Clinical utility of expanded carrier screening: reproductive behaviors of at-risk couples

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Introduction

Expanded carrier screening (ECS) analyzes dozens or hundreds of recessive disease genes for couples planning to have children. The literature on the clinical utility of ECS is scarce. We surveyed at-risk carrier couples, identified through ECS, to learn about their reproductive decisions.

Methods

Patients underwent ECS via Counsyl laboratory for up to 110 genes. At-risk carrier couples (ARCC) were those in which both partners were carriers for the same autosomal recessive diseases. We invited 537 ARCC who received their results between April 2014 and August 2015 to participate via email, SMS message, and paper survey in an Institutional Review Board-approved study questionnaire.

207,095 patients tested between 4/2014 and 8/2015 through Counsyl

103,550 patients (51,775 couples) informed us they were couples and received merged reports

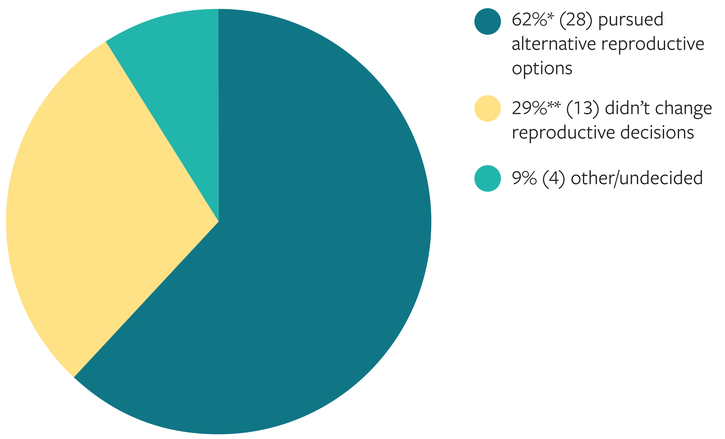
537 eligible couples identified—ARCC for profound, severe, or moderate diseases[1], without family history; Consented to be contacted for future research; Provided email address, phone number, and/or mailing address

Results

Of 537 eligible participants, 64 eligible ARCC completed the survey. 45 (70%) were not pregnant at time of screening.

Figure 1

Actions in the preconception context for 45 participants

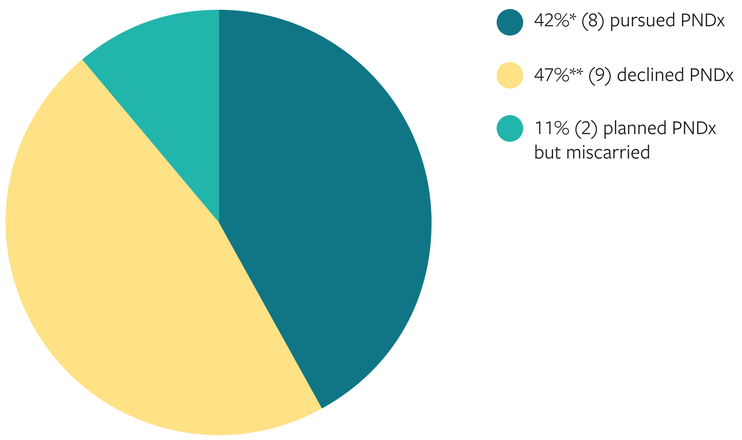


* Includes In Vitro Fertilization (IVF) with preimplantation diagnosis (PGD), prenatal diagnosis (PNDx) in future pregnancies, gamete donation, adoption, or no reproduction.

** Indicated perceived disease severity as a major reason.

Figure 2

Actions in the prenatal context for 19 participants

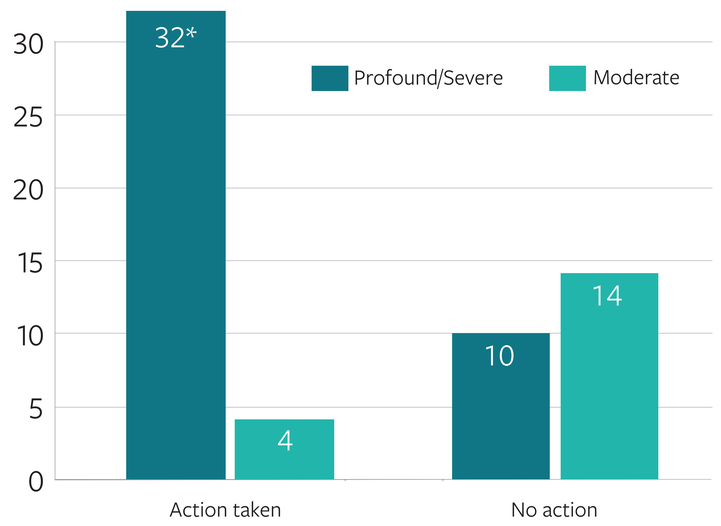


* 5 were unaffected and 3 were affected. 2 of the affected pregnancies were terminated and 1 was continued.

** Did not consider the condition sufficiently severe to pursue PNDx.

Figure 3

Disease severity and action taken/planned based on ECS results



Fisher's exact test revealed the association between the severity[1] of the disease (Profound/Severe vs Moderate) with changes in decision making was significant (p=0.000145), whereas the guideline status of diseases, controlled for severity[1] (Profound/Severe), was not (p=0.284). Diseases with universal or ethnicity based screening guidelines were Cystic fibrosis[2], Spinal muscular atrophy[3], and Hb Beta Chain-Related Hemoglobinopathy[4].

Table 1

Diseases and corresponding reproductive decisions in the preconception and prenatal contexts (N=64)

Disease	Severity[1]	Fraction of preconception planning or taking action	Fraction of prenatal taking action
Smith-Lemli-Opitz Syndrome (n=3)	Profound	2/2 (1 IVF+PGD)	1/1 (1 PNDx)
Carnitine Palmitoyltransferase II Deficiency (n=3)	Profound	1/2 (1 IVF+PGD, 1 Unclear)	1/1 (1 PNDx)
Gaucher Disease (n=1)	Profound		0/1 (1 Miscarriage)
Hereditary Fructose Intolerance (n=1)	Profound		0/1
Krabbe Disease (n=1)	Profound	1/1 (1 IVF+PGD)	
Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD) (n=1)	Profound	1/1 (1 IVF+PGD)	
Phenylalanine Hydroxylase Deficiency, including PKU (n=1)	Profound	1/1 1 (IVF+PGD)	
Cystic Fibrosis (n=15)	Severe	9/9 (7 IVF+PGD, 2 PNDx)	4/6 (4 PNDx, 1 Miscarriage)
Biotinidase Deficiency (n=9)	Severe	1/6 (1 IVF+PGD, 2 Unclear)	1/3 (1 PNDx)
Familial Mediterranean Fever (n=4)	Severe	2/2 (1 IVF+PGD, 1 PNDx)	1/2 (1 PNDx)
Hb Beta Chain-Related Hemoglobinopathy, including Beta Thalassemia and Sickle Cell Disease (n=3)	Severe	3/3 (2 IVF+PGD, 1 PNDx)	
Short Chain Acyl-CoA Dehydrogenase Deficiency (n=1)	Severe	1/1 (PNDx)	
Spinal Muscular Atrophy (n=1)	Severe	1/1 (1 IVF+PGD)	
Wilson Disease (n=1)	Severe	1/1 (1 IVF+PGD)	
Achromatopsia (n=1)	Moderate	0/1	
Alpha-1 Antitrypsin Deficiency (n=8)	Moderate	1/5 (1 IVF+PGD, 1 Unclear)	0/3
GJB2-related DFNB1 Nonsyndromic Hearing Loss and Deafness (n=9)	Moderate	2/8 (2 IVF+PGD)	0/1
Glycogen Storage Disease Type V (n=1)	Moderate	1/1 (1 PNDx)	

Conclusion

Most ARCC altered reproductive planning, demonstrating clinical utility of this information. Perceived severity of the condition factored into decision making with diseases classified as moderate[1] less likely to change planning.

REFERENCES: 1. Lazarin, G. A., Hawthorne, F., Collins, N. S., Platt, E. A., Evans, E. A., & Haque, I. S. (2014). Systematic Classification of Disease Severity for Evaluation of Expanded Carrier Screening Panels. *PloS One, 9*(12), e114391. **2.** American College of Obstetricians and Gynecologists Committee on Genetics. (2011). ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. *Obstetrics and Gynecology, 117*(4), 1028–1031. **3.** Prior, T. W., Nagan, N., Sugarman, E. A., Batish, S. D., & Braastad, C. (2011). Technical standards and guidelines for spinal muscular atrophy testing. *Genetics in Medicine: Official Journal of the American College of Medical Genetics, 13*(7), 686–694. **4.** ACOG Committee on Obstetrics. (2007). ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. *Obstetrics and Gynecology, 109*(1), 229–237.

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