

**A closer look at expanded carrier screening
from a preimplantation genetic diagnosis perspective**

Running Title: A closer look at ECS from a PGD perspective

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Abstract

Conventionally, the search for carrier status was based on ethnicity and/or family history and targeted to a restricted number of genetic conditions and mutations. This is now being replaced by extended panels testing for hundreds of genetic disorders with a broad range of phenotypes, in what is called “expanded carrier screening”. While the ultimate aim of these panels is to increase the reproductive autonomy of the individuals and couples by providing preconception knowledge that could lead to the broadest range of available options, including preimplantation genetic diagnosis (PGD), we argue that: (i) Given the number and heterogeneity of the conditions included in panels, it cannot be guaranteed that a couple who tests positive for one of those conditions will be eligible for PGD; patients should be informed of this potential limitation before undertaking screening. (ii) Family history is typically lacking in couples identified through panels as being at high-risk for certain disorders. This should promote a reflection on the inclusion of personal experience with a condition as a consideration for PGD in disorders with incomplete penetrance or for which treatment options are available. (iii) With the advent of next-generation sequencing panels, cases of couples in which one member carries a disease-causing variant and the other has a variant of uncertain significance found in the same gene are likely to become more common and need to be discussed from the PGD perspective. (iv) With comprehensive panels where healthy individuals are likely to be identified as carriers for several conditions, testing of carrier status for embryos and prioritisation of the embryos to transfer needs reassessing. We believe that these points should be included in the discussion on expanded carrier screening and that all stakeholders, patients included, must be aware of the challenges and limitations that may come with a positive result.

Key words

Expanded carrier screening; carrier screening panels; preimplantation genetic diagnosis; reproductive autonomy; reproductive choice.

Introduction

With advances in genetic testing, the practice of preconception carrier screening is evolving rapidly. The possibility now exists to screen for hundreds of rare conditions, allowing individuals or couples to be provided with a refined knowledge of the genetic disorders that may affect their offspring. It is hoped that this practice will be beneficial to the consumers by promoting a timely reproductive choice between several options, including preimplantation genetic diagnosis (PGD). With the introduction of expanded carrier screening (ECS) in Europe, a reflection is needed on how the aims of contemporary carrier screening are connected to the aims of PGD and on the particular challenges that ECS may bring to the current PGD practice.

Evolution of carrier screening

Carrier screening is a specific form of genetic screening that seeks to identify individuals carrying genetic mutations that place them at risk of having a child with a certain recessive disease (European Society of Human Genetics' PPPC, 2003). Traditionally, and according to the health screening principles set almost five decades ago on behalf of the World Health Organisation (WHO) (Wilson and Jungner, 1968), carrier screening is aimed at a high-risk population defined by ethnicity and/or family history and targets a restricted number of well-known, relatively common conditions.

Since the sequencing of the human genome was accomplished in 2001 (Lander et al., 2001; Venter et al., 2001), the molecular basis of an increasing number of monogenic disorders has been understood and the possibility arose for an extension of the number of conditions included in screening programmes. In fact, there are 23,621 disorders of known or suspected Mendelian inheritance described to date, of which 4,787 have an identified molecular basis (omim.org, last updated 29 July 2016). While most monogenic conditions are rare, they are responsible for a substantial burden from both the individual patients' and public health perspectives (Guttmacher and Collins, 2002). Additionally, data from the 1000 Genomes project confirmed that individuals typically carry 20-40 potentially damaging variants at conserved sites, of which 2-5 have a low enough frequency to be considered as pathological candidates (Abecasis et al., 2012).

The change in carrier screening practice began with the development of screening panels for a range of conditions targeting the Ashkenazi Jewish population (Leib et al., 2005; Scott et al., 2010; Baskovich et al., 2016; Gal et al., 2016) beyond the four to nine disorders recommended in professional guidelines (Gross et al., 2008; Monaghan et al., 2008; American College of Obstetricians and Gynecologists Committee on Genetics, 2009). This was soon followed by an extension of concept to include the entire population of reproductive age as the target audience, regardless of ethnic background (Srinivasan et al., 2010). This new approach, expanded carrier screening – referred by some as “pan-ethnic” (Tanner et al., 2014; Holtkamp et al., 2016) or “universal” (Simpson, 2010; Srinivasan et al., 2010) – allows the detection of carrier status for multiple recessive disorders “in couples or

persons who do not have an *a priori* increased risk of being a carrier based on their or their partners' personal or family history", thus allowing "testing of individuals regardless of ancestry or geographic origin" (Henneman et al., 2016).

The first paper on ECS was published in 2010 by authors affiliated with a commercial company offering this product (Srinivasan et al., 2010). In this publication, a single multiplex genotyping assay for more than 100 conditions was proposed to address "the long tail on Mendelian disease" and suggested as a routine part of preconceptional care (Srinivasan et al., 2010). Soon after, a different molecular approach was suggested for ECS, with the use of targeted next-generation sequencing (NGS) for 448 severe recessive disorders of childhood onset (Bell et al., 2011). Other publications on ECS followed, reporting on the use of either genotyping with an array-based platform (Lazarin et al., 2013; Tanner et al., 2014) or NGS (Hallam et al., 2014; Umbarger et al., 2014; Abuli et al., 2016).

Just two years ago, the audience of an international conference on prenatal diagnosis was unaware of the availability of ESC outside the United States of America (USA) (Langlois et al., 2015). More recent papers refer to a prospective (Plantinga et al., 2016) or actual (Martin et al., 2015; Abuli et al., 2016) offer of ECS in Europe and it is believed that an increasing number of laboratories is performing ECS in different continents (Henneman et al., 2016).

ECS as a means to maximise reproductive choice

According to the European recommendations on ECS, recently released on behalf of the European Society of Human Genetics (ESHG) and endorsed by the British

Society for Genetic Medicine, the primary purpose of ECS is to increase the reproductive autonomy of the individuals undergoing testing by creating awareness of carrier status and of the reproductive options available, therefore “maximizing meaningful choices” (Henneman et al., 2016). The options after carrier screening in general, and ECS in particular, include prenatal diagnosis, preimplantation genetic diagnosis (PGD), the use of gamete donors, natural conception with no further testing, adoption and refraining from having children. In some cultures, a change in the prospective reproductive partner is also considered. The decision on which option to pursue is highly variable among carrier couples, and has been found to be related to factors such as the severity of the disorder, beliefs regarding termination of pregnancy, religious considerations and waiting list for PGD (Henneman et al., 2001; Musters et al., 2010; van Lier et al., 2012; Derks-Smeets et al., 2014; Norton et al., 2014). In line with the aim of optimizing reproductive choice, it has been argued that the ideal timing for ECS is before pregnancy, when a broader range of options is available with fewer time constraints (Beaudet, 2015; Edwards et al., 2015; Henneman et al., 2016). Nevertheless, it should be noted that, particularly in countries where a large proportion of pregnancies is unplanned, the preconception window will often be missed (Langlois et al., 2015), and so will some of the reproductive options.

Issues regarding the composition of ECS panels

The composition of ECS panels has lacked an independent oversight (Rose, 2015) and is consequently varied in terms of severity and age-of-onset of the conditions included. For instance, while in Europe publications refer to childhood-onset disorders (Martin et al., 2015; Abuli et al., 2016; Plantinga et al., 2016), a well-known

commercial company in the USA is explicitly including adult-onset disorders and conditions associated with a mild phenotype (Lazarin et al., 2013). An option to ensure that the focus is placed on the information that is relevant from a reproductive viewpoint is to restrict the panel to serious, untreatable and childhood-onset conditions, only reporting the results as positive if both elements of the couples are carriers for the same condition (Plantinga et al., 2016). Although this approach would be associated with a lower chance of finding and reporting a clinically relevant disease risk for the screened individuals themselves, it is not current practice in the commercial setting.

Another issue relates to the molecular approaches in use, array-based genotyping and NGS, and the specific information that will be derived from each of these (Henneman et al., 2016). For genotyping, apprehensions relate to the potentially low capacity of a predefined set of mutations to detect carriers (carrier detection rate), the subsequent alteration in the risk of an individual actually being a carrier after having tested negative (residual risk), and how these variables depend on carrier frequency and, therefore, ethnicity (Simpson, 2010; Edwards et al., 2015; Henneman et al., 2016). The use of NGS may naturally be associated with an increased detection rate when compared to targeted genotyping because the potential exists for mutations to be detected beyond a predefined list (Hoffman et al., 2013; Hallam et al., 2014). However, the interpretation regarding the pathogenicity of sequence variations is not straightforward. Not only have databases in use for this purpose been found to contain a surprisingly high number of errors (Bell et al., 2011; Beaudet, 2015), recent evidence suggests that the relationship between mutation

and phenotype may not be as well-defined as previously assumed (Winand et al., 2014; Chen et al., 2016).

ECS in infertility practice

The discussion of the role of ECS in infertility practice is emerging (Martin et al., 2015; Franasiak et al., 2016; Gil-Arribas et al., 2016). In a focus group research on the perspectives from genetics professionals on ECS, it was felt that patients who were already undergoing *in vitro* fertilisation (IVF) were likely to be particularly interested in ECS, as it would be easier to add PGD to an already decided IVF cycle than it would be for fertile couples to undergo IVF in order to have PGD (Cho et al., 2013). On the other hand, it has been argued that routinely offering ECS in this setting may be discriminatory against non-IVF patients (Gil-Arribas et al., 2016), which we believe to be a non-issue as long as ECS is also offered to fertile couples seeking preconceptional care. Regardless, the use of ECS as a guide to a decision for targeted PGD may overcome some of the issues related to a broader application of preimplantation genetic diagnosis/screening (PGD/S) using high-throughput technology (Hens et al., 2013; Harper et al., 2014), such as the association of those methods with a high likelihood of incidental findings.

Another prospective application in this setting refers to gamete donors' comprehensive screening. This allows for exclusion as donors of females carrying mutations for X-linked recessive disorders, as well as blinded-matching to recipients where a mutation is present which could lead to an autosomal recessive condition in the offspring (Martin et al., 2015; Abuli et al., 2016; Silver et al., 2016). An ESHRE Task Force document states that the transition to ECS for screening of gamete

donors is not obvious and raises a number of ethical and clinical concerns (Dondorp et al., 2014). In a time when the integration and disclosure of carrier status information of historical gamete donors to their donor-conceived offspring is being raised as an issue (Harper et al., 2016), ECS provides a timely opportunity to integrate that information before, rather than after, donation. However, it is unclear if and how the information of the donors who screen positive through ECS, but are not rejected due to the implementation of a blinded-matching programme that excludes a high-risk “pairing”, should be transmitted to their offspring. In cases of disclosure of carrier status, there is a compelling case towards the provision of access, by request of adults conceived with the use of donor gamete(s), to the clinically relevant genetic information of the donor(s).

In a setting where ECS was routinely offered to patients undergoing infertility evaluation and performed in the vast majority of cases using an array-based platform, 0.29% (8 in 3,738) of the screened couples tested positive for the same autosomal recessive condition (Franasiak et al., 2016). However, three of these couples were previously known carriers for cystic fibrosis and were referred specifically for PGD for that reason. As such, *de novo* findings with an impact on the reproductive risk were found in only 1 in 748 couples (Franasiak et al., 2016). In Europe, a much higher rate of carrier couples in a similar context has been found, with 5% of couples being carriers for the same condition (Martin et al., 2015). This may be explained by the use of a comprehensive targeted-NGS panel covering 549 genes, as opposed to the lower coverage of the different panels reported by Franasiak et al.

PGD as an option after ECS

Among the different reproductive options available, PGD provides carrier couples with embryo selection at a preimplantation stage, under the goal of conceiving an unaffected child that is genetically related to both elements of the couple. For some couples, PGD is preferable to prenatal diagnosis for a specific condition, as the later encompasses the consideration of terminating an affected pregnancy, which may be deemed burdensome or unacceptable (De Wert et al., 2014). In a restrictive “medical model”, the aim of PGD is to eliminate a high-risk of having an affected child. However, an ESHRE Task Force has endorsed a broader view in 2014 (De Wert et al., 2014) to account for more complex aims such as the health of a third generation, which we believe should be addressed in light of the recent developments in ECS.

The connection between ECS and PGD seems close and, by being offered a preconception test aimed at increasing their reproductive options, it is legitimate for couples to reasonably assume that, were they to be found at a high-risk of having an affected child with one of the conditions included in such panel, PGD would be available as one of the options. However, as will be discussed, this assumption may not be fully accurate.

i) Availability of and eligibility to PGD after ECS

Analysing the literature on ECS, PGD has been deemed by genetics professionals as “the most expedite way” to address a couple’s high reproductive risk after a positive ECS result (Cho et al., 2013). In the specific context of the USA, it has however been recognised that the limited insurance coverage for IVF may be a limiting factor of the options faced by couples after a positive result (Cho et al.,

2013). It has also been previously mentioned that some reproductive options may not be available, or even legal, after a couples' carrier status has been identified for a condition with unclear implications for the future (Wienke et al., 2014). Depending on the country, this may be the case for adult-onset or non-severe conditions that are also ineligible for prenatal diagnosis and termination of pregnancy under the national legislation. However, in order to do PGD a form of assisted reproduction is necessary in order to get access to the embryos. Therefore, in comparison to PND, PGD is less often available, more expensive and results in a live born child in only about 25% of treatment cycles. We find this concerning, as couples will be provided with information of a rather unsettling nature, not necessarily coupled with a means to deal with their increased reproductive risk. Remarkably, the issues of availability of and eligibility for PGD after a positive test have generally been absent from the discussion on the controversies surrounding ECS (Langlois et al., 2015; Lazarin and Goldberg, 2016).

One of the commercial companies offering ECS in Europe described that they included in their panel disorders with a known molecular basis that had been reported by the European Society of Human Reproduction and Embryology (ESHRE) as having been indications for PGD (Martin et al., 2015). By no means does this mean, however, that *only* those conditions were included. In fact, the list of monogenic disorders included in the source referred by the authors, the XII PGD Consortium data (Moutou et al., 2014), comprises 60 autosomal recessive and 34 X-linked disorders. Even taking into account the fact that the ESHRE authors grouped the different types of the same disorder into a single element of their list, this is very different to the 623 disease phenotypes, correspondent to 549 genes,

that were included in the ECS panel (Martin et al., 2015). The fact that PGD has not been reported during that period for the remaining disorders does not mean that they would not be considered eligible. However, the opposite assumption cannot be made. As such, patients should not embark on ECS under the belief that the option of PGD will be unquestionable in light of a positive result. We advocate that the composition of panels should take availability of and eligibility to PGD into account and that adaptations should be offered, ideally tailored at a national level, to match the goal of an increased reproductive autonomy.

ii) Relevance of personal history with a condition

A case has been highlighted where a couple discovered through ECS that they were carriers for a type of autosomal recessive hearing loss and deafness, GJB-2 related, and underwent PGD for that indication (Franasiak et al., 2016). This is a condition which shows variable expression (i.e., is associated with a range of severity in terms of phenotype) and reduced penetrance (i.e., not all individuals with the mutation will be affected by the disorder) (Snoeckx et al., 2005). The authors noted that this is not an uncommon practice in PGD, as mutations for conditions with reduced penetrance or where treatment options are available have historically been selected against to lessen “the burden of medical disease on the family” (Franasiak et al., 2016). In agreement with this, it has been stated on behalf of ESHRE that a consideration at an individual basis should be given to PGD for disorders with incomplete penetrance in view of, among other factors, “the seriousness of the disease in the particular [family] (...) and personal experiences and circumstances of the individual applicants” (De Wert et al., 2014). The fact that couples who are firstly identified as

carriers for a genetic disorder through ECS are likely not to have a family history or personal experience with the condition brings a new element to the table – how to best decide on the eligibility for PGD in such cases? If the reproductive autonomy of the patients is taken as the primordial concern, then we believe PGD should always be offered, regardless of personal experience, provided the couples are well informed about the incapacity to accurately predict a phenotype. Still, it is important for this situation, where there is a real risk of having a child affected by the condition that is being targeted, not to be confused with patient autonomy at all costs (as would be the case for social sex selection). While it may increase the number of PGD cycles in potentially unnecessary cases, this appears to be the only approach in which a reaction is available for patients who underwent ECS. We strongly feel, however, that a more cautious decision of which genes to include in panels may partly overcome this issue.

iii) Approach to VOUS

Interestingly, a Centre in Reproductive Medicine from Europe performing ECS by targeted-NGS is reporting variants of uncertain/unknown significance (VOUS – variants for which the pathogenicity of the genetic alteration cannot be confirmed nor discarded) to patients by default (Abuli et al., 2016). Another Centre, where VOUS are reported if a pathogenic variant is found in the partner for the same gene, details that “the option to ask for PGD was introduced sometimes” in this context (Martin et al., 2015). While the American College of Medical Genetics recommends in most cases against reporting of VOUS generated as a result of sequencing (Green et al., 2013), in Europe no such clear professional position exists (Hehir-Kwa et al., 2015). Whereas by principle one would think that VOUS are not an eligible indication for

PGD, the combination of a pathogenic variant in one member of the couple with a VOUS in the other might become a common scenario after ECS which needs further assessment from the PGD perspective. We believe this would be the only case in which VOUS should be reported and acted upon, which once again highlights the importance of ECS as a test to be performed by reproductive couples, rather than individuals.

iv) Testing of and prioritisation among *in vitro* embryos

Another issue that is likely to be amplified with the increased knowledge of carrier status is the conduct regarding carrier embryos in a PGD cycle (Hens et al., 2013). If a panel is applied to prospective parents where the carrier burden (i.e., the average number of conditions for which an individual is found to be a carrier after taking the test) is 2.8 (Bell et al., 2011), chances are that all, or almost all, embryos will be a carrier for at least one condition. Should the embryos be tested for this carrier status? According to ESHRE, “there is no good reason for rejecting PGD in order to avoid health problems in a third generation” (De Wert et al., 2014). However, the example provided was that of sex selection to avoid transmitting an X-linked mutation to a female offspring, where the reproductive risk for the third generation would be high (De Wert et al., 2014). Should the same principle apply to rare autosomal recessive conditions? In a world where many believe that “the more information the better”, and given the parental desire to provide children with the easiest possible route in life, patients may feel that this would be appealing, despite of a low risk, to avoid any reproductive barriers in a third generation.

Also, should the occasional non-carrier embryo be prioritised for uterine transfer regardless of morphology? In view of EHSRE's "more permissible" recommendations for acceptable PGD-indications when PGD is added to an already indicated IVF/ICSI cycle or to a PGD procedure for another, more serious, disorder (De Wert et al., 2014), the increasing number of individuals/couples who will knowingly be at a high-risk of transmitting *several* mutations commands a further exploration of what the ideal attitude towards this scenario would be. Finally, if a carrier embryo is to be transferred, should prospective parents be aware of this status? We believe that would be a violation of the future child's rights not to know and not to have their genetic information available to others (beyond what may be for their health benefit as children). However, with the possible "normalisation" of an "ECS plus PGD pack" and its extension to general IVF practice, that may well be the sort of information that ends up being transmitted to the future parents.

ECS plus PGD beyond monogenic disorders

Pressure to extend the scope of ECS to include more variants associated with a predisposition to adult-onset disorders or even non-health related traits cannot be excluded. In fact, a commercial company advertising genetic testing has patented a method for gamete donor selection beyond disease-related mutations, including assessment of potential fitness (Sterckx et al., 2013; Wojcicki et al., 2013). In a recent survey with a sample deemed as representative of the USA population, 14.6% and 18.9% of the respondents were in favour of PGD for physical and personality traits, respectively (Winkelman et al., 2015). Also, there are supporters in the general population of PGD for physical and personality traits (Winkelman et al., 2015) and the prospect of genome editing (Xiao-Jie et al., 2015) may theoretically

overcome the issue of a limited baseline pool of genes to choose from. How PGD will evolve based on an increased preconceptional knowledge of the genetic make-up of individuals of reproductive age is unclear. We find the suggestion that ECS will be worth a future review considering “the embryo as a patient” (Gil-Arribas et al., 2016) concerning.

Conclusion

The increased availability of ECS is likely to change the manner in which PGD is perceived. While it is likely that more couples will benefit from this reproductive option and avoid a family burden of severe, life changing conditions, one must not fall into temptation of an unreasoned offer of a “ECS plus PGD package” without a careful and integrated consideration of its caveats. In particular, with the best interest of the patient as our primary concern, we should refrain from offers that bring nothing but increased cost and anxiety. As such, it is essential for the communication between stakeholders in ECS and PGD to be strengthened, with the development of broader policies including both forms of reproductive testing and, in particular, their relationship to one another.

Authors’ roles

CVM was involved in all steps, from the conception to writing of the manuscript. JCH provided expert advice on the topic and revised the manuscript critically for important intellectual content.

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Conflict of interest

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