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## Considerations of expanded carrier screening: Lessons learned from combined malonic and methylmalonic aciduria.

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## ORIGINAL ARTICLE

# Considerations of expanded carrier screening: Lessons learned from combined malonic and methylmalonic aciduria

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## Abstract

**Background:** Expanded carrier screening (ECS) utilizes high-throughput next-generation sequencing to evaluate an individual's carrier status for multiple conditions. Combined malonic and methylmalonic aciduria (CMAMMA) due to *ACSF3* deficiency is a rare inherited disease included in such screening panels. Some cases have been reported with metabolic symptoms in childhood yet other cases describe a benign clinical course, suggesting the clinical phenotype is not well defined.

**Methods/Case Report:** Clinical and laboratory findings during the prenatal period were obtained retrospectively from medical records.

**Results:** A 37-year-old nulliparous woman and her partner were each identified as carriers of *ACSF3* variants and presented at 9 weeks gestation for prenatal genetic consultation. The couple received extensive genetic counseling and proceeded with chorionic villus sampling at 11 weeks gestation. Subsequent analysis confirmed that the fetus inherited both parental *ACSF* variants. The couple was devastated by the results and after reviewing options of pregnancy continuation and termination, they decided to terminate the pregnancy. Following this decision, the patient was diagnosed with acute stress disorder.

**Conclusion:** This case highlights how expanded carrier screening adds complexity to reproductive decision-making. Stronger guidelines and additional research are needed to direct and evaluate the timing, composition, and implementation of ECS panels.

## KEYWORDS

*ACSF*, CMAMMA, expanded carrier screening, genetic counseling

## 1 | INTRODUCTION

Combined malonic and methylmalonic aciduria, or CMAMMA, is a rare disease for which the *ACSF3* gene (OMIM #614265) was recently identified by exome sequencing as the most common underlying genetic cause (Alfares et al., 2011; Sloan et al., 2011). The *ACSF3* gene encodes a mitochondrial malonyl- and methylmalonyl-CoA synthetase,

which acylates malonic and methylmalonic acid to their CoA derivatives for further use in mitochondrial metabolism (Bowman & Wolfgang, 2019). The clinical phenotype of this recently described condition is variable, and the natural history remains to be fully defined. Although some reports describe severe symptoms and signs, including metabolic acidosis, developmental delay, gastrointestinal disease, failure to thrive, seizures, cardiomyopathy, and dysmorphic facial

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features, others document a benign clinical course in affected adults and children (Alfares et al., 2011; Sloan et al., 2011). In this report, we describe a couple referred for reproductive genetic counseling, each identified as carriers of *ACSF3* variants through expanded carrier screening, and discuss how the genetic results affected their reproductive decision-making.

## 2 | CASE

A 37-year-old G2P0010 woman and her partner presented for reproductive genetic counseling at 9w2d gestation. Prior to the visit, the patient and her partner had pursued fertility treatment and had undergone expanded genetic carrier screening as part of their preconception evaluation, where they were identified as carriers of *ACSF3*. The patient was heterozygous for the pathogenic c.1672C>T (p.R558W) variant, while her partner was found to carry the likely pathogenic variant c.1608G>A (p.W536X). They were in the process of seeking preimplantation genetic testing for this condition when they spontaneously conceived the current pregnancy. They subsequently presented to reproductive genetic counseling to discuss options for prenatal genetic diagnosis. The couple was counseled on the broad spectrum of the phenotype and the possibility of the fetus being clinically unaffected despite inheriting both parental variants. The couple proceeded with chorionic villus sampling (CVS) that was performed at 11w5d gestation. Direct-targeted analysis of the parental variants confirmed that the fetus inherited both parental *ACSF3* variants. The couple was devastated by the results and after reviewing options of pregnancy continuation and termination, they decided to terminate the pregnancy. Following this decision, the patient was diagnosed with acute stress disorder.

## 3 | METHODS

### 3.1 | Ethical compliance

IRB approval from Thomas Jefferson University is not required for case report publications. Consent has been obtained from the patient.

### 3.2 | Genetic information

The GenBank version number for *ACSF3* has the NCBI Reference Sequence: NG\_031961.1. The c.1672C>T (p.R558W) variant discussed in this case has been reported in the Ensembl database as a mutation in exon 11 of the gene, transcript: ENST00000317447. The c.1608G>A (p.W536X) variant discussed in this case has been reported in the

Ensembl database as a mutation in exon 10 of the gene, transcript: ENST00000317447.

## 4 | DISCUSSION

Reproductive carrier screening is an important component of preconception and prenatal care, and seeks to identify couples at risk for conceiving a child with a particular genetic condition. Carrier screening began in the 1970s with the discovery of the biochemical cause of Tay-Sachs disease (Wapner & Biggio, 2019). Programs aimed at identifying carriers of this disease in the Jewish community helped to significantly decrease the incidence of this severe and devastating disorder, and in turn, became the model for community and ethnic-based screening programs. Expanded carrier screening (ECS) utilizes high-throughput next-generation sequencing to evaluate an individual's carrier status for multiple conditions. ACOG Committee Opinion #690 states that "expanded carrier screening is an acceptable screening strategy for preconception and prenatal carrier screening that must be tied to appropriate counseling in a shared decision-making process between physician and patient (ACOG, 2017)." Additional considerations for carrier screening include prevalence of the condition, carrier frequency of mutant alleles, detection rates, age of onset, condition severity and residual risk (Edwards et al., 2015). In 2009, the advent of next-generation sequencing enabled the identification of multiple disorders without regard for the considerations delineated in current screening guidelines, and has resulted in expanded carrier screening (Haque et al., 2016).

Although the goal of ECS is to inform reproductive decision-making, the rapid expansion of commercial laboratory genetic testing, fueled by corporate competition, has extended the scope of the panel to include disorders beyond those specified in recommended screening guidelines. At this time, there are currently no specific guidelines regarding which disorders should be included on ECS panels. Per the American College of Obstetricians and Gynecologists (ACOG), ECS should meet several of the following criteria: (a) a carrier frequency of 1 in 100 or greater; (b) a well-defined phenotype; (c) a detrimental effect on quality of life; (d) causes cognitive or physical impairment; (e) requires surgical or medical intervention; or (f) has onset early in life. The American College of Genetics and Genomics (ACMG) adopts a similar stance; however, ACMG's criteria provide more structured guidance. For example, ACMG agrees that a condition should have a well-defined phenotype. ACMG also asserts that in cases of variable expressivity, incomplete penetrance, and for disorders associated with a mild phenotype, inclusion of such disorders on screening panels should be optional and transparent to facilitate reproductive decision-making (Grody et al., 2013). The aforementioned criteria

from these two well-established professional organizations serve practitioners with guidelines to determine which conditions should be included on ECS; however, neither set of guidelines recommends specific disorders to be tested. The criteria are vague and leave room for interpretation, especially those set forth by ACOG. At this time, the content of ECS panels has been dictated by commercial laboratories, and there is significant variation in gene/disease content between panels. In a study comparing 16 ECS providers, the range of recessive disorders screened for was found to be 41 – 1792 and the number of genes ranged from 40 to 1556. More striking, is that of the genes screened for by these panels only three genes were screened by all 16 panels (Chokoshvili et al., 2018). Due to ambiguity in the guidelines set forth by ACOG and ACMG, commercial laboratories are able to offer larger multi-gene panels, often at the same price as a smaller panel of genes. Although patients may instinctively be drawn to larger expanded carrier screening panels, they are often unaware of the implications of positive results, and thus unable to contextualize the importance of genetic testing. Although ACOG and ACMG provide criteria that should be met for inclusion on an expanded carrier screening panel, we suggest forming a task force to create a list of recommended genes for an expanded carrier screening panel based on these criteria. A similar list was developed by ACMG for genes associated with adult-onset medically actionable conditions. This list of 59 genes provides guidance for reporting the appropriate secondary findings on whole genome or whole exome sequencing.

The couple we present faced a 25% risk of having a fetus with CMAMMA and utilized diagnostic testing to confirm the fetus inherited both pathogenic variants. Neither the parents nor their healthcare advocates were able to qualify how CMAMMA would manifest, given the variability in clinical phenotype. Thus, even though ECS informed this couple's reproductive decision-making, it led them to more questions and uncertainty. As a result, practitioners and patients are left to determine whether “bigger” is actually “better” when deciding which panel to select, especially since cost tends not to vary much with the size of the panel.

CMAMMA due to *ACSF3* deficiency is a condition that, despite having specific biochemical manifestations, lacks a well-defined clinical phenotype. In some reported cases of CMAMMA, the disease has a detrimental effect on the quality of life; however, in others, the disease presents with a clinically benign course. It may or may not cause cognitive or physical impairment, and it may or may not require medical intervention. Finally, the disease may present in children or adults. Thus, in some cases of CMAMMA, the disease meets the ACOG criteria for inclusion on an ECS panel and in other cases, it meets none (Sloane et al., 2011).

Approximately 4 hours over the course of three different Maternal-Fetal Medicine Genetics appointments were spent

counseling this couple. Although the couple understood that the fetus could be clinically asymptomatic despite inheriting two pathogenic variants, they ultimately decided to terminate the pregnancy. This decision later had a significant influence on the patient's emotional and psychological state, to the point where she was diagnosed with acute stress disorder. This case demonstrates the need to evaluate the impact of ECS on patients and healthcare organizations, while paying special attention to the components of carrier screening panels, the extra demands on genetic and reproductive counseling, the burden of cost, and the patient's emotional and psychological well-being (Wapner & Biggio, 2019).

Beyond consideration of how to implement the suggested criteria for inclusion of disorders on ECS panels and the counseling required by use of such panels, it is important to consider the impact of the information attained by ECS panels. Guo and Gregg (2019) used population data to estimate gene carrier rates of pathogenic and likely pathogenic variants associated with a severe recessive condition. They then simulated hypothetical ECS panels and discovered that although gene carrier rates are high for any panel of genes, the proportion of at-risk couples is comparatively much lower. They posit that when considering what to include on a screening panel, three main costs should be considered: (a) technical cost; (b) cost of interpretation and counseling; (c) and cost of anxiety to the patient. In 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, further research on the following areas is suggested for optimal implementation of expanded carrier screening: curated data repository of variants and phenotypes, education of healthcare providers and patients, educational resources for providers and patients, evaluation of patient and provider attitudes toward ECS, and cost of ECS (Grody et al., 2013). While the discussion regarding recommendations and considerations for ECS continues, more specific guidance on what to include on these panels is needed. The ambiguity allows companies offering ECS to disregard this discussion and compete in the marketplace using the number of genes on their panels as a selling point (Edwards et al., 2015). Clinicians lack the appropriate resources to counsel patients on the wide variety of disorders included in ECS and are often attempting to counsel patients after the results become available. Caution must be exercised as ECS continues to participate in preconception and prenatal decision-making, and more specific guidance is needed to evaluate the timing, composition, and implementation of ECS panels. Thorough pre-test counseling is strongly recommended prior to ordering expanded carrier screening for a patient. Patients should be informed that the clinical spectrum of some disorders on the test's panel is poorly understood; however, our knowledge of these conditions will

likely improve over time as expanded carrier screening becomes more commonplace and more data become available. In particular disorders where the phenotype is variable as in CMAMMA, we suggest natural history studies be performed to guide inclusion or exclusion on ECS. Expanded carrier screening empowers patients with knowledge of their carrier status; yet, it can also leave patients and healthcare providers struggling to apply and understand this knowledge and how it pertains to pregnancy.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

## AUTHOR CONTRIBUTIONS


H.K. and S.R. conceived of the presented idea. M.G., S.R., J.S., and H.K. wrote the manuscript in consultation with C.V. and M.M. All authors provided critical feedback and helped shape the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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