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A retrospective study assessing the performance of expanded carrier screening in consanguineous couples

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I. Introduction

Carrier screening is recommended in the reproductive setting to identify patients with increased reproductive risks for genetic disorders. Expanded carrier screening (ECS), defined as universally screening for more conditions than those currently recommended by screening guidelines, has allowed for the identification of individuals at increased risk for less common single gene disorders. Autosomal recessive conditions pose a significant risk to pregnancies of consanguineous couples and ECS may be particularly beneficial among this subset of patients. The American College of Obstetrics and Gynecology committee opinion #690 recommends consanguineous couples undergo genetic counseling to discuss increased risk for recessive conditions. However, this guideline does not specify which type of carrier screening is most appropriate in this patient population. The purpose of this study was to evaluate the performance of ECS among consanguineous couples in identifying at-risk pregnancies.

II. Methods

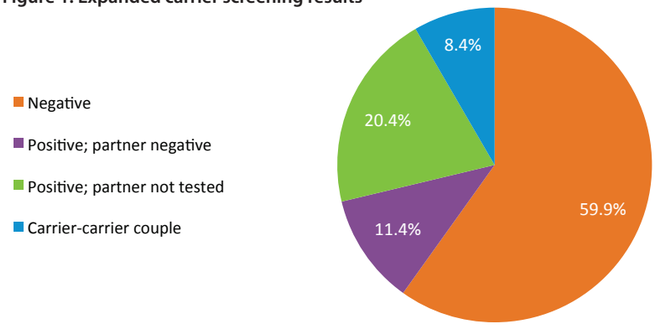
A review was undertaken of patients seen for genetic counseling from January, 2017 – August, 2020 to identify patients who reported consanguinity. All patients who reported some degree of consanguinity were offered ECS and the testing decisions at the time of genetic counseling were documented and evaluated. The ECS panels, including the genes and conditions screened for, were chosen by the ordering physician and varied among our patient cohort. Patients who had panels based on ethnicity or only included conditions currently recommended by screening guidelines were excluded. Medical records were examined for patients who indicated that they were interested in ECS. Results of ECS were obtained either by laboratory reports or genetic counseling reports/clinic notes. When a patient was identified as a carrier, a search was performed to obtain testing decisions or available results for the reproductive partner.

III. Results

A total of 1,003 patients reported consanguinity during this study time period and 612 patients indicated a desire to pursue ECS at the time of genetic counseling. Information regarding the results of ECS was available for 334 (54.6%) of these patients, 200 (59.9%) of which had negative ECS results. 134 patients had positive ECS results, 66 of whom pursued follow-up testing for their reproductive partner with 38 partners having negative carrier testing.

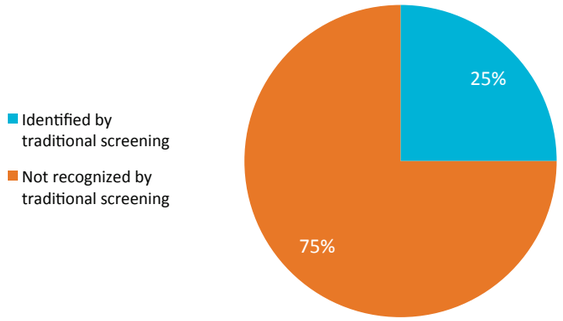
Overall, 28 (8.4%) of the 334 patients with available ECS results were identified as carriers of an autosomal recessive condition for which their current reproductive partner was also found to a carrier, herein referred to as carrier-carrier couples (**Figure 1**).

Figure 1. Expanded carrier screening results



An evaluation of the single gene disorders identified in the carrier-carrier couples revealed that 7 (25.0%) of the 28 carrier-carrier couples would have been identified by traditional carrier screening protocols driven by ethnicity-based screening for hemoglobinopathies, Ashkenazi Jewish conditions or routine population screening for cystic fibrosis and spinal muscular atrophy. In contrast, 21 (75.0%) of the 28 carrier-carrier couples were both carriers for conditions that would not have been recognized by traditional carrier screening (**Figure 2**).

Figure 2. Comparison of findings by traditional carrier screening vs expanded screening



Among the carrier-carrier couples, 2 couples were at 25% risk for 2 conditions and 1 couple was at 25% risk for 3 conditions. An additional 68 (20.4%) of the 334 patients had positive results on their ECS but the carrier status of their reproductive partner was unknown. Among these 68 patients, 55 (80.9%) patients were identified by ECS to carry a condition that would not be detected by traditional screening protocols.

Conditions Identified in Carrier-Carrier Couples	
Condition	**Frequency identified in carrier-carrier couples**
Alpha thalassemia	1±
Beta hemoglobinopathies	5
Cystic fibrosis	1
Spinal muscular atrophy	1
3-Methylcrotonyl-CoA carboxylase 1 deficiency	1*
Adenosine deaminase deficiency	1
Aromatic l-amino acid decarboxylase deficiency	1
Biotinidase deficiency	1
Combined oxidative phosphorylation deficiency 3	1
Congenital adrenal hyperplasia	1±
Deafness and hearing loss, GJB2 related	2
Deafness, autosomal recessive 77	1*
Familial Mediterranean fever	1
Galactosemia	2
Lamellar ichthyosis	1
Mucopolysaccharidosis, type IIIA	1
Nijmegen breakage syndrome	1
Phenylalanine hydroxylase deficiency	3**
Pompe disease	2
Primary ciliary dyskinesia	1
Propionic acidemia	1**
Retinitis pigmentosa	1±
Usher syndrome, type 2C	1

± carrier-carrier couple identified as at risk for 3 conditions
* carrier-carrier couple a identified as at risk for 2 conditions
** carrier-carrier couple b identified as at risk for 2 conditions

IV. Conclusions

Expanded carrier screening enhances the reproductive risk assessment for consanguineous couples by providing an opportunity to identify risks for single gene disorders that may not be identified using traditional carrier screening protocols. Carrier-carrier couples may benefit from prenatal or postnatal diagnostic testing as well as the opportunity to pursue preimplantation genetic testing if risk is identified prior to conception. One limitation of this study is that different ECS panels were utilized based on the ordering physician's preference. Future studies comparing the performance of different ECS panels may guide the development of the most-effective ECS panel for this patient population. Traditional carrier screening protocols would have failed to identify the majority of the carrier-carrier couples identified by ECS in this study. Therefore, this study provides evidence that ECS is the most appropriate method of screening for consanguineous couples seeking reproductive risk information and should be considered to guide future development of recommendations related to this patient population.

V. References

Carrier screening in the age of genomic medicine. Committee Opinion No. 690. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017; 129:e35-40.

Carrier screening for genetic conditions. Committee Opinion No. 691. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017; 129:e41-55.

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