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The Use of Expanded Carrier Screening in Reproductive Medicine

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Plain language summary

Expanded carrier screening (ECS) is a genetic screening test carried out by analysing a blood sample. This screen can be used to detect whether the individual unknowingly carries gene variants associated with common genetic conditions, such as cystic fibrosis, that may be passed on to their children. It is typically performed in reproductive medicine for those who are considering having a family either naturally or via fertility treatment. Many donor sperm and egg banks, particularly in the USA and Europe, also perform blanket ECS testing on all their prospective sperm and egg donors. ECS is not currently routine practice in the UK, but a growing number of patients are requesting it before treatment.

All of us carry gene variants of some sort that may cause autosomal recessive disease in their children if their partner or donor also carry a variant in the same gene. An autosomal recessive disease means two copies of an abnormal gene must be present in order for the disease or trait (such as cystic fibrosis or sickle cell disease) to develop. One copy of the variant means the person is a carrier but does not have the condition. Two copies, i.e. from the mother and father, means the child has a 25% chance of having the genetic disease. Carrying a gene variant does not mean that the individual would necessarily have any symptoms of the disease or any features of the condition.

Genetic tests for specific conditions are currently available either before or during pregnancy for prospective parents who have a family or personal history of a genetic condition, or for those from ethnic backgrounds where certain conditions – such as haemoglobinopathies (blood disorders) – are common, prompting referral to a clinical genetics department.

Expanded carrier screens may test for more than 100 genetic conditions. The list of conditions screened for is called a panel. Common panels are 250 or 600 genes. Not all expanded carrier screens that are available analyse the same genes. Some may test for genes that do not cause serious disease, or cause diseases that occur in later life; others test for genes that cause severe conditions in childhood. There is no agreement as to which panel of genes should be tested for in an ECS.

Understanding the screening that is being offered, and the meaning of any results, is complicated and requires support from appropriately trained professionals to best inform the prospective parent or parents.

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This is the first edition of this paper. This guidance is for healthcare professionals who care for women, non-binary and trans people.

1 | INTRODUCTION

Expanded carrier screening (ECS) is a blanket blood test for many genetically associated diseases. This paper will discuss the use of ECS in reproductive medicine, with regards to the current context of its use, the clinical and technical considerations of performing ECS and the ethics to be considered. It is important that healthcare professionals recommending the use of ECS in a clinical context are fully informed about its value in the clinical setting, and the risks and benefits that it may bring. This knowledge will ensure that people undergoing ECS will be able to provide informed consent after a discussion with their healthcare professional around the personalised risks and benefits.

This guidance is for healthcare professionals who care for women, non-binary and trans people. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex recorded at birth.

2 | THE CONTEXT OF EXPANDED CARRIER SCREENING

Many private molecular genomics laboratories now offer ECS to provide preconception information, and this is being applied to gamete donors, particularly in the USA. It is not always easy to ascertain whether these laboratories are accredited with any reliable organisation, or subject to quality control.[1] Commercial companies that offer direct to consumer genetic/genomic testing, including ECS, have been increasing their internet marketing activities both in the UK and overseas, and are in fact targeting healthy people.[2] The NHS England (NHSE) National Genomic Test Directory[3] states that carrier testing for partners of carriers should only be offered where the carrier frequency is higher than 1 in 70 (in relevant populations); where the gene is suitable for carrier testing (pseudogenes and/or high rates of benign variant make some very difficult); and/or where the identification of an affected fetus would have a sufficiently predictable effect to make reproductive choices.

Although the Human Fertilisation and Embryology Authority provides guidance to UK fertility clinics about donor screening,[4] there is currently no national guidance in the UK specific to ECS, and there are currently no requirements for UK fertility clinics to carry out ECS, or for gamete donors. Furthermore, most donors would not meet the criteria for testing set out in the NHSE National Genomic Test Directory.[3] This is at odds with USA-based sperm banks. There is some emerging evidence[5,6] however, that ECS may be of value in consanguineous couples, where it has been reported that around 12–28% of couples may have likely pathogenic or pathogenic variants not previously known to them. Larger studies on more populations are required.

There is consistent evidence of an increasing use of ECS – and a subsequent increase in the attendance to either NHS primary or secondary care services of patients requiring further explanation/interpretation of ECS results – adding to the burden of care.[2] These patients may already be known to be a carrier for a specific condition or, are otherwise healthy people in the process of attempting pregnancy, or women who are already pregnant. Prospective parents seeking assisted reproductive technology, especially if already undergoing preimplantation genetic testing for monogenic disease, may be interested in ECS. Their primary concern is to avoid the transmission of a genetic disease to their offspring, and therefore may be wishing to expand their screening options.[7] In addition, there are those who have used, or are in the process of using, donor gametes that have undergone ECS either in private UK clinics or abroad.

3 | TECHNICAL CONSIDERATIONS OF EXPANDED CARRIER SCREENING

All humans are carriers for several autosomal recessive disorders.[8] This often has no implication for the individual's health, and there is only an offspring risk if they reproduce with an individual who is a carrier for the same gene variant.

Currently available ECS panels include as few as 41 conditions and as many as 1556.[9] Very few of the 500–600 genes tested on the most common ECS panels in the USA satisfy the criteria recommended by the NHSE National Genomic Test Directory.[3] A carrier rate of 1 in 70 represents a prevalence of the condition/disease of roughly 1 in 20 000. A person selecting a gamete donor known to be a carrier of a disorder with a carrier rate of 1 in 70 will themselves have a 1 in 70 chance of being a carrier for that condition, and if they were a carrier, a 1 in 4 (25%) chance of having an affected child. This means that, in the absence of carrier testing of the recipient, the chance of a child being affected by the condition is 1 in 280 (0.36%). While carrier rates differ with ethnicity, the benefit of using ECS is that it is more accurate than using self-reported ethnicity and ethnicity-based panels.[10]

Providers of ECS vary considerably, with some offering testing for diseases with a low prevalence, variable expressivity and incomplete penetrance, late onset, or mild phenotype. Some providers do not have a standardised best practice or regulatory oversight.[1] The accuracy of ECS results are not always clear regarding what class of variant (pathogenic, likely pathogenic, or uncertain significance) has been found, and the level of reliability. Variant reports therefore need to be approached with caution and independently evaluated.[1] Most of the potential donors imported from the USA, and other areas which apply ECS, come with the information that they are carriers for often very severe genetic disorders for which the recipient cannot readily access genetic testing without a considerable (and probably unnecessary) outlay to

a private geneticist and laboratory. In most circumstances, the rarity of the disorder should provide reassurance to an at-risk couple, but without clinical genetics advice, this may be challenging for most fertility specialists.

4 | CLINICAL CONSIDERATIONS OF EXPANDED CARRIER SCREENING

While on the one hand ECS enables informed preconception decision-making, responsible implementation raises technical, legal, ethical, and social questions. As all individuals carry variants causative for autosomal recessive disorders, the larger the panel used (typically either 250 or 600 genes), the more likely it will be to find a recessive gene variant. It is worthwhile should the prospective parents be carriers of variants of the same gene, however, some conditions are more severe than others. Leung et al.[9] recently suggested an approach to detection rate and residual risk based on disease allele frequencies, using cystic fibrosis as their proof of concept. The American College of Medical Genetics and Genomics, in their practice resource paper,[11] suggested a tiered approach to screening based on prevalence: tier 1 = historical risk-based (cystic fibrosis and spinal muscular atrophy); tier 2 = at least 1 in 100 + tier 1; tier 3 = 1 in 200 or more + tier 2 and tier 4 = rarer conditions + tier 3. Others have suggested this grading is confusing both for patients and generalist care providers.[12]

Access to genetic counselling both pre- and post screening is essential should a healthcare provider be considering offering ECS as part of their reproductive work-up. Prospective parents can use this information for reproductive decision-making when both are carriers of the same disease. Various options are available to prevent the birth of an affected child, such as prenatal testing, IVF using donor gametes, or preimplantation genetic testing of the embryos accepting the risk, or deciding not to have children.

5 | ETHICAL CONSIDERATIONS OF EXPANDED CARRIER SCREENING

Ethical considerations of ECS for couples, regardless of their a priori carrier risk, has been extensively discussed in other papers.[7,13] The consensus seems to suggest that ECS panels should only contain genes associated with severe/childhood onset diseases.

However, fertility specialists in the UK are encountering patients who have either sourced their own donor from overseas who has had ECS, or have had direct-to-consumer ECS themselves. Alternatively, fertility services may have procured their own donor gametes from Europe or the USA where ECS is common practice. This places fertility specialists in a difficult situation as they may not know enough about the conditions to be able to give accurate advice. This could lead to unnecessary anxiety and test requests, donor gametes being rejected, or the birth of a child with a genetic condition. The recipient and their partner should be made aware that regardless of any screening results, there remains a residual risk. Plus, if the recipient is not a carrier, any offspring conceived from the donor will have a 50:50 chance of being a carrier, which will need to be shared with them at the appropriate age, especially if it is a condition with a high carrier frequency.

Where clinics use donors from banks where ECS is routine, another issue to consider is the inequity of care between couples going through fertility treatment using their own gametes, who have not had ECS, compared to prospective parents having donor conception with ECS.[14]

There is variability of engagement between genetic and fertility services throughout the UK. This creates inequity in regard to the level of information given, testing options and pre-test counselling to enable an informed choice. The European Society of Human Genetics recommends that the provision of genetic information and counselling as well as testing should be provided by appropriately trained professionals. However, what is appropriate genetic counselling and how much genomics knowledge would be needed to provide this are not defined. Furthermore, as genomic testing becomes more complex, more collaboration is needed between clinical genetics and fertility services to provide appropriate genetic counselling.

This highlights the importance of continuing professional education regarding genetics and carrier screening for those providing fertility care, as well as close working with clinical genetics colleagues.

As ECS panels increase in size, the more likely it is that donors will be identified as carriers. And as some countries exclude donors who are carriers, there will be fewer donors available, and this may lead to an increase in waiting time and cost of treatment.

6 | OPINION

- The use of ECS is growing in patients seeking fertility treatment both with own and donor gametes. An understanding of ECS is therefore important for all clinicians working within fertility and reproductive medicine.
- All humans carry several autosomal recessive conditions, however there is insufficient evidence to recommend testing all couples routinely prenatally, as the chance of an affected child is very low.
- Targeted carrier screening prior to conception is appropriate for prospective parents at high risk of carrying a gene known to cause severe disease either due to personal or family history, or population/ethnicity prevalence.
- There is a lack of standardisation among the ECS panels offered commercially, and understanding of the panel used is essential before interpretation of any results.
- Although choosing a larger panel may be beneficial as it would cover more genes, it is recommended that panels with the same gene coverage are used for both individuals, donors and couples to enable direct comparison.

- Interpretation of ECS results needs to be approached with caution and carried out by appropriately trained healthcare professionals with sufficient knowledge of clinical genetics.
- Further work is needed to determine the appropriate genes to be included in ECS panels considering population and ethnicity variations, and balancing benefit to patients and their future offspring with the risk of unnecessary screening, anxiety, and counselling.

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DISCLOSURE OF INTERESTS

Full disclosure of interests are available as supporting information.

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