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Preference for secondary findings in prenatal and pediatric exome sequencing

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Abstract

Objective: We aimed to determine the frequency of accepting secondary findings in families undergoing exome sequencing in prenatal and pediatric settings.

Methods: This was a secondary analysis of prospectively enrolled patients undergoing trio exome sequencing for congenital anomalies or developmental disorders in prenatal and pediatric settings, in which families were offered receiving secondary findings (initially assessed in the proband and, if identified, then in the parents). The primary outcome was frequency of accepting secondary findings. Secondary outcomes included frequency of acceptance in prenatal versus pediatric settings, and sociodemographic differences between those who accepted versus declined secondary findings.

Results: There were 682 families included in the cohort (289 prenatal and 393 pediatric). Overall, 84% (576/682) of families accepted secondary findings: 86.2% (249/289) of families undergoing prenatal versus 83.2% (327/393) pediatric ($p = 0.30$) testing. Secondary findings were identified in 2.6% (15/576) of cases, with no difference between prenatal and pediatric settings. There were no differences in sociodemographics between families that accepted versus declined secondary findings.

Conclusion: The majority of families undergoing exome sequencing accepted secondary findings; this did not differ in prenatal versus pediatric settings. This highlights the need for guidance surrounding the offer of secondary findings in the prenatal setting.

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DATA AVAILABILITY STATEMENT

Data from this study may be made available upon request. Please contact the primary author at katherine.swanson@ucsf.edu to make requests.

1 | INTRODUCTION

Exome sequencing is a useful tool for establishing a genetic diagnosis in both prenatal and pediatric settings. For prenatally identified fetal anomalies, the diagnostic yield of pathogenic and likely pathogenic variants identified on exome sequencing varies by type of anomaly but is overall 8.5%–29% based on large, recently published series.[1–5] For pediatric congenital anomalies, intellectual disability, or developmental delay, the reported diagnostic yield of pathogenic and likely pathogenic variants is approximately 30%.[6,7] As exome sequencing becomes more available in the clinical setting and our understanding of phenotypic features and disease-causing variants improves, it is likely that the utility of exome sequencing will continue to increase.

In addition to establishing a genetic diagnosis for the primary indication, exome sequencing can also identify genetic variants that are unrelated to the reason testing was initially undertaken. The American College of Medical Genetics and Genomics (ACMG) recommends that when clinical exome sequencing is performed in the postnatal setting, pathogenic or likely pathogenic variants in 59 clinically actionable genes should be specifically assessed, and should be reported if identified. These variants are “secondary” to the primary purpose of the test and include, among others, genes associated with cancer syndromes, cardiomyopathies, and arrhythmias for which risk may be mitigated by early surveillance or other management strategies.[8–10] The ACMG also recommends that patients be offered the opportunity to opt out of receiving secondary findings. However, ACMG guidance specifically does not apply to fetal testing and there are no current professional society guidelines regarding whether secondary findings in the fetus should be reported in the prenatal setting, although a recent position statement of International Society for Prenatal Diagnosis (ISPD), Perinatal Quality Foundation (PQF), and Society for Maternal-Fetal Medicine (SMFM) recommends that pre-test counseling regarding prenatal exome or genome sequencing should include discussion of the inclusion or exclusion of secondary findings.[8,11]

Controversy exists about reporting of secondary findings in the pediatric setting, with disagreement about whether this practice is ethically appropriate in children who are not able to make their own decisions about receiving these findings.[12] The role of assessing and reporting of secondary findings in the prenatal setting is even more controversial. Proponents of returning secondary findings in a prenatal setting argue that identification of clinically actionable variants could enable management strategies in childhood to mitigate risk (e.g. for life-threatening arrhythmias), and other affected family members may benefit as well through cascade testing or by gaining information about modifiable genetic risk. Those opposed argue that the ethical, social, and psychological ramifications of identifying risk factors for largely adult onset disorders in a fetus or young child outweigh the potential benefits.[13] In spite of this controversy, parents of children undergoing exome sequencing often choose reporting of secondary findings for their children. To date, parental desire for receipt of these findings in the prenatal setting has not been studied.[14–16]

The objective of this study was to determine the frequency of accepting secondary findings in prenatal and pediatric populations, as well as to compare acceptance between these settings and across sociodemographic characteristics.

2 | MATERIALS & METHODS

This is a secondary analysis of data from two studies of prenatal and pediatric exome sequencing conducted through the University of California, San Francisco from August, 2017 through May, 2020. The findings of one study have been reported for prenatal cases with non-immune hydrops,[1] and participants were enrolled in this study from across the U.S. The second study enrolled prenatal and pediatric cases of fetal anomalies, pediatric congenital anomalies, and pediatric cases with developmental delays, and is ongoing. Exome sequencing was performed as part of the research study, with results disclosed to families. Children could be up to 25 years of age at the time of enrollment. The majority of cases had chromosomal microarray (CMA) with non-diagnostic results prior to enrollment; a small proportion had non-diagnostic results of karyotype only. Institutional Review Board approval was obtained (#17-21,662 and #17-22,420), and written informed consent was obtained from the pregnant patient (in the prenatal setting), parent(s) of the child (in the pediatric setting), or participant (if 18 years or older).

The primary outcome was overall frequency of accepting secondary findings in prenatal and pediatric populations. Secondary outcomes were the acceptance of secondary findings in prenatal versus pediatric settings, across sociodemographic characteristics, and for prenatal cases, in continuing versus non-continuing pregnancies. Prior to exome sequencing, all families were counseled by a genetic counselor or geneticist regarding secondary findings, and given the opportunity to choose whether or not they wanted to receive results if any secondary findings were identified in the proband. Following the UCSF Genomic Medicine Laboratory (GML) protocol and as discussed further below, if a reportable secondary finding was identified in the proband, inheritance was determined in parental samples submitted for exome sequencing. Counseling regarding secondary findings was performed by licensed clinical genetic counselors or geneticists as part of the informed consent process based on information in the study consent forms (Supplemental materials). Genetic counselors or geneticists discussed with each family the potential benefits of learning about secondary findings such as early implementation of cancer screening protocols for the proband, parents, or extended family. Potential risks associated with secondary findings were also discussed, including that our laboratory protocol is only to identify secondary findings that are present in the proband, variants can be re-classified over time and many diseases have variable expressivity or reduced penetrance, additional indications for medical testing or surveillance that may arise, limitations in insurance coverage that may result if a secondary finding is identified regardless of symptoms or other health, and limitations in existing regulations that cover protection of genetic testing information. Secondary findings eligible for return to families were those in 59 genes with clinical actionability as identified by the ACMG.[10] Participating families underwent trio exome sequencing, meaning that samples were obtained from the proband as well as both biological parents. If only one parent was available, duo exome sequencing was performed. Only secondary findings identified in the proband were assessed in the parents, and only variants meeting criteria for

known pathogenicity or expected pathogenicity, as defined by the ACMG, were reported.[17] Sociodemographic characteristics including age, self-reported race/ethnicity, highest level of education, relationship status, and use of an interpreter were ascertained. Acceptance of secondary findings was analyzed per family and cases in which the parents disagreed regarding acceptance of secondary findings were anlayzed separately.

The UCSF GML performed the clinial exome sequencing, as previously described.[1] Briefly, the GML is a Clinical Laboratory Improvements Amendments (CLIA)-accredited laboratory, and sequencing results were returned to the participant in a formal clinical report. The Illumina NovaSeq 6000, or HiSeq 2500 Sequencer on Rapid Run mode was used for sequencing. Variant call format files were uploaded for variant filtering into Ingenuity Variant Analysis (Qiagen) before March 2020 and into Moon (Diploid, Invitae) beginning in March 2020. Our laboratory process involves sequencing of the proband and initial identification of variants that are considered significant. Only after this initial variant filtering was the parents' DNA analyzed for variants that were present in the proband (child or fetus). Complete analysis of parental exome sequencing was not performed. Parents are made aware of this during the consent process.

Fisher's exact and Chi square tests compared proportions as appropriate. Wilcoxon rank-sum tests compared nonparametric continuous variables. A p-value of <0.05%; or 95% CI not crossing one was used to define statistical significance. Statistical analyses were performed using Stata version 15.1 (College Station, TX).

3 | RESULTS

A total of 694 families underwent exome sequencing. Of these, 605 had concordant parental preferences regarding receipt of secondary findings, 77 were analyzed as a duo with only one parent available, and in 12 cases there were discordant parental preferences. Therefore 682 families were included in the primary analyses and 12 cases were excluded. All of the families with discordant preferences were in the pediatric cohort. Table 1 displays the sociodemographic characteristics of pediatric families with concordant and discordant preferences regarding secondary findings; no significant differences emerged.

Among the families with concordant parental preferences regarding secondary findings, 42.4% (289/682) and 57.6% (393/682) underwent exome sequencing in the prenatal and pediatric settings, respectively. There were significant sociodemographic differences between the prenatal and pediatric subgroups (Table 2), with parents in the prenatal setting being younger (median maternal age 32 vs. 34 years; median paternal age 34 vs. 37 years), having higher levels of education (Bachelor's degree or higher in 43.6% of prenatal mothers vs. 17.3% of pediatric mothers and 36.3% of prenatal fathers vs. 12.4% of pediatric fathers), and more often married (64.0% prenatal vs. 49.9% pediatric). Parents in the prenatal setting were also more commonly non-Hispanic White and Asian than parents in the pediatric setting.

Overall, 84.5% (576/682) of families with concordant parental preferences or those with only one participating parent agreed to receive secondary findings. Parents in the prenatal

and pediatric settings accepted secondary findings at similar frequencies: 86.2% (249/289) and 83.2% (327/393), respectively ($p = 0.30$). Secondary findings were identified in 2.6% (15/576) of families that consented to their receipt, and this did not differ between prenatal and pediatric settings (2.8% vs. 1.8%, $p = 0.43$). Acceptance of secondary findings in the prenatal setting did not differ between those who had ongoing pregnancies at enrollment (129/155%, 83.2%) compared to those who terminated or spontaneously lost the pregnancy prior to enrollment (120/134%, 89.6%) ($p = 0.12$). Additionally, sociodemographic characteristics of families that accepted versus declined secondary findings reporting were not significantly different (Table 3).

Families in the prenatal setting were no more or less likely than those in the pediatric setting to agree to reporting of secondary findings, with an odds ratio of 1.25 (95% confidence interval 0.82–1.92). After adjusting for sociodemographic characteristics that differed among cohorts (age, race, marital status, and highest level of education), there remained no difference in preferences for secondary findings when comparing those undergoing exome sequencing in the prenatal versus pediatric setting (adjusted odds ratio 1.62, 95% CI 0.84–3.11).

4 | DISCUSSION

In this secondary analysis of data from two large prenatal and pediatric exome sequencing studies, the vast majority of families (84.5%) accepted the receipt of secondary findings, and among these, secondary findings were identified in 2.6%. The request to receive secondary findings did not differ between prenatal and pediatric settings, and there were no clear differences in sociodemographic characteristics between those that accepted secondary findings and those that did not. Furthermore, in prenatal cases, there was no difference in acceptance of secondary findings between those with ongoing pregnancies compared with those who experienced pregnancy loss or termination prior to enrollment in the study.

Our findings suggest that while providers and professional societies debate whether secondary findings should be reported in the prenatal and pediatric periods, families facing this decision largely desire this information. While this topic has not been well studied previously, particularly for prenatal populations, our findings are consistent with those reported in previous studies of exome sequencing for child probands with a suspected genetic condition (primarily in the setting of neurologic disorders, congenital anomalies, and metabolic disorders); 82%–96% of families in these studies desired reporting of secondary findings.[16,18] Another study of 13 families whose children underwent exome sequencing in the setting of a suspected genetic condition showed that families who choose to receive secondary findings felt this knowledge would give them a sense of control and help to avoid negative health outcomes.[15]

Previous studies have suggested that patients may not truly understand what is being tested for or reported when secondary findings are assessed in the setting of exome sequencing.[19,20] It is certainly possible that some of the parents in this study did not truly understand what testing was being offered or how it may (or may not) be useful. However, understanding among families undergoing prenatal exome sequencing is unlikely to be

significantly different than among those who undergo exome sequencing in the pediatric context and cannot justify the difference in guidance regarding the offer of secondary findings in the prenatal and pediatric periods.

It is also likely that the language used by genetic counselors and geneticists during the consent process impacts whether or not families choose to receive secondary findings; as such, frequency of accepting secondary findings may be different in different settings. Some providers may focus on the potential benefits of surveillance and risk management strategies that may be employed when secondary findings are identified. Others may focus on the anxiety that may arise if secondary findings are identified, the cost and potential discomfort of surveillance and management. We suspect that the counseling families receive impacts their decision making regarding secondary findings, as has been suggested with other genetic testing modalities.[21,22]

The ACMG provides recommendations regarding reporting of secondary findings and recommends that they are offered to patients undergoing clinical exome sequencing "irrespective of age but excluding fetal samples", leaving no guidance for the prenatal setting.[8] While a joint statement by the ISPD, SMFM, and PQF does not specifically recommend offering secondary findings, it does state that pre-test counseling should include information about whether secondary findings will be disclosed.[11] Our study provides important data on patient preferences for secondary findings in the prenatal setting and highlights that guidance from professional societies on secondary findings from prenatal exome sequencing is essential. This is particularly important as clinical exome sequencing becomes more commonly used in prenatal settings. While this study does not address the ethical challenges of offering and interpreting secondary findings in the prenatal period, the absence of guidance on this issue likely makes counseling even more challenging for both providers and families. Additionally, it likely contributes to variability in how patients are counseled, and may further contribute to disparities in genetic testing.

This study also contributes novel information about the acceptance of secondary findings among families undergoing exome sequencing in the setting of pregnancy loss compared to ongoing pregnancies. In the case of pregnancy loss, secondary findings would clearly not improve or change outcomes for the fetus, yet the frequency of acceptance was not different than in those with ongoing pregnancies. It may be that parents considered this as an opportunity to obtain information about their own health risks or potentially regarding the health of other family members as well. This is substantiated by other studies in which participants who chose to receive secondary findings viewed this information as having an impact on their family members.[14] Similarly, learning about secondary findings may allow parents to make different choices regarding reproduction if they plan subsequent pregnancies (e.g. preimplantation genetic testing to prevent transmission to offspring). It is worth noting that while at our institution secondary findings are only assessed in parents if present in the proband, other labs may assess for secondary findings in all members of the trio. In such situations, parental interest in learning about their own health may increase the likelihood of accepting secondary findings.

This study has several strengths. It includes a large, diverse, prospectively collected cohort of families from across the country undergoing clinical exome sequencing in exclusively prenatal and pediatric settings. It provides contemporary data regarding the interest of families in receipt of secondary findings with exome sequencing, and contributes valuable information for genetic counseling given the paucity of data on this subject. However, this study also has limitations. While this is a diverse cohort, patients referred to a tertiary care center may not be generalizable to those in other settings. Further, not all racial/ethnic groups are well represented in this study, particularly in the prenatal cohort. Prenatal participants were those who chose to undergo prenatal diagnostic testing and thus may not be generalizable to all pregnancies with fetal anomalies. Additionally, we do not have granular data on the reasons why families made different decisions regarding acceptance of secondary findings or how they used this information, though work in this area is ongoing.

Overall, this study demonstrates that the large majority of families undergoing clinical exome sequencing in prenatal and pediatric settings accept reporting of secondary findings, and the frequency of acceptance of secondary findings is comparable among prenatal and pediatric families. This information is valuable to clinicians as the use of exome sequencing increases in the clinical setting, and can inform guidance provided by professional societies regarding patient interest in secondary findings in prenatal and pediatric populations. Further research is indicated regarding reasons for families' decisions about secondary findings and how this information is utilized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICTS OF INTEREST

Ultragenyx has provided financial support for studies conducted through the UCSF Center for Maternal-Fetal Precision Medicine. Dr. Norton is a consultant to Invitae and has received research funding from Natera, but this funding was not applied to this study. The other authors declare no conflicts of interest.

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Key Points

What's already known about this topic?

- Clinically actionable secondary findings may be identified when clinical exome sequencing is performed.
- Reporting of secondary findings in the prenatal and pediatric settings is ethically challenging; the American College of Medical Genetics & Genomics recommends that this information be offered in the pediatric setting.
- There is no professional guidance and limited information about patient preferences surrounding secondary findings when exome sequencing is performed in the prenatal setting.

What does this study add?

- A majority of families undergoing exome sequencing in both the pediatric and prenatal settings request the reporting of secondary findings.
- Frequency of requesting secondary findings was similar among families undergoing prenatal and pediatric exome sequencing.
- Frequency of requesting secondary findings was similar among families undergoing prenatal exome sequencing with ongoing pregnancies and after pregnancy termination or loss.

TABLE 1

Sociodemographic characteristics of the pediatric cohort by concordance of parental preferences for receiving secondary findings

	Discordant parental preferences *N* = 12	Concordant parental preferences *N* = 330[a]	*p* value
Median maternal age at enrollment (IQR)-weeks	33.5 (30–37)	34 (28–39)	0.81
Median paternal age at enrollment (IQR)-weeks	37.5 (33–42)	37 (31–44)	0.97
Maternal race/ethnicity			0.27
American Indian/Alaska Native	1 (8.3)	2 (0.6)	
Asian	1 (8.3)	34 (10.3)	
Native Hawaiian/Pacific islander	0 (0)	4 (1.2)	
Non-hispanic Black	0 (0)	11 (3.3)	
Non-hispanic White	3 (25.0)	72 (21.8)	
Hispanic or Latina	5 (41.7)	143 (43.3)	
Unknown	1 (8.3)	41 (12.4)	
Multiracial	1 (8.3)	23 (7.0)	
Paternal race/ethnicity			0.97
American Indian/Alaska Native	0 (0)	4 (1.2)	
Asian	1 (8.3)	28 (8.5)	
Native Hawaiian/Pacific islander	0 (0)	4 (1.2)	
Non-hispanic Black	0 (0)	13 (3.9)	
Non-hispanic White	4 (33.3)	81 (24.5)	
Hispanic or Latino	5 (41.7)	133 (40.3)	
Unknown	1 (8.3)	52 (15.7)	
Multiracial	1 (8.3)	15 (4.5)	
Highest level of maternal education			0.99
Less than high school	3 (25.0)	69 (20.9)	
High school diploma or equivalent	3 (25.0)	74 (22.4)	
Some college or Associate’s degree	3 (25.0)	75 (22.7)	
Bachelor’s degree	1 (8.3)	37 (11.2)	
Professional or graduate degree	1 (8.3)	27 (8.2)	
Unknown	1 (8.3)	48 (14.5)	
Highest level of paternal education			0.17

	Discordant parental preferences *N* = 12	Concordant parental preferences *N* = 330[a]	*p* value
Less than high school	2 (16.7)	61 (18.5)	
High school diploma or equivalent	1 (8.3)	72 (21.8)	
Some college or Associate's degree	0 (0)	53 (16.1)	
Bachelor's degree	2 (16.7)	29 (8.8)	
Professional or graduate degree	0 (0)	19 (5.8)	
Unknown	7 (58.3)	96 (29.1)	
Maternal relationship status			0.32
Single	1 (8.3)	20 (6.1)	
Married	6 (50.0)	189 (57.3)	
In a relationship	2 (16.7)	66 (20.0)	
Divorced or separated	2 (16.7)	13 (3.9)	
Widowed	0 (0)	0 (0)	
Unknown	1 (8.3)	42 (12.7)	
Use of interpreter	6 (50.0)	132 (40.0)	0.49

Note: Proportions presented as N (%). Continuous variables presented as median (IQR).

Abbreviation: IQR, interquartile range.

[a]Excluding families in which duo or proband only exome sequencing was performed.

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TABLE 2

Sociodemographic characteristics by prenatal versus pediatric consent for exome sequencing

	Prenatal (*N* = 289)	Pediatric (*N* = 393)	*p* value
Median maternal age at enrollment (IQR)-weeks	32 (29–35)	34 (28–41)	0.003
Median paternal age at enrollment (IQR)-weeks	34 (31–38)	37 (31–44)	<0.001
Maternal race/ethnicity			<0.001
American Indian/Alaska Native	0 (0.0)	3 (0.8)	
Asian	43 (14.9)	37 (9.4)	
Native Hawaiian/Pacific islander	1 (0.3)	5 (1.3)	
Non-hispanic Black	6 (2.1)	17 (4.3)	
Non-hispanic White	125 (43.3)	82 (20.9)	
Hispanic or Latina	49 (16.9)	178 (45.3)	
Unknown	46 (15.9)	46 (11.7)	
Multiracial	19 (6.6)	25 (6.4)	
Paternal race/ethnicity			<0.001
American indian/Alaska Native	1 (0.3)	4 (1.0)	
Asian	41 (14.2)	29 (7.4)	
Native Hawaiian/Pacific islander	0 (0.0)	5 (1.3)	
Non-hispanic Black	7 (2.4)	21 (5.3)	
Non-hispanic White	122 (42.2)	84 (21.4)	
Hispanic or Latino	47 (16.3)	156 (39.7)	
Unknown	68 (23.5)	78 (19.8)	
Multiracial	3 (1.0)	16 (4.1)	
Highest level of maternal education			<0.001
Less than high school	5 (1.7)	90 (22.9)	
High school diploma or equivalent	24 (8.3)	89 (22.6)	
Some college or Associate’s degree	43 (14.9)	91 (23.2)	
Bachelor’s degree	65 (22.5)	41 (10.4)	
Professional or graduate degree	61 (21.1)	27 (6.9)	
Unknown	91 (31.5)	55 (14.0)	
Highest level of paternal education			<0.001
Less than high school	12 (4.2)	61 (15.5)	

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	Prenatal (*N* = 289)	Pediatric (*N* = 393)	*p* value
High school diploma or equivalent	33 (11.4)	72 (18.3)	
Some college or Associate's degree	37 (12.8)	53 (13.5)	
Bachelor's degree	61 (21.1)	30 (7.6)	
Professional or graduate degree	44 (15.2)	19 (4.8)	
Unknown	102 (35.3)	158 (40.2)	
Maternal relationship status			<0.001
Single	12 (4.2)	46 (11.7)	
Married	185 (64.0)	196 (49.9)	
In a relationship	48 (16.7)	80 (20.4)	
Divorced or separated	0 (0.0)	19 (4.8)	
Widowed	0 (0.0)	4 (1.0)	
Unknown	44 (15.2)	48 (12.2)	
Use of interpreter	27 (9.3)	155 (39.4)	<0.001

Note: Proportions presented as N (%). Continuous variables presented as median (IQR).

Abbreviation: IQR, interquartile range.

TABLE 3

Sociodemographic characteristics by acceptance of secondary findings

	Accepted secondary findings (*N* = 576)	Declined secondary findings (*N* = 106)	*p*-value
Prenatal	249 (43.2)	40 (37.7)	0.3
Median maternal age at enrollment (IQR)-weeks	33 (29–37)	34 (30–37)	0.59
Median paternal age at enrollment (IQR)-weeks	35 (31–40)	35.5 (31–39)	0.88
Maternal race/ethnicity			0.72
American Indian/Alaska Native	3 (0.5)	0 (0.0)	
Asian	64 (11.1)	16 (15.0)	
Native Hawaiian/Pacific islander	5 (0.9)	1 (0.9)	
Non-hispanic Black	22 (3.8)	1 (0.9)	
Non-hispanic White	176 (30.6)	31 (29.2)	
Hispanic or Latina	189 (32.8)	38 (35.8)	
Unknown	79 (13.7)	13 (12.2)	
Multiracial	38 (6.6)	6 (5.7)	
Paternal race/ethnicity			0.45
American Indian/Alaska Native	5 (0.9)	0 (0.0)	
Asian	56 (9.7)	14 (13.2)	
Native Hawaiian/Pacific islander	4 (0.7)	1 (0.9)	
Non-hispanic Black	27 (4.7)	1 (0.9)	
Non-hispanic White	172 (29.9)	34 (32.1)	
Hispanic or Latino	168 (29.2)	35 (33.0)	
Unknown	127 (22.0)	19 (17.9)	
Multiracial	17 (2.9)	2 (1.9)	
Highest level of maternal education			0.64
Less than high school	79 (13.7)	16 (15.1)	
High school diploma or equivalent	96 (16.7)	17 (16.0)	
Some college or Associate’s degree	115 (20.0)	19 (17.9)	
Bachelor’s degree	92 (16.0)	14 (13.2)	
Professional or graduate degree	69 (12.0)	19 (17.9)	
Unknown	125 (21.7)	21 (19.8)	
Highest level of paternal education			0.92

	Accepted secondary findings (*N* = 576)	Declined secondary findings (*N* = 106)	*p*-value
Less than high school	60 (10.4)	13 (12.2)	
High school diploma or equivalent	90 (15.6)	15 (14.2)	
Some college or Associate's degree	75 (13.0)	15 (14.2)	
Bachelor's degree	77 (13.4)	14 (13.2)	
Professional or graduate degree	51 (8.9)	12 (11.3)	
Unknown	223 (38.7)	37 (35.9)	
Maternal relationship status			0.41
Single	47 (8.2)	11 (10.4)	
Married	319 (55.4)	62 (58.5)	
In a relationship	108 (18.8)	20 (18.9)	
Divorced or separated	19 (3.3)	0 (0.0)	
Widowed	4 (0.8)	0 (0.0)	
Unknown	79 (13.7)	13 (12.2)	
Use of interpreter	152 (26.4)	30 (28.3)	0.68
Termination or stillbirth of proband[a]	120 (48.4)	14 (35.0)	0.12

Note: Proportions presented as N (%). Continuous variables presented as median (interquartile range).

Abbreviation: IQR, interquartile range.

[a]Only prenatal subjects included, *N* = 288