Clinical Utility of Expanded Carrier Screening: Results-Guided Actionability and Outcomes

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Conflict of Interest Declaration

Abstract

Purpose: Expanded carrier screening (ECS) informs couples of their risk of having offspring affected by certain genetic conditions. Limited data exists assessing the actions and reproductive outcomes of at-risk couples (ARCs). We describe the impact of ECS on planned and actual pregnancy management in the largest sample of ARCs studied to date.

Methods: Couples who elected ECS and were found to be at high risk of having a pregnancy affected by at least one of 176 genetic conditions were invited to complete a survey about their actions and pregnancy management.

Results: Three hundred ninety-one ARCs completed the survey. Among those screened before becoming pregnant, 77% planned or pursued actions to avoid having affected offspring. Among those screened during pregnancy, 37% elected prenatal diagnostic testing (PNDx) for that pregnancy. In subsequent pregnancies that occurred in both the preconception and prenatal screening groups, PNDx was pursued in 29%. The decision to decline PNDx was most frequently based on the fear of procedure-related miscarriage, as well as the belief that termination would not be pursued in the event of a positive diagnosis.

Conclusions: ECS results impacted couples' reproductive decision-making and led to altered pregnancy management that effectively eliminates the risk of having affected offspring.

Key Words: expanded carrier screening; prenatal diagnosis; pregnancy management; clinical utility; at-risk couple

Introduction

Serious recessive and X-linked conditions affect an estimated 1 in 300 pregnancies.[1] However, universal

screening for only the two conditions recommended by current guidelines, cystic fibrosis (CF) and spinal

muscular atrophy,[2-4] misses nearly 70% of carriers of rare disease[5] and fails to detect between 13% and

94% of pregnancies affected with profound and severe conditions, depending on ethnicity.[6,7] Expanded

carrier screening (ECS), i.e., testing reproductive partners' carrier status for a large number of recessive

and X-linked conditions without regard to ethnicity, addresses this gap. When ECS is undertaken during

the preconception period, results enable interventions to avoid affected pregnancies, such as in vitro

fertilization (IVF) with preimplantation genetic testing for monogenic conditions (PGT-M); and when

undertaken during the prenatal period, results facilitate prenatal diagnostic testing (PNDx;

amniocentesis or chorionic villus sampling, CVS) and pregnancy management (including termination).

The American College of Obstetricians and Gynecologists (ACOG) recognizes ECS as an acceptable

strategy for carrier screening,[8] and together with American College of Medical Genetics and Genomics,

the Society for Maternal-Fetal Medicine, the National Society of Genetic Counselors, and the Perinatal

Quality Foundation, acknowledges the unique benefits and considerations of ECS.[9]

For certain conditions, population-wide carrier screening has well-established clinical utility, i.e., the

improvement in health outcomes as a result of preconception screening, prenatal diagnosis, and early

identification of affected pregnancies that enables condition-specific counseling and management.[9]

Between 1970 and 2000, screening for Tay-Sachs disease carrier status reduced the incidence of Tay-

Sachs disease in the U.S. and Canadian Ashkenazi Jewish population by 90%.[10,11] Similarly, the

prevalences of CF- and thalassemia-affected births were reduced in other countries and in parts of the

U.S. following the institution of carrier screening programs.[12-15]

Although ECS has been in existence for nearly a decade, evidence of its clinical utility has only recently emerged. In a study of 64 at-risk couples (ARCs; defined as a reproductive couple in which both individuals carry pathogenic variants in the same gene, or a female carries an X-linked pathogenic variant) identified through ECS, 76% of those at-risk for severe or profound conditions took or planned to take action to reduce the risk of an affected birth, including IVF with PGT-M and PNDx.[16] In a separate study conducted among couples undergoing IVF, all ARCs in the sample (8/8) underwent or planned to undergo PGT-M to avert an affected birth.[17] Though conducted on cohorts with relatively few ARCs, these studies suggest that ECS enables reproductive decision-making that reduces the risk of having affected offspring, potentially leading to reduced incidence for a broad range of screened conditions and in diverse populations.

To characterize in more detail the clinical utility of ECS, we studied the actions taken by nearly 400 ARCs after receiving ECS results for up to 176 conditions. Results demonstrate that more than three-quarters of ARCs screened preconceptionally planned or pursued actions that reduced the risk of having affected offspring, and more than one-third of ARCs screened prenatally underwent PNDx to inform pregnancy management, providing further evidence that ECS guides reproductive decision-making and impacts pregnancy outcomes.

Materials and Methods

Cohort Generation

To generate a survey cohort, data for more than 270,000 individuals who had received ECS from Counsyl (Family Prep Screen or Foresight™ Carrier Screen) between September 1, 2015, and December 31, 2017 were queried for females who: 1. were found to be carriers of a pathogenic or likely pathogenic variant

conferring risk for at least one of 176 autosomal recessive or X-linked conditions currently included in Counsyl's Foresight ECS;[1] 2. were aged 18 years or older; 3. had consented to being contacted about participating in research at Counsyl; and 4. for those carrying pathogenic or likely pathogenic variants associated with autosomal recessive conditions, had reproductive partners meeting the same eligibility criteria and who were confirmed by Counsyl as being carriers of a pathogenic variant in the same gene. Couples carrying only variants known to cause mild presentations of biotinidase deficiency (D444H), NPHS2-related nephrotic syndrome (R229Q), and 21-OH deficient congenital adrenal hyperplasia (CAH) (CYP21A2 gene duplication) were excluded.

The resulting cohort was validated via software to ensure that an email address was on file for the female member of each ARC, and that the email address did not appear twice in the cohort as that could indicate a female having more than one male reproductive partner and thus constituting more than one ARC. Further, inclusion criteria for 40 randomly selected individuals in the cohort were verified by Counsyl staff not involved in the study as a quality-control check of the software-directed validation. After final validation, the cohort invited to participate comprised 1,701 ARCs whose current or future pregnancies were at risk for 78 conditions in aggregate.

Survey Development

Survey questions were developed by reviewing and expanding on a previously published survey of ARCs.[16] Questions were also reviewed by two pediatric geneticists not affiliated with Counsyl to ensure the accuracy of clinical content. Questions were divided into five sections, as indicated in Figure 1, and are available in Supplementary Figure 1.

Survey questions were programmed into commercial software (Logician®, Decision Analyst Inc., Arlington, TX) to eliminate logic errors, prevent omissions, define acceptable and unacceptable answer codes, and build in skip patterns; and to provide the web-based platform for response collection. Questions were pre-tested with four ARCs to determine understandability, appropriate wording, completion of questions as intended, and approximate time to complete the survey. Individual ARCs were observed as they navigated through the online survey, and revisions were made based on their feedback.

Survey Fielding

The survey was fielded by Decision Analyst, Inc. between the dates of February 28, 2018, and March 19, 2018. Female members of 1,701 ARCs were invited by email to participate. After invitations were sent, 42 emails were undeliverable, likely due to incorrect email addresses on file or email accounts that were no longer in use. This effectively reduced the cohort to 1,659 ARCs. To complete the survey, respondents were directed to a Decision Analyst, Inc.-hosted online survey site, which included an explanation of the research project and asked for consent to participate. A total of four reminders were sent to non-responders over the course of the 19-day survey period. Those who completed the survey after the initial invitation or first reminder were eligible to receive a $30 incentive or to donate $30 to charity. This incentive was increased to $55 with the second, third, and fourth reminders.

Data Analysis

Data management and tabulation were accomplished via UNCLE® (Hermosa Beach, CA), and analysis performed by SPSS (IBM, Armonk, NY). Descriptive statistics were used to characterize general data trends. Statistical significance between proportions was determined using chi-square analysis; a result was considered significant when $p < 0.05$ at the 95% confidence level. Confidence intervals were

determined using the Jeffreys method.[18] To compare actions among ARCs by disease severity, conditions were categorized by severity according to the method described by Lazarin et al.[7] For ARCs reporting that their pregnancies were at risk for more than one condition, the category corresponding to the more severe condition was used. Couples indicating that their pregnancies were at risk for CAH were placed into the moderate risk category since no distinction was made between classic and non-classic CAH.

Institutional Review Board Approval

This study was reviewed and designated as exempt on January 29, 2018 by Western Institutional Review Board (WIRB Work Order # 1-1058643-1).

Results

Cohort Characteristics

Three hundred ninety-one respondents completed the survey for an overall response rate of 24%. Ninety-five percent of respondents were between the ages of 25 and 44 years, and 39% were pregnant when they received their ECS results, with the remainder not pregnant (60%) or preferring not to indicate pregnancy status (0.5%) (Table 1). Among those who were not pregnant, 54% were undergoing or planning to undergo IVF at the time they received their ECS results. Respondents were geographically dispersed, and along with their reproductive partners, represented more than 15 ethnicities and more than 9 religions (Table 1). ARCs reported being at risk for pregnancies affected by 53 different conditions, with profound, severe, and moderate conditions represented (Supplementary Table 1). Ten percent and 1.8% of respondents reported being at risk for pregnancies affected by two or three conditions, respectively (Supplementary Table 1).

Actions Taken or Planned as a Result of Preconception Screening

Of respondents screened preconceptionally (Fig. 1, blue), 77% reported planning or pursuing actions

that impact pregnancy management and/or reduce the risk of an affected pregnancy (Table 2). These

included IVF with PGT-M (59%); PNDx (by amniocentesis or CVS) (20%); use of a donor gamete (7.7%);

adoption (5.1%); and no longer planning to get pregnant (3.8%). Preconception respondents planned or

pursued other actions that do not directly affect pregnancy management: once pregnant, inform other

doctors of the risk for the condition (29%, n=69); and test children or other family members for the

condition (15%, n=36) (not shown). Only 4.6% of respondents (n=11) did not plan or pursue any action

(not shown).

When stratified by condition severity,[7] the proportion of respondents planning or pursuing actions was

highest among those whose future pregnancies were at risk for a profound condition (91%), followed by

a severe condition (77%), and a moderate condition (62%) (Table 2). However, only the difference

between the profound and moderate groups was statistically significant at the 95% confidence level

(p=0.004). This pattern was present for each of the actions except for no longer planning a pregnancy

(Table 2), but no other differences were found to be statistically significant.

Diagnostic Testing After Prenatal Screening

Of respondents screened prenatally (Fig. 1, pink), 37% reported having undergone PNDx (by

amniocentesis or CVS) (Table 3). When stratified by condition severity, the proportion of respondents

having undergone PNDx was highest for pregnancies at risk for profound conditions (47%), followed by

severe (n=38%) and moderate (29%), but differences were not statistically significant (Table 3). Of

pregnancies that underwent PNDx, 36% were found to be affected; 40% of affected pregnancies were

terminated (Table 3). Conditions for which pregnancies were found to be affected are listed in

Supplementary Table 2.

Respondents screened prenatally who did not undergo PNDx and whose pregnancies resulted in a live birth were asked if they had pursued diagnostic testing after the baby's birth or planned to do so in the near future; 62% answered in the affirmative (Table 3). When stratified by severity, the inverse pattern of that seen for PNDx was observed, i.e., the proportion of respondents who pursued or planned postnatal diagnosis was smallest for pregnancies at risk for profound conditions (14%), followed by severe (62%) and moderate (93%) (Table 3). These differences were statistically significant at the 95% confidence level (profound vs. severe: p=0.02, severe vs. moderate: p=0.03, profound vs. moderate: p=0.0003).

Respondents screened prenatally who did not undergo PNDx were asked the reason(s) that they chose not to undergo such testing. Top reasons cited were: to avoid the increased risk of miscarriage associated with amniocentesis and CVS (35%), that results would not have led to pregnancy termination (27%), and a perception that the risk of an affected pregnancy was low (26%) (Supplementary Table 3).

Actions Taken in Subsequent Pregnancies

ARCs screened both before and during pregnancy were asked to report actions undertaken for pregnancies conceived subsequent to receiving ECS results. These are pregnancies conceived after those screened preconceptionally received their results, and pregnancies conceived after the one during which those screened prenatally received their results (Fig. 1, yellow). One hundred twenty-six and 40 subsequent pregnancies were reported by ARCs screened preconceptionally and prenatally, respectively (Table 4). Among all subsequent pregnancies, 35% were achieved by IVF with PGT-M. ARCs screened before becoming pregnant were significantly more likely to achieve subsequent pregnancies by

undergoing IVF with PGT-M (40%) than were those screened during a previous pregnancy (20%) (p=0.02) (Table 4).

Nearly one-third (29%) of subsequent pregnancies underwent PNDx; no significant difference in this proportion was found among those screened before becoming pregnant (29%) versus those screened during a previous pregnancy (28%) (Table 4). The proportion that underwent PNDx in a subsequent pregnancy also was not significantly different than the proportion that underwent PNDx in the pregnancy during which ECS results were received (37%; Table 3). Among subsequent pregnancies that underwent PNDx, 29% were found to be affected; 75% of affected pregnancies were terminated (Table 4). Conditions for which pregnancies were found to be affected are listed in Supplementary Table 2. Taken together with pregnancies during which results were received, the termination rate for affected pregnancies was 53% (Supplementary Table 2).

ARCs who reported subsequent pregnancies and did not undergo PNDx were asked the reason(s) that they chose not to undergo such testing. Top reasons cited were: it was not necessary because the pregnancy was achieved by IVF with PGT-M (28%), a perception that the risk of an affected pregnancy was low (17%), to avoid the increased risk of miscarriage associated with amniocentesis and CVS (14%), the pregnancy miscarried before testing could be performed (14%), and that results would not have led to pregnancy termination (10%) (Supplementary Table 3). Compared to reasons cited by those who were pregnant when they received their screening results, significantly fewer cited the risk of miscarriage (p=0.0005) and an unwillingness to terminate the pregnancy (p=0.001) as reasons for not undergoing PNDx during a subsequent pregnancy (Supplementary Table 3). Of respondents who did not undergo PNDx and whose subsequent pregnancies resulted in a live birth, 45% planned or pursued diagnostic testing after the baby's birth (Table 4).

Discussion

Our study describes the clinical utility of ECS among the largest cohort of ARCs studied to date. It examined actions of a geographically, ethnically, and religiously diverse cohort of couples screened for up to 176 conditions both in the preconception and prenatal stages. Because Mendelian diseases are rare, past studies of ARC behavior have examined small cohorts. For example, in a study of more than 3,700 couples receiving ECS in a fertility clinic, only 8 ARCs were identified;[17] and in a sample of over 100,000 couples who received ECS, 537 ARCs were identified, only 64 of which participated in the outcomes portion of the study.[16] Our study of 391 ARCs—gathered from more than 270,000 total individuals who had undergone ECS—therefore makes a substantial contribution to the evidence base supporting ECS as an impactful tool for reproductive decision-making.

Widespread clinical adoption and insurance coverage of health care interventions often rely on demonstrations of clinical utility.[19] In the context of genetic testing, clinical utility is defined based on the value of the test result: information that leads to an improved health outcome, including diagnosis, treatment, management, or disease prevention, that will benefit a patient or his/her family members.[20] Our study demonstrates the clinical utility of ECS: more than three-quarters of ARCs tested preconceptionally planned or took action to avert an affected pregnancy (IVF with PGT-M, use of donor gametes, adoption, or avoidance of pregnancy) (Table 2), and more than one-third tested prenatally took action to establish a prenatal diagnosis (Table 3). ARCs in our study terminated more than half of affected pregnancies, demonstrating the substantial impact of ECS results on pregnancy management. More than one-third of the pregnancies conceived subsequent to receiving ECS results were achieved using IVF with PGT-M (Table 4), effectively preventing an affected pregnancy and demonstrating the utility of knowing carrier status before becoming pregnant.

The proportion of ARCs identified while pregnant and electing PNDx in this study (37%, Table 3) is consistent with that found in a previous ECS outcomes study (42%).[16] It is also consistent with observations for other widely-adopted screening tests: 39% of those with a trisomy 21 positive non-invasive prenatal screen and 45% of those with a trisomy 21 positive maternal serum screen elect to undergo invasive diagnostic testing.[21,22] Among pregnant women who decline amniocentesis or CVS following a trisomy 21 positive maternal serum screen, the risk of procedure related miscarriage is the most commonly cited reason.[21] We found the same: among ARCs receiving ECS results when they were pregnant, the most frequently cited reason for not pursuing PNDx was the risk of miscarriage (Supplementary Table 3). ARCs in our study also reported that they did not undergo PNDx because they would not have pursued pregnancy termination in the event of a positive result. As actionability of a positive result extends beyond pregnancy termination to include altered or enhanced pregnancy management, rapid diagnosis of a neonate suspected to be affected, and immediate intervention or treatment after birth, this result suggests that patients could benefit from education and/or genetic counseling that explains the range of benefits of establishing a diagnosis prenatally.

In pregnancies conceived subsequent to the receipt of ECS results (Fig. 1, yellow), the top reasons cited for not pursuing PNDx were different than those cited for pregnancies during which ECS results were received. ARCs most frequently believed PNDx was not necessary because the pregnancy had been achieved by IVF with PGT-M, reflecting the large number of ARCs in this group who had undergone IVF with PGT-M (Supplementary Table 3). They also believed that PNDx was not necessary because they perceived their pregnancy to be at low risk of being affected (Supplementary Table 3). Those undergoing assisted reproductive technologies are less likely to elect amniocentesis or CVS than those whose

pregnancies are spontaneous[23,24] despite guidelines recommending that couples undergoing PGT-M be counseled that confirmatory PNDx is necessary due to the technical challenges of PGT.[25]

In addition to enabling PNDx, ECS results enable targeted postnatal diagnostic testing for conditions that may otherwise be difficult to recognize and that could lead to a years-long diagnostic odyssey that includes suboptimal or ineffective treatment.[26] In our study, a large proportion of ARCs who declined PNDx planned or had already pursued postnatal diagnostic testing (62% of those pregnant when they received results and 45% who received results prior to subsequent pregnancies) (Tables 3 and 4), suggesting that a diagnosis was established that enabled treatment or other care, or that the condition for which the pregnancy had been at risk was ruled out. Knowing that postnatal diagnostic testing is an option may diminish the imperative to undergo PNDx. Some patients may mistakenly consider newborn screening (NBS), conducted in the first few days after birth, to be sufficient to detect serious genetic disease. However, as ACOG has acknowledged, NBS does not diminish the potential benefits of carrier screening.[8]

Our data suggest that, whether undergoing ECS preconceptionally or prenatally, the severity of the condition affected ARCs' decisions to plan or pursue actions. This is consistent with conclusions made previously,[16] as well as the finding that categorizing conditions by severity is valuable to prospective parents as they consider the actions they might undertake after receiving ECS results.[27] Importantly, ECS for select moderate severity conditions had demonstrable clinical utility: nearly two-thirds of ARCs at risk for future pregnancies with moderate severity conditions reported planning or pursuing actions (Table 2), and nearly one-third of ARCs whose pregnancy was at risk for a moderate condition elected PNDx (Table 3).

Our study had limitations that should be noted. It relied on patients to recall their actions stemming from ECS results. Patient memory is sometimes inaccurate; for example, the proportion of ARCs reporting being at risk for two or three conditions (10% and 8%, respectively) is higher than would have been expected based on the estimated number of such ARCs in the general population. We also cannot rule out response bias; those who took action based on ECS results may have been more willing than those who did not to report on such actions. Conversely, some invited ARCs may have declined to participate altogether given the sensitive nature of pregnancy management. Among our cohort screened preconceptionally, 54% were undergoing or planning to undergo IVF at the time that they received ECS results, suggesting that the cohort over-represented couples who seek fertility assistance. The cohort was also enriched with ARCs whose current or future pregnancies were at risk for conditions that are more frequent in the population, including fragile X syndrome, cystic fibrosis, and GJB2-related DFNB1 nonsyndromic hearing loss and deafness. We sought to diminish any outsized effects these conditions may have had by analyzing actions in aggregate and by condition severity.

The data here demonstrate that ECS prompts changes in pregnancy management resulting in fewer births affected with serious genetic diseases. The frequency of these changes is consistent across carrier screening studies and with data for aneuploidy screening, for which clinical utility is generally accepted. This trend suggests clinical value in screening for diseases that have historically gone undetected.

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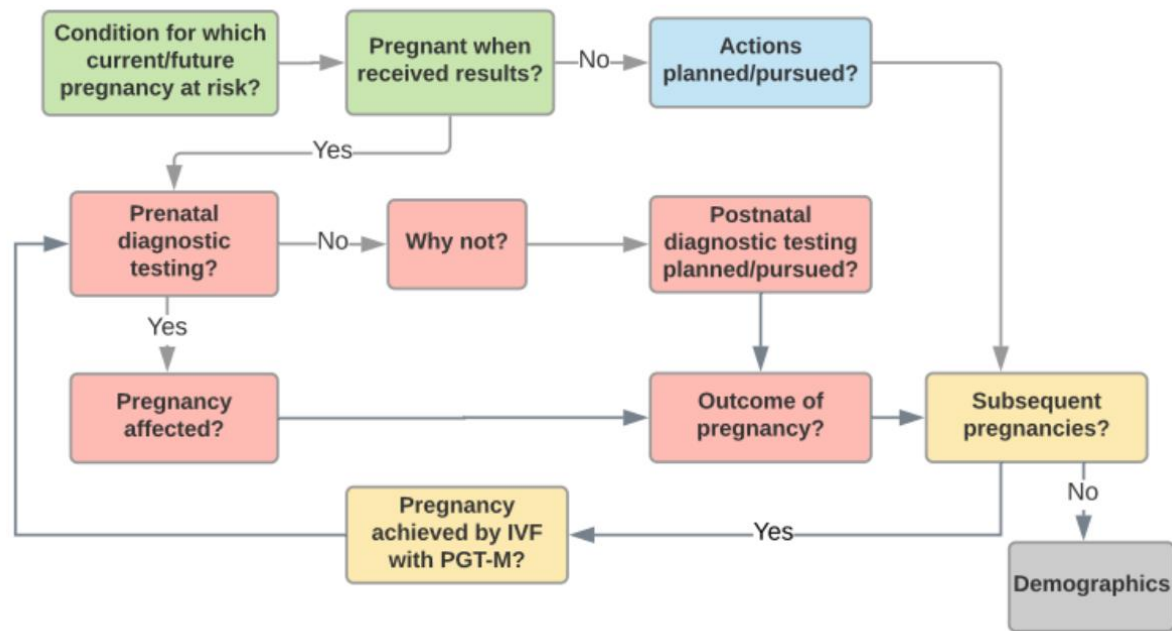
Figure 1. Survey flow. Survey questions were divided into five sections, denoted by color: foundational

information such as condition(s) for which respondents were found to be carriers and pregnancy status

at the time of receiving results (green); actions planned or pursued by those receiving ECS results before

pregnancy (blue); actions pursued by those receiving ECS results during pregnancy (pink); actions

pursued in subsequent pregnancies (yellow); and demographic information (gray).

Table 1. Respondent demographics.

Characteristics	Total Respondents, n (%)	
Total Respondents	391 (100)	
Age of female partner[a]		
18-24	14 (3.6)	
25-34	211 (54)	
35-44	160 (41)	
45+	6 (1.5)	
Pregnant when received results[a]		
Yes	154 (39)	
0-13 weeks pregnant	72 (47)	
14-26 weeks pregnant	74 (48)	
27 or more weeks pregnant	5 (3.2)	
Did not answer/Did not recall	3 (1.9)	
No	235 (60)	
Planning or undergoing IVF when received results[b]	122 (54)	
Prefer not to say	2 (0.5)	
Geographic region[a]		
Northeast	85 (22)	
Midwest	50 (13)	
South	125 (32)	
West	128 (33)	
Outside U.S.	3 (0.8)	
Ethnicity[c]	Female Partner	Male Partner
Northern European	119 (30)	113 (29)
Other/Mixed Caucasian	114 (29)	107 (27)
Ashkenazi Jewish	75 (19)	70 (18)
Southern European	34 (8.7)	38 (9.7)
East Asian	34 (8.7)	24 (6.1)
Hispanic	19 (4.9)	28 (7.4)
South Asian	16 (4.1)	17 (4.3)
African or African American	14 (3.6)	17 (4.3)
Southeast Asian	11 (2.8)	9 (2.3)
Middle Eastern	9 (2.3)	10 (2.6)
French Canadian or Cajun	9 (2.3)	7 (1.8)
Native American	3 (0.8)	5 (1.3)
Pacific Islander	0 (0)	2 (0.5)
Other	3 (0.8)	1 (0.3)
Unknown	2 (0.3)	3 (0.8)
Prefer not to say	11 (2.8)	13 (3.3)
Religion[a]	Female Partner	Male Partner
No religious affiliation	89 (23)	101 (26)
Jewish	70 (18)	62 (16)
Protestant	67 (17)	55 (14)
Catholic	65 (17)	67 (17)
Agnostic	26 (6.6)	66 (17)
Atheist	11 (2.8)	23 (5.9)
Hindu	7 (1.8)	6 (1.5)
Buddhist	6 (1.5)	3 (0.8)
Muslim	5 (1.3)	7 (1.8)
Mormon	3 (0.8)	5 (1.3)
Other	17 (4.3)	15 (3.8)
Prefer not to say	25 (6.4)	25 (6.4)

IVF: In vitro fertilization.

a.   Percents sum to just under or over 100% due to rounding.

b.   8 ARCs did not answer whether they were undergoing IVF at the time of ECS; percent is therefore calculated out of 227.

c.   Percents sum to greater than 100% because respondents could pick more than one answer.

Table 2. Actions planned or pursued by ARCs screened during the preconception period.

	All Severities, n (%; CI)	Profound, n (%; CI)	Severe, n (%; CI)	Moderate, n (%; CI)	Severity Unassigned,[a] n (%; CI)
Screened Preconceptionally	235 (100)	34 (14)	153 (65)	34 (14)	14 (5.9)
Planned/pursued any of the following actions:[b]	180 (77; 71-82)	31 (91; 78-97) [c]	118 (77; 70-83)	21 (62; 45-77) [c]	9 (64; 38-85)
IVF with PGT-M	139 (59; 53-65)	23 (68; 51-81)	92 (60; 52-68)	20 (59; 42-74)	4 (29; 11-55)
PNDx	48 (20; 16-26)	8 (24; 12-40)	31 (20; 14-27)	6 (18; 8-33)	3 (21; 6-47)
Donor gamete	18 (7.7; 5-12)	4 (12; 4-26)	11 (7.2; 4-12)	1 (2.9; 0-13)	2 (14; 3-38)
Adoption	12 (5.1; 3-8)	3 (8.8; 3-22)	9 (5.9; 3-10)	0 (0; 0-7)	0 (0; 0-16)
No longer planning to get pregnant	9 (3.8; 2-7)	1 (2.9; 0-13)	6 (3.9; 2-8)	1 (2.9; 0-13)	1 (7; 0.7-29)

ARC: At-risk couple. CI: confidence interval, 95%. IVF: In vitro fertilization. PGT-M: Preimplantation genetic testing for monogenic conditions. PNDx: Prenatal diagnostic testing.

a. These ARCs did not recall, were not clear about, or did not answer the condition for which their future pregnancies were at risk and therefore could not be not assigned to severity classifications.
b. Respondents could choose more than one option, so percents of individual actions could sum to greater than 100.
c. Difference between Profound and Moderate is statistically significant (p=0.004).

Table 3. Actions and outcomes of ARCs screened during the prenatal period.

	All Severities, n (%; CI)	Profound, n (%; CI)	Severe, n (%; CI)	Moderate, n (%; CI)	Severity Unassigned,[a] n (%; CI)
Screened Prenatally	154 (100)	15 (9.7)	104 (68)	28 (18)	7 (4.5)
Underwent PNDx	56 (37; 29-35)[b]	7 (47; 24-71)	40 (38; 30-49)	8 (29; 15-47)	1 (14; 1.6-50)
Pregnancies affected	20 (36; 23-48)[c]	4 (57; 23-86)	11 (28; 16-43)[d]	4 (50; 20-80)	1 (100; 15-100)
Pregnancy outcome:[e]					
Terminated	8 (40; 21-62)	2 (50; 12-88)	5 (45; 20-73)	1 (25; 3-72)	0 (0; 0-85)
Live birth	8 (40; 21-62)	1 (25; 3-72)	5 (45; 20-73)	2 (50; 12-88)	0 (0; 0-85)
Not born yet	3 (15; 4-35)	1 (25; 3-72)	0 (0; 0-26)	1 (25; 3-72)	1 (100; 15-100)
Stillborn	1 (5.0; 0.5-21)	0 (0; 0-49)	1 (9.1; 1-35)	0 (0; 0-49)	0 (0; 0-85)
Did not undergo PNDx	95 (63; 55-70)[b]	8 (53; 29-76)	62 (60; 50-69)	19 (68; 49-82)	6 (86; 50-98)
Pregnancy outcome:					
Live birth	71 (75; 70-86)	7 (88; 55-99)	47 (76; 64-85)	14 (74; 52-89)	3 (50; 17-83)
Planned/pursued postnatal diagnosis	44 (62; 50-73)	1 (14; 2-50)[f]	29 (62; 47-75)[f]	13 (93; 71-99)[f]	1 (33; 3.9-82)
Not born yet	20 (21; 14-30)	0 (0; 0-26)	14 (23; 14-35)	4 (21; 7.6-43)	2 (33; 7.7-71)
Miscarried	2 (2.1; 0-7)	0 (0; 0-26)	1 (1.6; 0-7)	1 (5.3; 0.6-22)	0 (0; 0-33)
Terminated	2 (2.1; 0-7)	1 (13; 1-45)	0 (0; 0-4)	0 (0; 0-12)	1 (17; 1.9-55)

ARC: At-risk couple. CI: Confidence interval, 95%. PNDx: Prenatal diagnostic testing.

a. These ARCs did not recall, were not clear about, or did not answer the conditions for which their pregnancies were at risk and therefore could not be categorized by severity.

b. Out of 154 ARCs screened prenatally, 3 did not indicate if they underwent PNDx. Percent is therefore calculated out of 151 screened prenatally.

c. 1 ARC was still awaiting results. Percent is therefore calculated out of 55 pregnancies that underwent PNDx.

d. 1 ARC was still awaiting results. Percent is therefore calculated out of 39 pregnancies at risk for severe conditions that underwent PNDx.

e. Conditions with which pregnancies were found to be affected are indicated in Supplementary Table 3.

f. Differences are statistically significant at the 95% confidence level: profound vs. severe: p=0.02, severe vs. moderate: p=0.03, profound vs. moderate: p=0.0003.

Table 4. Actions and outcomes of pregnancies occurring subsequent to ECS test results.

	Total, n (%, CI)	Screened before becoming pregnant, n (%, CI)	Screened during previous pregnancy, n (%, CI)
Subsequent pregnancies	166 (100)	126 (76)	40 (24)
Achieved by IVF with PGT-M	58 (35; 28-42)	50 (40; 31-48)[a]	8 (20; 10-34)[a]
Underwent PNDx	48 (29; 22-36)	37 (29; 22-38)	11 (28; 16-34)
Pregnancies affected	12 (29; 17-44)[b]	11 (34; 20-52)[c]	1 (11; 1-41)[d]
Pregnancy outcome:[e]			
Terminated	9 (75; 47-92)	8 (73; 43-92)	1 (100; 15-100)
Live birth	3 (25; 8-53)	3 (27; 8-57)	0 (0; 0-85)
Did not undergo PNDx	118 (71; 51-69)	89 (71; 62-78)	29 (72; 57-84)
Pregnancy outcome:[f]			
Live birth	51 (44; 35-53)	42 (47; 37-58)	9 (32; 17-51)
Planned/pursued postnatal diagnosis	23 (45; 32-59)	20 (48; 33-62)	4 (44; 17-45)
Not born yet	43 (37; 28-46)	28 (31; 23-42)	15 (54; 36-71)
Miscarried	20 (17; 11-25)	17 (19; 12-28)	3 (11; 3-26)
Terminated	3 (2.6; 1-7)	2 (2.2; 0-7)	1 (3.6; 0-16)

CI: Confidence interval, 95%. IVF: In vitro fertilization. PGT-M: Preimplantation genetic testing for monogenic conditions. PNDx: Prenatal diagnostic testing.

a. Difference is statistically significant at 95% confidence level (p=0.02).
b. 7 of 48 that underwent PNDx are still waiting on the results. Percent affected is therefore calculated out of 41.
c. 5 of 37 that underwent PNDx are still waiting on results. Percent affected is therefore calculated out of 32.
d. 2 of 11 that underwent PNDx are still waiting on results. Percent affected is calculated out of 9.
e. Conditions for which pregnancies were found to be affected are indicated in Supplementary Table 3.
f. 1 of 29 screened during a previous pregnancy that did not undergo PNDx did not indicate pregnancy outcome. Percents are therefore calculated out of 117 (total pregnancies that did not undergo PNDx) or 28 (screened during a previous pregnancy and did not undergo PNDx).

Supplementary Figure 1. Survey questions as fielded.

Thank you for agreeing to complete this brief survey. Your individual answers will be anonymous and strictly confidential.

S1. What is your sex?
(Choose One Answer)

1   Male
2   Female

S2. What is your age?
(Please Type A Whole Number In The Box Below)

S3. Did you or your partner undergo carrier screening within the last 3 years? As a reminder, carrier screening is a test that determines whether you or your partner carry a gene variation that could be passed on to your children, increasing their risk for certain diseases.
(Choose One Answer)

1   Yes
2   No
3   Don't recall

If "Yes" on S3:
Do you agree to participate in this confidential survey?
(Choose One Answer)

1   Yes
2   No

Q1. For what condition(s) were you told that your pregnancy or future pregnancy was at increased risk?

1   Alpha thalassemia
2   Aspartylglycosaminuria
3   Ataxia-telangiectasia
4   ATP7A-related disorders (including Menkes syndrome and Occipital Horn syndrome)
5   Bardet-Biedl syndrome, BBS1-related
6   Bardet-Biedl syndrome, BBS10-related
7   Biotinidase deficiency
8   Canavan disease
9   Carnitine palmitoyltransferase IA deficiency
10   Carnitine palmitoyltransferase II deficiency
11   Citrullinemia type 1
12   COL4A4-related Alport syndrome
13   Congenital adrenal hyperplasia (classic or non-classic)
14   Congenital disorder of glycosylation type Ia
15   Congenital disorder of glycosylation type Ic
16   Congenital Finnish nephrosis
17   Cystic fibrosis
18   Cystinosis
19   Dystrophinopathy (including Duchenne/Becker muscular dystrophy)
20   Fabry disease
21   Familial dysautonomia
22   Familial Mediterranean fever

23 Fanconi anemia complementation group A
24 Fragile X syndrome
25 Galactosemia
26 Gaucher disease
27 GJB2-related DFNB1 nonsyndromic hearing loss and deafness
28 Glutaric acidemia type 1
29 Glycogen storage disease type Ia
30 HADHA-related disorders (including Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency)
31 Hb beta chain-related hemoglobinopathy (including beta-thalassemia and Sickle Cell disease)
32 Hereditary fructose intolerance
33 Herlitz junctional epidermolysis bullosa, LAMB3-related
34 Hexosaminidase A deficiency (including Tay-Sachs disease)
35 Homocystinuria caused by cystathionine beta-synthase deficiency
36 Hypophosphatasia, autosomal recessive
37 Krabbe disease
38 LAMA2-related muscular dystrophy
39 Lipoamide dehydrogenase deficiency
40 Maple syrup urine disease type 1B
41 Medium chain acyl-CoA dehydrogenase deficiency
42 Metachromatic leukodystrophy
43 Methylmalonic aciduria and homocystinuria, cblC type
44 MKS1-related disorders
45 Mucopolysaccaridosis type II
46 Mucopolysaccharidosis type I (Hurler syndrome)
47 MUT-related methylmalonic acidemia
48 NEB-related nemaline myopathy
49 Niemann-Pick disease type C
50 Nijmegen breakage syndrome
51 Ornithine transcarbamylase deficiency
52 Pendred syndrome
53 PEX1-related Zellweger syndrome spectrum
54 Phenylalanine hydroxylase deficiency (including phenylketonuria)
55 PKHD1-related autosomal recessive polycystic kidney disease (also known as autosomal recessive polycystic kidney disease)
56 Polyglandular autoimmune syndrome type 1
57 Pompe disease
58 Primary carnitine deficiency
59 Primary hyperoxaluria type 1
60 Rhizomelic chondrodysplasia punctata type 1
61 Sandhoff disease
62 Short chain acyl-CoA dehydrogenase deficiency
63 Smith-Lemli-Opitz syndrome
64 Spinal muscular atrophy
65 Steroid-resistant nephrotic syndrome
66 Sulfate transporter-related osteochondrodysplasia
67 Tyrosinemia type I
68 USH2A-related disorders (including Usher syndrome type 2)
69 Usher syndrome type 3
70 Very long chain acyl-CoA dehydrogenase deficiency
71 Wilson disease
72 X-linked adrenoleukodystrophy
73 X-linked Alport syndrome
74 X-linked congenital adrenal hypoplasia
75 X-linked juvenile retinoschisis
76 X-linked myotubular myopathy
77 X-linked severe combined immunodeficiency
78 Waiting on results of diagnostic test
79 Other Condition (Please Type In The Other Condition)
80 The pregnancy was found not to be affected
81 Don't recall

Q2. Were you pregnant when you received your carrier screening results?
(Choose One Answer)

1   Yes
2   No
3   Prefer not to answer

"PREFER NOT TO ANSWER" BLOCK

If "Prefer not to answer" on Q2:
Q3. After receiving your carrier screening results, what option(s) did you pursue or are you planning to pursue in the future? (Choose All That Apply)

1   In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD)
2   Sperm or egg donation
3   Adoption
4   Prenatal diagnostic testing such as chorionic villus sampling (CVS) or amniocentesis
5   If or when pregnant, inform other doctors that the baby might be at risk for {condition(s) indicated in Q1}
6   No longer planning to get pregnant
7   Testing other children or family members for {condition(s) indicated in Q1}
9   Other (Please Type In The Other Option)
8   Not planning to pursue any alternative options

"NOT PREGNANT" BLOCK

If "No" on Q2:
Q4. When you received your carrier screening results, were you undergoing or planning to undergo in vitro fertilization (IVF)?
(Choose One Answer)

1   Yes
2   No

If "No" on Q2:
Q5. After receiving your carrier screening results, what option(s) did you pursue or are you planning to pursue in the future? (Choose All That Apply)

1   In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD)
2   Use of donor sperm or egg
3   Adoption
4   Prenatal diagnostic testing such as chorionic villus sampling (CVS) or amniocentesis
5   Once pregnant, inform other doctors that baby might be at risk for {condition(s) indicated in Q1}
6   No longer planning to get pregnant
7   Test children or other family members for {condition(s) indicated in Q1}
9   Other (Please Type In The Other Option)
8   Not planning to pursue any other options

"PREGNANT" BLOCK

If "Yes" on Q2:
For the next few questions, please answer based on the pregnancy during which you received your carrier screening results. We'll ask about other pregnancies later.

Q6. How many weeks was your pregnancy at the time you received your carrier screening results? (Choose One Answer)

1   0-13 weeks (first trimester)
2   14-26 weeks (second trimester)

3   27 weeks or more (third trimester)
4   Don't recall

Q7. After receiving your carrier screening results, did you pursue prenatal diagnostic testing such as chorionic villus sampling (CVS) or amniocentesis for {condition(s) indicated in Q1}? (Choose One Answer)

1   Yes
2   No

If "No" on Q7:
Q8: What are some of the reasons you chose not to pursue prenatal diagnostic testing? (Please Type Your Answers In The Box Below. Please Be Specific And Include Any Details You Feel Comfortable Sharing.)

[   ]

If "No" on Q7:
Q9: What was the outcome of the pregnancy? (Choose One Answer)

1   The pregnancy was continued and resulted in a live birth
2   The pregnancy was continued and the baby hasn't been born yet
3   The pregnancy was continued and was stillborn
4   The pregnancy miscarried
5   The pregnancy was terminated

Q10: If "The pregnancy was continued and resulted in a live birth" on Q9: Was the baby tested after he or she was born for {condition(s) indicated in Q1}? (Choose One Answer)

1   Yes, the baby was tested
2   No, but we plan to have the baby tested in the future
3   No, and we do not currently plan to have the baby tested

If "Yes" on Q7:
Q11: Which of the following condition(s) did the prenatal diagnostic test show that your pregnancy was affected with? (Choose All That Apply)

1   Alpha thalassemia
2   Aspartylglycosaminuria
3   Ataxia-telangiectasia
4   ATP7A-related disorders (including Menkes syndrome and Occipital Horn syndrome)
5   Bardet-Biedl syndrome, BBS1-related
6   Bardet-Biedl syndrome, BBS10-related
7   Biotinidase deficiency
8   Canavan disease
9   Carnitine palmitoyltransferase IA deficiency
10   Carnitine palmitoyltransferase II deficiency
11   Citrullinemia type 1
12   COL4A4-related Alport syndrome
13   Congenital adrenal hyperplasia (classic or non-classic)
14   Congenital disorder of glycosylation type Ia
15   Congenital disorder of glycosylation type Ic
16   Congenital Finnish nephrosis
17   Cystic fibrosis
18   Cystinosis
19   Dystrophinopathy (including Duchenne/Becker muscular dystrophy)
20   Fabry disease
21   Familial dysautonomia
22   Familial Mediterranean fever

23   Fanconi anemia complementation group A
24   Fragile X syndrome
25   Galactosemia
26   Gaucher disease
27   GJB2-related DFNB1 nonsyndromic hearing loss and deafness
28   Glutaric acidemia type 1
29   Glycogen storage disease type Ia
30   HADHA-related disorders (including Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency)
31   Hb beta chain-related hemoglobinopathy (including beta-thalassemia and Sickle Cell disease)
32   Hereditary fructose intolerance
33   Herlitz junctional epidermolysis bullosa, LAMB3-related
34   Hexosaminidase A deficiency (including Tay-Sachs disease)
35   Homocystinuria caused by cystathionine beta-synthase deficiency
36   Hypophosphatasia, autosomal recessive
37   Krabbe disease
38   LAMA2-related muscular dystrophy
39   Lipoamide dehydrogenase deficiency
40   Maple syrup urine disease type 1B
41   Medium chain acyl-CoA dehydrogenase deficiency
42   Metachromatic leukodystrophy
43   Methylmalonic aciduria and homocystinuria, cblC type
44   MKS1-related disorders
45   Mucopolysaccaridosis type II
46   Mucopolysaccharidosis type I (Hurler syndrome)
47   MUT-related methylmalonic acidemia
48   NEB-related nemaline myopathy
49   Niemann-Pick disease type C
50   Nijmegen breakage syndrome
51   Ornithine transcarbamylase deficiency
52   Pendred syndrome
53   PEX1-related Zellweger syndrome spectrum
54   Phenylalanine hydroxylase deficiency (including phenylketonuria)
55   PKHD1-related autosomal recessive polycystic kidney disease (also known as autosomal recessive polycystic
      kidney disease)
56   Polyglandular autoimmune syndrome type 1
57   Pompe disease
58   Primary carnitine deficiency
59   Primary hyperoxaluria type 1
60   Rhizomelic chondrodysplasia punctata type 1
61   Sandhoff disease
62   Short chain acyl-CoA dehydrogenase deficiency
63   Smith-Lemli-Opitz syndrome
64   Spinal muscular atrophy
65   Steroid-resistant nephrotic syndrome
66   Sulfate transporter-related osteochondrodysplasia
67   Tyrosinemia type I
68   USH2A-related disorders (including Usher syndrome type 2)
69   Usher syndrome type 3
70   Very long chain acyl-CoA dehydrogenase deficiency
71   Wilson disease
72   X-linked adrenoleukodystrophy
73   X-linked Alport syndrome
74   X-linked congenital adrenal hypoplasia
75   X-linked juvenile retinoschisis
76   X-linked myotubular myopathy
77   X-linked severe combined immunodeficiency
78   Waiting on results of diagnostic test
79   Other Condition (Please Type In The Other Condition)
80   The pregnancy was found not to be affected
81   Don't recall

If "Yes" on Q7:
Q12: What was the outcome of the pregnancy after learning the final test result? (Choose One Answer)

1   The pregnancy was continued and resulted in a live birth
2   The pregnancy was continued and the baby hasn't been born yet
3   The pregnancy was continued and was stillborn
4   The pregnancy miscarried
5   The pregnancy was terminated

SUBSEQUENT PREGNANCIES BLOCK

Q13: How many times have you been pregnant since receiving your carrier screening results? (Choose One Answer)

0   0
1   1
2   2 or more

If "1" or "2 or more" on Q13:
For the next few questions, please answer based on the next pregnancy <u>after</u> you received your carrier screening results.

Q14: In the next pregnancy after you received your carrier screening results, did you undergo in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD)? (Choose One Answer)

1   Yes
2   No

If "1" or "2 or more" on Q13:
Q15: In the next pregnancy after you received your carrier screening results, did you pursue prenatal diagnostic testing such as chorionic villus sampling (CVS) or amniocentesis?
(Choose One Answer)

1   Yes
2   No

If "No" on Q15:
Q16: What were some of the reasons you chose not to pursue prenatal diagnostic testing? (Please Type Your Answers In The Box Below. Please Be Specific And Include Any Details You Feel Comfortable Sharing.)

[   ]

If "No" on Q15:
Q17: What was the outcome of the pregnancy? (Choose One Answer)

1   The pregnancy was continued and resulted in a live birth
2   The pregnancy was continued and the baby hasn't been born yet
3   The pregnancy was continued and was stillborn
4   The pregnancy miscarried
5   The pregnancy was terminated

If "The pregnancy was continued and resulted in a live birth" on Q17:
Q18: Was the baby tested after he or she was born for {condition(s) indicated in Q1}?
(Choose One Answer)

1   Yes, the baby was tested
2   No, but we plan to have the baby tested in the future

3   No, and we do not currently plan to have the baby tested

If "Yes" on Q15:
Q19: Which of the following condition(s) did the final test show that your pregnancy was affected with?
(Choose All That Apply)

1   Alpha thalassemia
2   Aspartylglycosaminuria
3   Ataxia-telangiectasia
4   ATP7A-related disorders (including Menkes syndrome and Occipital Horn syndrome)
5   Bardet-Biedl syndrome, BBS1-related
6   Bardet-Biedl syndrome, BBS10-related
7   Biotinidase deficiency
8   Canavan disease
9   Carnitine palmitoyltransferase IA deficiency
10   Carnitine palmitoyltransferase II deficiency
11   Citrullinemia type 1
12   COL4A4-related Alport syndrome
13   Congenital adrenal hyperplasia (classic or non-classic)
14   Congenital disorder of glycosylation type Ia
15   Congenital disorder of glycosylation type Ic
16   Congenital Finnish nephrosis
17   Cystic fibrosis
18   Cystinosis
19   Dystrophinopathy (including Duchenne/Becker muscular dystrophy)
20   Fabry disease
21   Familial dysautonomia
22   Familial Mediterranean fever
23   Fanconi anemia complementation group A
24   Fragile X syndrome
25   Galactosemia
26   Gaucher disease
27   GJB2-related DFNB1 nonsyndromic hearing loss and deafness
28   Glutaric acidemia type 1
29   Glycogen storage disease type Ia
30   HADHA-related disorders (including Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency)
31   Hb beta chain-related hemoglobinopathy (including beta-thalassemia and Sickle Cell disease)
32   Hereditary fructose intolerance
33   Herlitz junctional epidermolysis bullosa, LAMB3-related
34   Hexosaminidase A deficiency (including Tay-Sachs disease)
35   Homocystinuria caused by cystathionine beta-synthase deficiency
36   Hypophosphatasia, autosomal recessive
37   Krabbe disease
38   LAMA2-related muscular dystrophy
39   Lipoamide dehydrogenase deficiency
40   Maple syrup urine disease type 1B
41   Medium chain acyl-CoA dehydrogenase deficiency
42   Metachromatic leukodystrophy
43   Methylmalonic aciduria and homocystinuria, cblC type
44   MKS1-related disorders
45   Mucopolysaccaridosis type II
46   Mucopolysaccharidosis type I (Hurler syndrome)
47   MUT-related methylmalonic acidemia
48   NEB-related nemaline myopathy
49   Niemann-Pick disease type C
50   Nijmegen breakage syndrome
51   Ornithine transcarbamylase deficiency
52   Pendred syndrome
53   PEX1-related Zellweger syndrome spectrum
54   Phenylalanine hydroxylase deficiency (including phenylketonuria)

55   PKHD1-related autosomal recessive polycystic kidney disease (also known as autosomal recessive polycystic kidney disease)
56   Polyglandular autoimmune syndrome type 1
57   Pompe disease
58   Primary carnitine deficiency
59   Primary hyperoxaluria type 1
60   Rhizomelic chondrodysplasia punctata type 1
61   Sandhoff disease
62   Short chain acyl-CoA dehydrogenase deficiency
63   Smith-Lemli-Opitz syndrome
64   Spinal muscular atrophy
65   Steroid-resistant nephrotic syndrome
66   Sulfate transporter-related osteochondrodysplasia
67   Tyrosinemia type I
68   USH2A-related disorders (including Usher syndrome type 2)
69   Usher syndrome type 3
70   Very long chain acyl-CoA dehydrogenase deficiency
71   Wilson disease
72   X-linked adrenoleukodystrophy
73   X-linked Alport syndrome
74   X-linked congenital adrenal hypoplasia
75   X-linked juvenile retinoschisis
76   X-linked myotubular myopathy
77   X-linked severe combined immunodeficiency
78   Waiting on results of diagnostic test
79   Other Condition (Please Type In The Other Condition)
80   The pregnancy was found not to be affected
81   Don't recall

If "Yes" on Q15:
Q20: What was the outcome of the pregnancy after learning the final test result? (Choose One Answer)

1   The pregnancy was continued and resulted in a live birth
2   The pregnancy was continued and the baby hasn't been born yet
3   The pregnancy was continued and was stillborn
4   The pregnancy miscarried
5   The pregnancy was terminated

If "2 or more" on Q13:
Q21: In your <u>most recent</u> pregnancy, did you undergo in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD)? (Choose One Answer)

1   Yes
2   No

If "2 or more" on Q13:
Q22: In your <u>most recent</u> pregnancy, did you pursue prenatal diagnostic testing such as chorionic villus sampling (CVS) or amniocentesis? (Choose One Answer)

1   Yes
2   No

If "No" on Q22:
Q23: What were some of the reasons you chose not to pursue prenatal diagnostic testing? (Please Type Your Answers In The Box Below. Please Be Specific And Include Any Details You Feel Comfortable Sharing.)

If "No" on Q22:
Q24: What was the outcome of the pregnancy? (Choose One Answer)

1   The pregnancy was continued and resulted in a live birth
2   The pregnancy was continued and the baby hasn't been born yet
3   The pregnancy was continued and was stillborn
4   The pregnancy miscarried
5   The pregnancy was terminated

If "The pregnancy was continued and resulted in a live birth" on Q24:
Q25: Was the baby tested after he or she was born for {condition(s) indicated in Q1}? (Choose One Answer)

1   Yes, the baby was tested
2   No, but we plan to have the baby tested in the future
3   No, and we do not currently plan to have the baby tested

If "Yes" on Q22:
Q26: Which of the following condition(s) did the final test show that your pregnancy was affected with? (Choose All That Apply)

1   Alpha thalassemia
2   Aspartylglycosaminuria
3   Ataxia-telangiectasia
4   ATP7A-related disorders (including Menkes syndrome and Occipital Horn syndrome)
5   Bardet-Biedl syndrome, BBS1-related
6   Bardet-Biedl syndrome, BBS10-related
7   Biotinidase deficiency
8   Canavan disease
9   Carnitine palmitoyltransferase IA deficiency
10   Carnitine palmitoyltransferase II deficiency
11   Citrullinemia type 1
12   COL4A4-related Alport syndrome
13   Congenital adrenal hyperplasia (classic or non-classic)
14   Congenital disorder of glycosylation type Ia
15   Congenital disorder of glycosylation type Ic
16   Congenital Finnish nephrosis
17   Cystic fibrosis
18   Cystinosis
19   Dystrophinopathy (including Duchenne/Becker muscular dystrophy)
20   Fabry disease
21   Familial dysautonomia
22   Familial Mediterranean fever
23   Fanconi anemia complementation group A
24   Fragile X syndrome
25   Galactosemia
26   Gaucher disease
27   GJB2-related DFNB1 nonsyndromic hearing loss and deafness
28   Glutaric acidemia type 1
29   Glycogen storage disease type Ia
30   HADHA-related disorders (including Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency)
31   Hb beta chain-related hemoglobinopathy (including beta-thalassemia and Sickle Cell disease)
32   Hereditary fructose intolerance
33   Herlitz junctional epidermolysis bullosa, LAMB3-related
34   Hexosaminidase A deficiency (including Tay-Sachs disease)
35   Homocystinuria caused by cystathionine beta-synthase deficiency
36   Hypophosphatasia, autosomal recessive
37   Krabbe disease
38   LAMA2-related muscular dystrophy
39   Lipoamide dehydrogenase deficiency

40   Maple syrup urine disease type 1B
41   Medium chain acyl-CoA dehydrogenase deficiency
42   Metachromatic leukodystrophy
43   Methylmalonic aciduria and homocystinuria, cblC type
44   MKS1-related disorders
45   Mucopolysaccaridosis type II
46   Mucopolysaccharidosis type I (Hurler syndrome)
47   MUT-related methylmalonic acidemia
48   NEB-related nemaline myopathy
49   Niemann-Pick disease type C
50   Nijmegen breakage syndrome
51   Ornithine transcarbamylase deficiency
52   Pendred syndrome
53   PEX1-related Zellweger syndrome spectrum
54   Phenylalanine hydroxylase deficiency (including phenylketonuria)
55   PKHD1-related autosomal recessive polycystic kidney disease (also known as autosomal recessive polycystic kidney disease)
56   Polyglandular autoimmune syndrome type 1
57   Pompe disease
58   Primary carnitine deficiency
59   Primary hyperoxaluria type 1
60   Rhizomelic chondrodysplasia punctata type 1
61   Sandhoff disease
62   Short chain acyl-CoA dehydrogenase deficiency
63   Smith-Lemli-Opitz syndrome
64   Spinal muscular atrophy
65   Steroid-resistant nephrotic syndrome
66   Sulfate transporter-related osteochondrodysplasia
67   Tyrosinemia type I
68   USH2A-related disorders (including Usher syndrome type 2)
69   Usher syndrome type 3
70   Very long chain acyl-CoA dehydrogenase deficiency
71   Wilson disease
72   X-linked adrenoleukodystrophy
73   X-linked Alport syndrome
74   X-linked congenital adrenal hypoplasia
75   X-linked juvenile retinoschisis
76   X-linked myotubular myopathy
77   X-linked severe combined immunodeficiency
78   Waiting on results of diagnostic test
79   Other Condition (Please Type In The Other Condition)
80   The pregnancy was found not to be affected
81   Don't recall

If "Yes" on Q22:
Q27. What was the outcome of the pregnancy after learning the final test result?
(Choose One Answer)

1   The pregnancy was continued and resulted in a live birth
2   The pregnancy was continued and the baby hasn't been born yet
3   The pregnancy was continued and was stillborn
4   The pregnancy miscarried
5   The pregnancy was terminated

DEMOGRAPHIC SECTION

Q28: What was the age of the female partner at the time of her original carrier screening? (Choose One Answer)

1   Younger than 18

2   18-24
3   25-34
4   35-44
5   45 or over

Q29: What is the female partner's ethnicity? (Choose All That Apply)

1   Northern European (e.g., British, German)
2   Southern European (e.g., Italian, Greek)
3   French Canadian or Cajun
4   Ashkenazi Jewish
5   Other/Mixed Caucasian
6   East Asian (e.g., Chinese, Japanese)
7   South Asian (e.g., Indian, Pakistani)
8   Southeast Asian (e.g., Filipino, Vietnamese)
9   African or African American
10   Hispanic
11   Middle Eastern
12   Native American
13   Pacific Islander
14   Other (Please Type In The Other Ethnicity)
15   Unknown
16   Prefer not to say

Q30: What is the male partner's ethnicity?
(Choose All That Apply)

1   Northern European (e.g., British, German)
2   Southern European (e.g., Italian, Greek)
3   French Canadian or Cajun
4   Ashkenazi Jewish
5   Other/Mixed Caucasian
6   East Asian (e.g., Chinese, Japanese)
7   South Asian (e.g., Indian, Pakistani)
8   Southeast Asian (e.g., Filipino, Vietnamese)
9   African or African American
10   Hispanic
11   Middle Eastern
12   Native American
13   Pacific Islander
14   Other (Please Type In The Other Ethnicity)
15   Unknown
16   Prefer not to say

Q31: In what state did you live when you received your carrier screening results?
(Choose One Answer from drop-down list. Includes "Outside the U.S. option.)

Q32. What is the female partner's religious affiliation? (Choose One Answer)

1   Protestant
2   Catholic
3   Mormon
4   Jewish
5   Buddhist
6   Hindu
7   Muslim
8   Agnostic
9   Atheist

10   Other (Please Type In The Other Religion)
11   No religious affiliation
12   Unknown
13   Prefer not to say

Q33. What is the male partner's religious affiliation? (Choose One Answer)

1   Protestant
2   Catholic
3   Mormon
4   Jewish
5   Buddhist
6   Hindu
7   Muslim
8   Agnostic
9   Atheist
10   Other (Please Type In The Other Religion)
11   No religious affiliation
12   Unknown
13   Prefer not to say

Supplementary Table 1. Conditions reported by respondents, categorized by severity.

Condition(s) reported[a]	n (%)
Profound	50 (13)
Smith-Lemli-Opitz syndrome	6 (1.5)
Smith-Lemli-Opitz syndrome, Fragile X syndrome	4 (1.0)
Hexosaminidase A deficiency (Tay-Sachs disease)	4 (1.0)
Congenital disorder of glycosylation type Ia	3 (0.8)
Pompe disease	3 (0.8)
Gaucher disease	2 (0.5)
Gaucher disease, Fragile X syndrome	2 (0.5)
Niemann-Pick disease type C	2 (0.5)
Canavan disease	1 (0.2)
Canavan disease, Fragile X syndrome	1 (0.2)
Congenital disorder of glycosylation type Ia, Biotinidase deficiency, Cystic fibrosis	1 (0.2)
Congenital disorder of glycosylation type Ic	1 (0.2)
Familial dysautonomia, Fragile X syndrome	1 (0.2)
Galactosemia	1 (0.2)
Galactosemia, Fragile X syndrome	1 (0.2)
Gaucher disease, Familial Mediterranean fever	1 (0.2)
Gaucher disease, Biotinidase deficiency, Pendred syndrome	1 (0.2)
HADHA-related disorders (including Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency)	1 (0.2)
Hexosaminidase A deficiency (Tay-Sachs disease), Fragile X syndrome	1 (0.2)
Krabbe disease	1 (0.2)
Krabbe disease, GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1 (0.2)
Lipoamide dehydrogenase deficiency	1 (0.2)
Maple syrup urine disease type 1B, Fragile X syndrome	1 (0.2)
Maple syrup urine disease type 1B, Fragile X syndrome, Familial Mediterranean Fever	1 (0.2)
Medium chain acyl-CoA dehydrogenase deficiency	1 (0.2)
Medium chain acyl-CoA dehydrogenase deficiency, Fragile X syndrome	1 (0.2)
Metachromatic leukodystrophy	1 (0.2)
Mucopolysaccharidosis type I (Hurler syndrome)	1 (0.2)
PEX1-related Zellweger syndrome spectrum, Biotinidase deficiency	1 (0.2)
Rhizomelic chondrodysplasia punctata type 1	1 (0.2)
Tyrosinemia type I	1 (0.2)
X-linked adrenoleukodystrophy	1 (0.2)
Severe	258 (66)
Fragile X syndrome	128 (33)
Cystic fibrosis	38 (10)
Familial Mediterranean fever	9 (2.3)
Dystrophinopathy (including Duchenne/Becker muscular dystrophy)	8 (2.0)
Spinal muscular atrophy	8 (2.0)
Alpha thalassemia	7 (1.8)
Phenylalanine hydroxylase deficiency	5 (1.3)
Fabry disease	4 (1.0)
Hb beta chain-related hemoglobinopathy (including Beta-thalassemia and Sickle Cell disease)	4 (1.0)
Wilson disease	3 (0.8)
PKHD1-related autosomal recessive polycystic kidney disease	2 (0.5)
Alpha thalassemia, Congenital adrenal hyperplasia	2 (0.5)
Cystic fibrosis, Fragile X syndrome	2 (0.5)
Fragile X syndrome, Congenital adrenal hyperplasia	2 (0.5)
Fragile X syndrome, Spinal muscular atrophy	2 (0.5)
Alpha thalassemia, Biotinidase deficiency	1 (0.2)
Alpha thalassemia, Congenital adrenal hyperplasia, Fragile X syndrome	1 (0.2)

Alpha thalassemia, Fragile X syndrome	1 (0.2)
Alpha thalassemia, Hb beta chain-related hemoglobinopathy (including Beta-thalassemia and Sickle Cell disease)	1 (0.2)
Alpha thalassemia, Phenylalanine hydroxylase deficiency	1 (0.2)
Ataxia-telangiectasia	1 (0.2)
Bardet-Biedl syndrome BBS10-related, Cystic fibrosis	1 (0.2)
Biotinidase deficiency	1 (0.2)
Cystic fibrosis, GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1 (0.2)
Cystic fibrosis, Congenital adrenal hyperplasia	1 (0.2)
Cystic fibrosis, Hereditary fructose intolerance	1 (0.2)
Cystic fibrosis, Fragile X syndrome, Spinal muscular atrophy	1 (0.2)
Cystic fibrosis, Spinal muscular atrophy	1 (0.2)
Dystrophinopathy (including Duchenne/Becker muscular dystrophy), Glycogen storage disease type Ia	1 (0.2)
Dystrophinopathy (including Duchenne/Becker muscular dystrophy), Spinal muscular atrophy	1 (0.2)
Familial Mediterranean fever, Fragile X syndrome	1 (0.2)
Familial Mediterranean fever, GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1 (0.2)
Fanconi anemia complementation group A	1 (0.2)
Fragile X syndrome, GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1 (0.2)
Fragile X syndrome, Herlitz junctional epidermolysis bullosa LAMB3-related, GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1 (0.2)
Fragile X syndrome, Phenylalanine hydroxylase deficiency	1 (0.2)
Fragile X syndrome, Wilson disease	1 (0.2)
Glycogen storage disease type Ia	1 (0.2)
Hereditary fructose intolerance, Congenital adrenal hyperplasia	1 (0.2)
Herlitz junctional epidermolysis bullosa LAMB3-related, Primary hyperoxaluria type 1, Spinal muscular atrophy	1 (0.2)
Homocystinuria caused by cystathionine beta-synthase deficiency	1 (0.2)
Hypophosphatasia autosomal recessive	1 (0.2)
LAMA2-related muscular dystrophy	1 (0.2)
Nijmegen breakage syndrome	1 (0.2)
Spinal muscular atrophy, GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1 (0.2)
Sulfate transporter-related osteochondrodysplasia	1 (0.2)
Usher syndrome type	1 (0.2)
X-linked Alport syndrome	1 (0.2)
X-linked congenital adrenal hypoplasia	1 (0.2)
Moderate	62 (16)
GJB2-related DFNB1 nonsyndromic hearing loss and deafness	32 (8.2)
Congenital adrenal hyperplasia	25 (6.4)
Pendred syndrome	4 (1.0)
X-linked juvenile retinoschisis	1 (0.2)
Don't recall	17 (3.6)
None	2 (0.5)
Answer unclear	2 (0.5)
Total Respondents	**391 (100)**

d.   Percents sum to just over 100% due to rounding. Conditions listed on the same row and separated by commas represent participants reporting that their current or future pregnancies were at risk for both or all three conditions.

Supplementary Table 2. Outcomes of pregnancies found by PNDx to be affected, with condition listed.

	Total pregnancies, n (%)	Pregnancy during which ECS results were received, n	Pregnancies conceived after ECS results were received, n
Affected pregnancies	32	20	12
Terminated	17 (53)	8 (40)	9 (75)
Congenital adrenal hyperplasia	1	-	1
Cystic fibrosis	4	2	2
Fragile X syndrome	2	1	1
GJB2-related DFNB1 nonsyndromic hearing loss and deafness	2	1	1
HADHA-related disorders (including Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency)	1	1	-
Hypophosphatasia (autosomal recessive)	1	-	1
LAMA2-related muscular dystrophy	1	1	-
Niemann-Pick disease type C	2	1	1
Phenylalanine hydroxylase deficiency	1	1	-
Pompe disease	1	-	1
Spinal muscular atrophy	2	-	2
Live birth	11 (34)	8 (40)	3 (25)
Cystic fibrosis	1	1	-
Congenital adrenal hyperplasia	1	1	-
Congenital adrenal hypoplasia	1	1	-
Fragile X syndrome	5	2	3
GJB2-related DFNB1 nonsyndromic hearing loss and deafness	1	1	-
Pompe disease	1	1	-
Spinal muscular atrophy	1	1	-
Not born yet	3 (9.4)	3 (15)	0 (0)
Congenital adrenal hyperplasia	1	1	-
Medium chain acyl-CoA dehydrogenase deficiency	1	1	-
Unknown[a]	1	1	
Stillborn	1 (3.1)	1 (5.0)	0 (0)
PKHD1-related autosomal recessive polycystic kidney disease	1	1	-
Miscarried	0 (0)	0 (0)	0 (0)

a.   1 at-risk couple (ARC) could not recall the condition for which the pregnancy was found to be affected.

Supplementary Table 3. Reasons cited by ARCs choosing not to undergo prenatal diagnosis.

	All pregnancies, n (%; CI)	Pregnancy during screening, n (%; CI)	Subsequent pregnancy, n (%; CI)
Did not undergo prenatal diagnosis	213 (100)	95 (100)	118 (100)
Reason[a]			
Risk of miscarriage	50 (23; 18-29)	33 (35; 26-45)[b]	17 (14; 9-22)[b]
Perception of low risk of pregnancy being affected	45 (21; 16-27)	25 (26; 18-36)	20 (17; 11-24)
Would not have terminated the pregnancy	38 (18; 13-23)	26 (27; 19-37)[c]	12 (10; 6-17)[c]
Not necessary because IVF with PGT-M was performed	31 (15; 11-21)	0 (0; 0-3)	31 (28; 20-37)
Pregnancy miscarried before testing could be performed	16 (8; 5-12)	0 (0; 0-3)	16 (14; 8-21)
Condition phenotype not severe enough to warrant testing	12 (6; 3-10)	6 (6.3; 3-13)	6 (5.1; 2-10)
Planning post-natal testing instead	8 (4; 2-7)	5 (5.3; 2-11)	3 (2.5; 1-7)
No prenatal treatment options available	4 (1.9; 1-4)	3 (3.2; 1-8)	1 (0.8; 0-4)
Too late in the pregnancy to terminate	4 (1.9; 1-4)	3 (3.2; 1-8)	1 (0.8; 0-4)
Provider did not recommend testing	4 (1.9; 1-4)	2 (2.1; 0-7)	2 (1.7; 0-5)
Cost was too high	3 (1.4; 0-4)	1 (1.1; 0-5)	2 (1.7; 0-5)
Pregnancy was terminated before pursuing testing	2 (0.9; 0-3)	0 (0; 0-3)	2 (1.7; 0-5)
Too early in pregnancy to undergo testing	2 (0.9; 0-3)	0 (0; 0-3)	2 (1.7; 0-5)
Other/Did not specify	24 (11; 8-26)	7 (7.4; 3-14)	17 (14; 9-22)

ARC: At-risk couple. CI: confidence interval, 95%. IVF: In vitro fertilization. PGT-M: Preimplantation genetic testing for monogenic conditions.

a.   Percents will sum to greater than 100% because respondents could cite more than one reason.
b.   Significantly different at the 95% confidence level (p=0.0005).
c.   Significantly different at the 95% confidence level (p=0.001).