. This is because some genetic risks factors, including those associated with many polygenic and multifactorial disorders, as well as de novo mutations in monogenic disorders, cannot be easily identified. Although this does not mean that comprehensive screening should not be pursued, it clearly suggests that the current rhetoric of risk minimization often used by providers of third-party reproduction services should be moderated. It is critical to ensure that intended parents pursuing pregnancy through donor gametes are made

aware of the limitations of genetic testing and do not hold unrealistic expectations that using the service guarantees them a healthy child [28].

Implications of ECS for gamete donors

Performing ECS in the context of third-party reproduction means that increasingly many prospective gamete donors will be identified as being at risk of conceiving an affected child. Because ECS of gamete donors includes both dominant and recessive disorders, the implications of a test result for donors will depend on the mode of inheritance of the disorder(s) they are at risk of passing to their offspring.

Assuming a comprehensive, genome-wide ECS, it is likely that ECS will identify many ostensibly healthy donors who harbor a variant of uncertain significance associated with a dominant disorder. In some cases, in order to establish the pathogenicity of the variant, it may be necessary to perform additional medical examination of the donor and to gather further information about their family history. This, however, could be burdensome for donors. Exploring the attitudes and experiences of gamete donors has revealed that some donors already find the existing medical and genetic screening procedures to be excessive and overly intrusive [30]. Sperm and egg banks seeking to subject their population to additional screening should seek ways to minimize any psychological distress experienced by gamete donors in the screening process.

When a prospective donor is confirmed to carry a pathogenic allele associated with a dominant or an X-linked disorder, they may be excluded from participating in the donor program. However, rejecting donors on the grounds of their high reproductive risk could have significant negative emotional consequences for them. Rejected donors could experience lower sense of self-worth, perceiving themselves as unfit for reproduction [6, 28]. Therefore, rejected donors should be provided with genetic counseling in order to ensure they receive psychological support and are appropriately informed about the implications of their ECS test results for their own reproductive plans.

In autosomal recessive disorders, it is estimated that, on average, every individual is the carrier of a pathogenic mutation associated with more than two disorders [31]. Therefore, it can be expected that a comprehensive ECS test will identify nearly 100% of gamete donors as carriers of at least one autosomal recessive disorder. Because of this, in general, gamete donors need not be excluded due to their carrier status for an autosomal recessive disease [17]. However, carrier status for some autosomal recessive disorders could potentially influence decisions of some gamete donors with respect to their own reproductive plans. For example, donors who are identified as carriers

of relatively common autosomal recessive disorders may be prompted to seek screening for their reproductive partner. Given the potential relevance of this information for gamete donors, it is important that they have a possibility to learn their ECS test results. To this end, the interests of gamete donors would be best served if they are made aware of this potential finding and are provided with an option to receive their carrier status information, if they so choose.

Conclusion

The expansion of carrier screening in the context of third-party reproduction is expected to continue, possibly leading to genome-wide ECS in the near future. The main motivation for this expansion is to further reduce the incidence of monogenic diseases among children conceived through donor gametes. Owing to the diminishing costs and growing technical feasibility of multiplex genetic testing, providers of third-party reproduction services are poised to implement increasingly comprehensive ECS tests in their clinical practice. However, as discussed in the present article, these developments pose considerable ethical challenges. It is important that the ethical issues surrounding ECS in the context of third-party reproduction are adequately addressed as ECS becomes a common practice among the providers of third-party reproduction services.

Liens d'intérêt : Les auteurs déclarent n'avoir aucun lien d'intérêt en rapport avec cet article.

Références

1. Carrell DT, Cartmill D, Jones KP, Hatasaka HH, Peterson CM. Prospective, randomized, blinded evaluation of donor semen quality provided by seven commercial sperm banks. *Fertil Steril* 2002; 78(1): 16-21.
2. Budak E, Garrido N, Soares SR, et al. Improvements achieved in an oocyte donation program over a 10-year period: sequential increase in implantation and pregnancy rates and decrease in high-order multiple pregnancies. *Fertil Steril* 2007; 88(2): 342-9.
3. O'Reilly D, Bowen JM, Perampaladas K, Qureshi R, Xie F, Hughes E. Feasibility of an altruistic sperm donation program in Canada: results from a population-based model. *Reprod Health* 2017; 14(1): 8.
4. Kim HH. Family building by same-sex male couples via gestational surrogacy. *Semin Reprod Med* 2017; 35(5): 408-14.
5. Janssens PM, Thorn P, Castilla JA, et al. Evolving minimum standards in responsible international sperm donor offspring quota. *Reprod Biomed Online* 2015; 30(6): 568-80.
6. Dondorp W, De Wert G, Pennings G, et al. ESHRE Task Force on Ethics and Law 21: genetic screening of gamete donors: ethical issues. *Hum Reprod* 2014; 29(7): 1353-9.

-
7. Sims CA, Callum P, Ray M, Iger J, Falk RE. Genetic testing of sperm donors: survey of current practices. *Fertil Steril* 2010; 94(1): 126-9.
 8. Quaas AM, Melamed A, Chung K, Bendikson KA, Paulson RJ. Egg banking in the United States: current status of commercially available cryopreserved oocytes. *Fertil Steril* 2013; 99(3): 827-31.
 9. Isley L, Falk RE, Shamonki J, Sims CA, Callum P. Management of the risks for inherited disease in donor-conceived offspring. *Fertil Steril* 2016; 106(6): 1479-84.
 10. Landaburu I, Gonzalvo MC, Clavero A, et al. Genetic testing of sperm donors for cystic fibrosis and spinal muscular atrophy: evaluation of clinical utility. *Eur J Obstet Gynecol Reprod Biol* 2013; 170(1): 183-7.
 11. Reh A, Amarosa A, Licciardi F, Krey L, Berkeley AS, Kump L. Evaluating the necessity for universal screening of prospective oocyte donors using enhanced genetic and psychological testing. *Hum Reprod* 2010; 25(9): 2298-304.
 12. Lazarin GA, Haque IS. Expanded carrier screening: a review of early implementation and literature. *Semin Perinatol* 2016; 40(1): 29-34.
 13. Beauchamp KA, Wong KK, Taber KJ, et al. Clinical impact and cost effectiveness of a 176 condition expanded carrier screen. *J Mol Diagn* 2018; 20(6): 905.
 14. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? *Prenat Diagn* 2018; 38(1): 59-66.
 15. Quaas AM, Pennings G. The current status of oocyte banks: domestic and international perspectives. *Fertil Steril* 2018; 110(7): 1203-8.
 16. Martin J, Asan J, Yi YT, Alberola T, et al. Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile couples wishing to conceive through assisted reproductive technology. *Fertil Steril* 2015; 104(5): 1286-93.
 17. Silver AJ, Larson JL, Silver MJ, et al. Carrier screening is a deficient strategy for determining sperm donor eligibility and reducing risk of disease in recipient children. *Genet Test Mol Bioma* 2016; 20(6): 276-84.
 18. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. *Eur J Pediatr* 2000; 159(Suppl 3): S192-5.
 19. Zlotogora J. Population programs for the detection of couples at risk for severe monogenic genetic diseases. *Human genetics* 2009; 126(2): 247-53.
 20. Borry P, Clarke A, Dierickx K. Carrier screening for type 1 Gaucher disease: difficult questions. *Eur J Hum Genet* 2008; 16(2): 139-40.
 21. Chokoshvili D, Janssens S, Vears D, Borry P. Designing expanded carrier screening panels: results of a qualitative study with European geneticists. *Pers Med* 2016; 13(6): 553-62.
 22. Grody WW. Expanded carrier screening and the law of unintended consequences: from cystic fibrosis to fragile X. *Genet Med* 2011; 13(12): 996-7.
 23. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med* 2013; 15(6): 482-3.
 24. Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. *Eur J Hum Genet* 2016; 24(6): e1-12.
 25. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation and Society for Maternal-Fetal Medicine. *Obstet Gynecol* 2015; 125(3): 653-62.
 26. Johansen Taber KA, Beauchamp KA, Lazarin GA, Muzzey D, Arjunan A, Goldberg JD. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. *Genet Med* 2018 [Epub ahead of print].
 27. Myring J, Beckett W, Jassi R, et al. Shock, adjust, decide: reproductive decision making in cystic fibrosis (CF) carrier couples—a qualitative study. *J Genet Couns* 2011; 20(4): 404-17.
 28. Mertes H, Lindheim S R, Pennings G. Ethical quandaries around expanded carrier screening in third-party reproduction. *Fertil Steril* 2018; 109(2): 190-4.
 29. Winand R, Hens K, Dondorp W, et al. *In vitro* screening of embryos by whole-genome sequencing: now, in the future or never? *Hum Reprod* 2014; 29(4): 842-51.
 30. Amor DJ, Kerr A, Somanathan N, et al. Attitudes of sperm, egg and embryo donors and recipients towards genetic information and screening of donors. *Reprod Health* 2018; 15(1): 26.
 31. Bell CJ, Dinwiddie DL, Miller NA, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Sci Transl Med* 2011; 3(65): 65ra4.