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Perspectives and preferences regarding genomic secondary findings in underrepresented prenatal and pediatric populations: A mixed-methods approach

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Abstract

Purpose: Patients undergoing clinical exome sequencing (ES) are routinely offered the option to receive secondary findings (SF). However, little is known about the views of individuals from underrepresented minority pediatric or prenatal populations regarding SF.

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Ethics Declaration

This study was approved by the University of California San Francisco Institutional Review Board (IRB) (Protocols, 17-22504 and 17-23118). Participants were also recruited from Zuckerberg San Francisco General Hospital and Trauma Center, UCSF Benioff Children's Hospital Oakland, and Community Medical Center of Fresno. All institutions involved in human participant research received local IRB approval or used the University of California San Francisco IRB as the IRB of record. Written informed consent was obtained from all participants as required by the IRB. Program for Pediatric and Prenatal Genomic Sequencing has been registered as a clinical trial at clinicaltrials.gov with clinical trial numbers NCT03525431 (pediatric) and NCT03482141 (prenatal).

Conflict of Interest

The first author, S.R., completed most of the work on this manuscript while being an employee of the University of California San Francisco and has since moved to a role as a full-time employee and shareholder of AllStripes Research. She has no conflicts of interest to disclose in either role. The other authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2022.02.004) contains supplementary material, which is available to authorized users.

Methods: We explored the preferences for receiving hypothetical categories of SF (H-SF) and reasons for accepting or declining actual SF through surveying (n = 149) and/or interviewing (n = 47) 190 families undergoing pediatric or prenatal ES.

Results: Underrepresented minorities made up 75% of the probands. In total, 150 families (79%) accepted SF as part of their child/fetus's ES. Most families (63%) wanted all categories of H-SF. Those who declined SF as part of ES were less likely to want H-SF across all categories. Interview findings indicate that some families did not recall their SF decision. Preparing for the future was a major motivator for accepting SF, and concerns about privacy, discrimination, and psychological effect drove decliners.

Conclusion: A notable subset of families (37%) did not want at least 1 category of H-SF, suggesting more hesitancy about receiving all available results than previously reported. The lack of recollection of SF decisions suggests a need for alternative communication approaches. Results highlight the importance of the inclusion of diverse populations in genomic research.

Keywords

Exome sequencing; Genome sequencing; Secondary findings

Introduction

Secondary findings (SF) are results unrelated to the patient's primary indication for testing identified via broad genomic testing such as genome sequencing (GS) or exome sequencing (ES). Whether, when, and how to return SF from genomic sequencing represent long-standing debates in the genetics community. Previous publications on this topic offer viewpoints from stakeholders, including patients, clinicians, and professional bodies such as the American College of Medical Genetics and Genomics (ACMG). ACMG guidelines focus on the return of SF from ES or GS in clinical settings with adult and pediatric patients. These guidelines recommend that patients undergoing ES or GS have the option to receive SF for pathogenic or likely pathogenic variants in 73 genes associated with treatable and/or preventable conditions, primarily adult-onset, autosomal dominant conditions associated with hereditary cancer risk, cardiomyopathies, and arrhythmias.[1] The guidelines do not address prenatal sequencing; however, the ACMG has recommended that parents undergoing fetal sequencing should be given the opportunity to opt out of the SF outlined in the previous ACMG guidelines, as well as incidental findings and variants in non–disease genes. In addition, several professional societies recommend informing parents about the possibility of incidental findings or SF if they choose to undergo fetal sequencing.[2,3]

Existing research exploring parents' preferences regarding the return of hypothetical categories of SF (H-SF) from broad sequencing tests for themselves and their children indicate broad interest in receiving H-SF, with the vast majority of participants (69%-97%) expressing interest in all available findings.[4–7] Studies suggest that interest in H-SF goes beyond the ACMG-recommended SF result types, including pharmacogenetics, carrier status, and variants implicated in untreatable conditions.[8–14] Uncertain and nonactionable findings have garnered less interest in previous studies.[15,16] Improving quality of life, avoiding future regret, and parental responsibility drive decisions to receive SF both

hypothetical and in clinical testing.[9,15,17] Among those declining SF, recurrent themes in previous studies included concerns about psychological effect, privacy, and (for children) future autonomy.[10,18,19] However, existing studies have typically included primarily white populations and have had limited or no representation from underrepresented minority (URM) or prenatal patient populations, leading to a lack of understanding of the viewpoints and preferences of these groups.[20]

In this study, we endeavored to address these gaps by better characterizing the viewpoints of individuals from diverse racial and ethnic backgrounds, as well as prenatal patients, regarding the return of SF from genomic sequencing.

Materials and Methods

Study design and recruitment

We conducted a mixed-methods substudy of participants enrolled in the Program for Pediatric and Prenatal Genomic Sequencing (P3EGS) to better understand the views of diverse patient populations regarding SF. P3EGS is the University of California San Francisco site of the National Institutes of Health–funded Clinical Sequencing Evidence-Generating Research consortium, the objective of which is to study the clinical utility of genomic sequencing, with an emphasis on recruiting URM participants. P3EGS prospectively enrolled participants over 4 years and offered clinical ES for pediatric participants aged 0 to 25 years with suspected genetic conditions and pregnant women with fetal anomalies. At the time they consented to participate in the study and undergo ES, families were given the option to receive SF as per ACMG guidelines.[21] Families were also counseled that they must make the same choice to accept or decline SF for all family members being sequenced as per laboratory policy. Our mixed-methods substudy of P3EGS participants assessed viewpoints regarding hypothetical and actual SF.

Demographic information was collected at enrollment, including self-reported race and ethnicity of the proband's parent(s). The proband was classified as part of a URM group if either parent identified as any race or ethnicity other than White. The proband was classified as White if both parents selected that they did not have Latinx or Hispanic ethnicity and selected White/European for race and no other race categories.

We chose a mixed-methods approach to add depth to our data and build confidence that it accurately reflects the viewpoints of populations who have been historically underrepresented in genomics research. Our mixed-methods analysis was structured using a convergent approach (collection and analyses of quantitative and qualitative data are carried out concurrently, and interpretations of the 2 sets of results are integrated). The function of our analysis was complementarity, ie, we used qualitative and quantitative methods to answer a related series of questions (about real-life SF decisions in the qualitative data and about H-SF preferences in the quantitative data). This approach allowed us to use qualitative data to provide depth of understanding and quantitative data to provide breadth.[22]

Qualitative interviews

We conducted semistructured in-depth interviews with families selected via purposeful sampling to maximize representation across types of ES results, racial and ethnic groups, and primary language spoken. Interview guides were developed with questions probing participants' thought processes surrounding decisions to accept or decline SF and experiences receiving results. We conducted interviews through telephone, video conference, or in-person (before the COVID-19 pandemic) in English or Spanish. We interviewed families within 2 weeks of receiving ES results and again 6 to 7 months later. Interviews were audio-recorded, transcribed, and, when applicable, translated from Spanish to English. Transcripts were uploaded to the qualitative data analysis software Dedoose version 8.3.35 (SocioCultural Research Consultants).

An initial coding framework was developed using concepts derived from the interview guide and inductive codes derived from transcript review. Team members coded transcripts independently and then discussed them as a team to resolve discrepancies. Regular team meetings were held to adjust the coding framework, address inconsistencies in code applications, and develop themes.

Quantitative surveys

We drew on a validated measure by Fernandez et al[23] to develop an 11-item survey assessing participants' preferences for receiving categories of H-SF for themselves or their child/fetus. Participants indicated on a 4-point Likert scale the likelihood that they would want to receive H-SF stratified by factors including actionability, age of condition onset, the certainty of pathogenicity, and whether the result was for themselves or their child/fetus. The survey was pretested in the clinic, modified for clarity, and translated from English to Spanish. It was administered to participants 5 to 7 months after receiving ES results via email, mail, or telephone.

Statistical analysis

We calculated summary statistics for demographic characteristics of participating families. We then used χ^2 test or Fischer exact test (depending on the sample size) to assess whether these categories were associated with differences in preferences for receiving SF and H-SF. Findings were considered statistically significant at $P<.05$. All statistical analyses were performed using Stata 16 (StataCorp LLC).

Additional detail regarding materials and methods is available in Supplemental Methods and Materials.

Results

Participants

As of October 1, 2020, 734 families were enrolled in the P3EGS study, including 460 (63%) in the pediatric arm of the study and 274 (37%) in the prenatal arm. A total of 415 families were eligible to be surveyed or interviewed. Of these, 262 families received the H-SF survey and 149 (56.9%) completed it. We invited 81 families to be interviewed and 47 (58.0%)

completed at least 1 interview (including 6 families who also completed the survey) (Figure 1). In total, 54 families (28%) received positive ES results, 26 (14%) received inconclusive results, and 110 (58%) received negative results. Families who accepted SF as part of their child/fetus' ES comprised 79% (n = 150) of the cohort, with the remaining 40 (21%) families declining SF. In total, 7 families (4.6%) who accepted SF as part of ES received positive SF, including 5 pediatric and 2 prenatal families.

Demographic characteristics

Of the 190 families who completed the questionnaire and/or at least 1 interview, 140 (74%) were enrolled through the pediatric arm of the study and 50 (26%) through the prenatal arm. Prenatal participants comprised a lower percentage of substudy participants than the overall study population because of variance in the timing of onset of survey administration between pediatric and prenatal clinics. Of these 190 families who participated in the substudy, 143 (75%) were classified as URM, with Latinx/Hispanic being the most common subgroup (74/190, 39%) (Table 1). Participants were consented in 6 different languages and 46 families (24%) were consented in a language other than English.

Main themes

Interest in learning SF—Participants expressed interest in learning about SF, with 79% of the families accepting SF as part of their child/fetus's ES. No statistically significant differences were observed between pediatric and prenatal families' acceptance rates or between URM and White families (Table 2).

When surveyed about receiving categories of H-SF for themselves and/or their child, most families (94/149; 63%) said "definitely yes" or "maybe yes" to receiving all categories. There were no statistically significant differences between URM and White or pediatric and prenatal families in terms of declining at least 1 category of H-SF. However, there were significant differences between these groups in responses to individual categories of H-SF. For example, URM families were significantly less likely to respond "definitely yes" or "maybe yes" to accepting H-SF for themselves in the adult-onset actionable category (81% vs 95%, P = .04). Overall, participants were most likely to respond "maybe yes" or "definitely yes" to accepting childhood-onset actionable findings (134 of 149 [90%]) compared with other categories of H-SF.

Interviewed participants, particularly parents of pediatric participants, described several different motivations for accepting SF as part of their child's ES. Broadly, these themes revolved around the desire for maximal information and the ability to prepare for the future through early intervention or psychological preparation.

> Interviewer: Was that a difficult decision [to accept SF]?
>
> Mother: No, not for me. Because I'm a proactive person. I'd rather know and be able to know what to expect and how to deal with it than to wait and wonder what might come up. I'd rather know ahead of time and try and be proactive about something that is more likely than not to happen versus… To me, there's no upside to not knowing. I'm not a bury your head in the sand kind of person.

—FAM235, pediatric, positive primary result, negative for SF

Concerns about privacy, discrimination, and psychological distress—Although most participants accepted SF as part of their child/fetus's ES, 21% declined. Of 149 survey respondents, 55 (36.9%) responded "definitely no" or "maybe no" to receiving at least 1 category of H-SF. Participants who declined SF as part of ES often cited the psychological burden of knowing and fear of loss of privacy or discrimination.

> Father: Yes, we preferred not to accept it [SF] because we are going through a very serious situation, it's a very hard time and for the time being it's enough for us. That's why we decided…
>
> Mother: Not to increase our concerns.
>
> Father: On the contrary, we wanted them to tell us something… for example, when they told us that they couldn't find the brain and that she didn't have a brain, then it resulted that she did have it and that she only had a cyst there. That's the type of things you want to hear. Who wants to hear, "Oh, you're going to die on that date," or things like that?

—FAM230, prenatal, positive primary result, declined SF

In some cases, parents learned about potential risks related to accepting SF at their consent visit, and this information directly influenced their decision to accept or decline SF.

The challenge of uncertainty—Compared with other H-SF categories, surveyed participants were least likely to express interest (by responding "maybe yes" or "definitely yes") in receiving H-SF about uncertain results (variants of uncertain significance) in themselves (107/149; 71.8%) or their child (116/149; 77.9%) (Table 3). Prenatal families were significantly less likely than pediatric families to express interest in accepting uncertain H-SF results for their child/fetus (63% vs 83%, respectively, $P = .01$).

Interviewed participants were not asked directly about their feelings regarding uncertain H-SF but did discuss their concerns about uncertainty more broadly. Following is an example of a mother describing uncertainty as the primary stress of receiving an inconclusive result:

> And they were unable to give me a diagnosis. It's frustrating and stressing because you can think he could have something worse. Also knowing what he has for example, if they had told me, "He has Down Syndrome," you know what the picture is like and you have more information about what to expect in the future. But if you don't know, the uncertainty is terrible and honestly, I don't like that.

—FAM 224, pediatric, inconclusive primary result, negative for SF

Confusion, discordance, and not remembering—One of the most striking themes identified in interviews is that of participants not remembering the discussion of SF at any point in their study participation. Of those who did recall discussing the option of SF, many

misunderstood or misremembered who would be tested for SF and who would get a test report, did not know what types of results could be reported, conflated SF with primary findings, or confused the decision they made about SF with other choices made at consent (such as the choice to share data for research). In addition, a subset of participants reported declining SF as part of ES, when in fact, they had accepted SF or believed that they had accepted SF for their child but not themselves (participants were required to decide to accept or decline SF for the whole family).

Some interviewees, particularly prenatal participants, reported no recollection of any discussion of SF as part of their consent or results discussions. Other families—both prenatal and pediatric—reported remembering the conversation but recalled few details. For example, following is a mother describing her divided attention during the study enrollment session—a situation encountered frequently in pediatric genetics clinics:

> Interviewer: …can you tell me what else you remember about that explanation [of SF given by the clinician]?
>
> Mother: I only remember that they gave me the option to participate in what you mentioned about one of us having some kind of cancer or other type of illness, but that's all I can recall, because my daughter was very restless, she didn't want to be there anymore.
>
> —FAM085, pediatric, inconclusive primary result, declined SF

Despite families receiving pre-enrollment genetic counseling advising that parents would not receive separate test reports, parents frequently expressed confusion or uncertainty about whether they would receive their own test results and sometimes frustration at having not received such results. Some parents expressed concern about receiving SF types that were not offered as part of their child/fetus's ES. For example, 1 family mistakenly believed that they could learn about Alzheimer's disease risk by accepting SF:

> I think afterwards we thought about the implications. We didn't necessarily think about them all in the moment, but we did understand that you could find out if you have a cancer risk or an Alzheimer's risk or some other thing that could be a preexisting condition. I don't think in the conversation itself we necessarily said do we actually – you know, what does this come back to? You know, what does that mean and how do we react to it? - that part is, you know, it took some time to kind of process that and think that through and get to that stage of conversation.
>
> —FAM260, prenatal, positive primary result, negative SF

The conceptual complexity and context-dependent nature of decision-making surrounding SF was echoed in our quantitative data, in particular by the discordance between families' responses to survey questions about H-SF and choices in real life (informed by genetic counseling) to accept or decline SF as part of their child/fetus's ES. Our H-SF survey included 2 questions about participants' willingness to receive SF for adult-onset actionable conditions, which align closely with the ACMG-recommended SF they were offered as part of their child/fetus's ES.[15] Of the 31 survey respondents who declined SF as part of ES, 21

(67.7%) responded “definitely yes” or “maybe yes” to the first of these questions, Question 1 (Q1) (regarding adult-onset actionable findings for themselves—see supplemental file entitled H-SF Survey), and 22 (71.0%) responded affirmatively to the second, Q7 (regarding adult-onset actionable findings for their child). Similarly, of the 108 families who accepted SF, 11 (10.2%) responded “definitely no” or “maybe no” to Q1 and 12 (11.1%) to Q7.

Discussion

Our mixed-methods approach to investigate SF viewpoints in diverse pediatric and prenatal populations suggests general interest in receiving SF and H-SF. However, it reveals a notable minority who prefer not to receive some or all types of SF or H-SF. In addition, many families were confused about SF or did not recall discussing them, suggesting that families who indicate interest in receiving SF may not fully understand the decision (Table 4).

The limited previous studies describing SF acceptance for patients undergoing genomic sequencing have reported acceptance rates between 69% and 97%—similar to the rate of acceptance for SF as part of ES in our study (79%). The reasons our interviewed participants cited for accepting SF are also similar to those described in previous studies, including the desire to prepare psychologically should a health risk exist.[4,7,9,17] These real-life acceptance rates are also similar to those of survey respondents in previous studies who, when asked about a range of H-SF, had expressed a desire to receive all available H-SF (66-87%).[8,10,12] Rini et al[15] found lower acceptance rates for all available findings, likely because they only asked about nonactionable findings.

Respondents to our H-SF survey, however, were less likely to accept all categories of findings (63%) than what has been previously reported. In addition, although we did not observe a statistically significant difference between URM and White families regarding SF acceptance as part of ES, URM families were significantly less likely to accept 1 specific category of H-SF—adult-onset actionable findings. These findings are likely related to interview findings that participants who either declined SF or expressed reservations cited concerns about privacy, risk of discrimination with regard to life insurance or future opportunities more broadly, and potential psychological effect, echoing the findings in previous studies.[10,18,19]

Literature on the views of URM patients regarding SF or H-SF is sparse because studies on this subject have primarily included White/European participants. However, there are limited previous studies that identified more reticence to accepting SF or H-SF in URM populations, including the finding by Fiallos et al[24] that accepting SF was associated with self-reported European ancestry (although this difference resolved when patients were consented by a genetic counselor). The literature does offer additional context for our findings in the form of studies exploring views, knowledge, and uptake of genetic testing more broadly among URM patients. Such studies suggest that patients who self-identify as part of URM groups may be more wary of genetic testing and have higher levels of medical mistrust and lower levels of awareness of knowledge about genetic testing, all of which may correlate with decreased uptake of genetic testing.[25–27] Recent literature also suggests that genetic literacy correlates with more positive attitudes toward genetic testing.[28,29] As

studies suggest lower health literacy in general and lower genetic literacy may be more common in URM populations, these factors may have played a role in our results.[30–32] This underscores the need for further exploration of the relationship between genetic literacy and attitudes toward SF in particular, as well as increased access to culturally-appropriate genetics educational resources for diverse populations.

Additional prevalent themes in our study include misunderstanding or misremembering, lack of recollection of discussing SF, and discordance between families' decision to accept or decline SF in real life and choices they made regarding similar categories of H-SF in the survey. Interviewed participants frequently misunderstood interviewers' questions about their decision to accept or decline SF (despite the question being asked in multiple ways), often conflating SF and primary findings or confusing the decision they made regarding SF and other decisions they made as part of research participation, echoing the findings of Sapp et al[33] that a substantial minority of participants confused primary findings and SF. In addition, some interviewed participants—particularly prenatal families—had no recollection of learning about SF, suggesting a potential effect of the increased stress of the prenatal setting.

We observed notable discordance between families' choices to accept or decline SF as part of their child/fetus's ES and responses to survey questions regarding similar categories of H-SF. Many factors could explain discordance other than confusion, including the possibility that views shifted over time or that different contexts—such as an in-person decision about SF made in discussion with a genetic counselor vs a written survey administered at home—affected decision-making. Another possibility is that the parent responding to the survey was not the same parent driving the decision to accept SF as part of their child/fetus's testing. In addition, language barriers and the use of interpreters may have played a role. However, given prior evidence of confusion surrounding SF in our qualitative data and previous studies, it seems probable that confusion may explain at least some of this discordance.[34] The extent of the confusion or complete lack of recollection of discussing SF in our cohort suggests that further exploration is necessary to better characterize patient understanding of SF and to develop more effective communication approaches.[34–36]

Although interviewed participants were not directly asked about their feelings regarding uncertain H-SF, their views on uncertain genomic findings more broadly, including uncertain primary ES findings, are relevant. Broad genetic testing such as ES raises many opportunities for uncertainty, which was reflected in interviewees' experiences, including those of receiving inconclusive results, diagnoses of poorly described conditions, and negative results prolonging uncertainty. Interviewees' descriptions of uncertainty support a hypothesis that parents may be more reticent to accept uncertain H-SF in anticipation of adding to the concern, frustration, and anxiety that has already been part of their lived experience. Stress and anxiety caused by uncertain results may be heightened in a prenatal context, in which families have minimal time to process ultrasound abnormalities, outcomes are variable, and some families face difficult decisions about pregnancy termination. In keeping with this hypothesis, surveyed prenatal families were significantly less likely to respond affirmatively to receiving uncertain (variants of uncertain significance) SF in their fetus than pediatric families were for their child.

Our study had several limitations. Although diverse, some groups were not well-represented in our cohort, including Black or African-American participants. In addition, there are limits to the comparisons that can be made between our study and previous studies on this topic because differences in which SF or H-SF are offered and how they are categorized may affect responses. The framing of survey and interview questions and the amount of detail provided may also influence participant preferences.[12] We were unable to identify which parent/guardian responded to survey questions and therefore could not determine whether mothers were overrepresented in our responses, as we have observed in prior literature.[11,13,37–39] In addition, our sample size presented limitations—it may have limited our ability to detect statistically significant results, we likely had low power to compare URM and White groups, and we were unable to examine heterogeneity within URM categories owing to sample size.

In conclusion, although this study and previous studies showed broad interest in receiving SF, our survey respondents indicated more hesitation to receiving all available categories of H-SF than what has been previously described and also showed statistically significant differences in acceptance rates between groups for specific categories of H-SF, suggesting a potential benefit to a more customizable approach to SF. In addition, our findings suggest that patients may misremember decisions surrounding SF or have uncertainty or confusion about their options. Further study of the views of diverse populations regarding SF, as well as exploration of alternative approaches to offering and communicating about SF, could inform the development of policies surrounding SF and lead to improved patient autonomy and more informed decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Data are available upon request.

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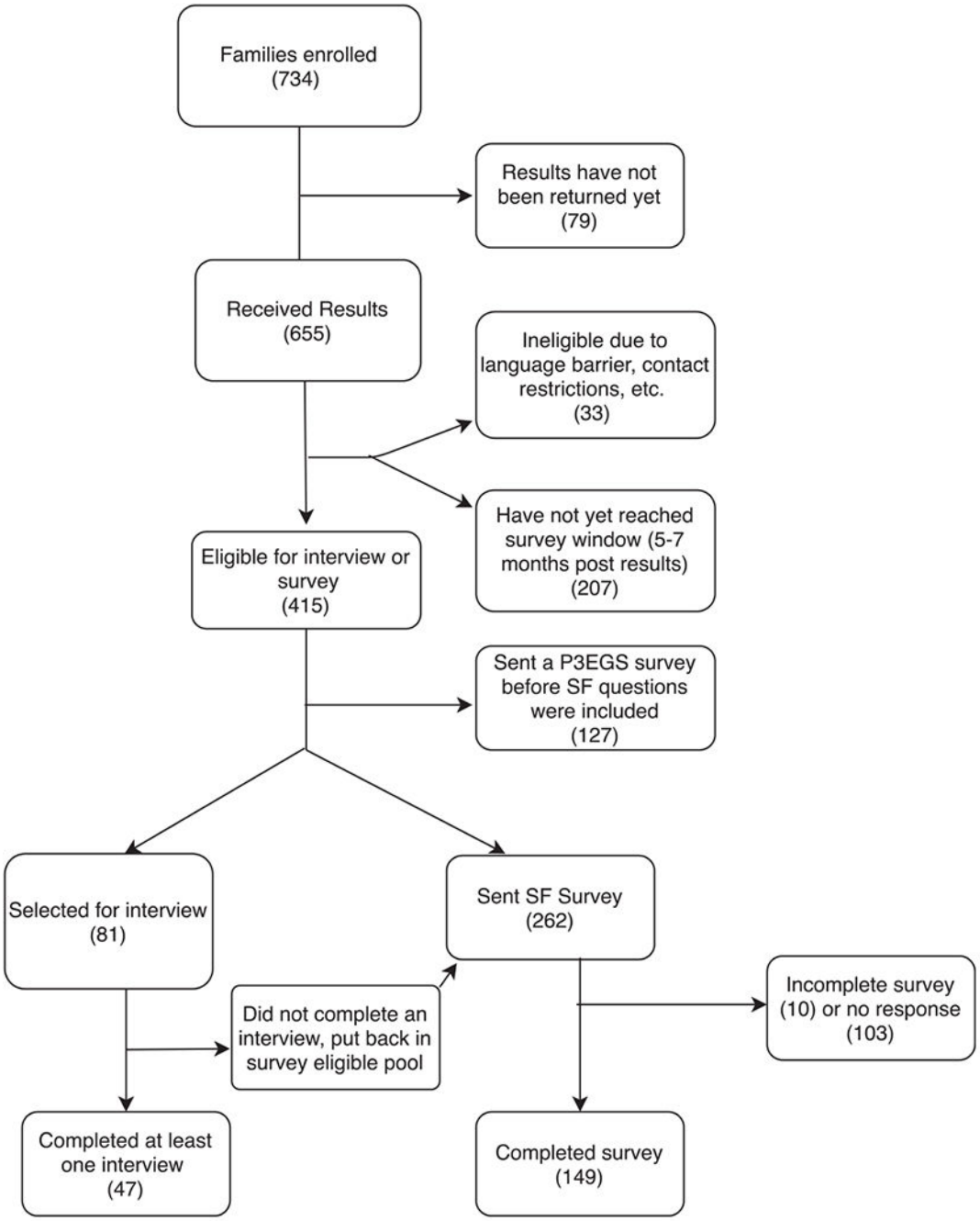

Figure 1. Study participation process flow diagram.

P3EGS, Program for Pediatric and Prenatal Genomic Sequencing; SF, secondary findings.

Table 1

Demographic characteristics of participating families

Demographics of Participating Families	Total[a] (*N* = 190)	Percentage of Total Families	Interviewed Families (*n* = 47)	Percentage of Interviewed Families	Surveyed Families (*n* = 149)	Percentage of Surveyed Families
Pediatric families	140	73.7	32	68.1	111	74.5
Prenatal families	50	26.3	15	31.9	38	25.5
URM	143	75.3	40	85.1	107	71.8
Native American/American Indian/Native Alaskan	2	1.1	0	0.0	2	1.3
Black/African-American	6	3.2	2	4.3	5	3.4
Latinx/Hispanic	74	38.9	21	44.7	53	35.6
Middle Eastern/North African	7	3.7	2	4.3	5	3.4
Asian	15	7.9	4	8.5	12	8.1
More than 1 race/ethnicity	39	20.5	11	23.4	30	20.1
White	47	24.7	7	14.9	43	28.9
Accepted SF as part of ES	150	78.9	37	78.7	118	79.2
Declined SF as part of ES	40	21.1	10	21.3	31	20.8
Positive ES results	54	28.4	22	46.8	34	22.8
Inconclusive ES results	26	13.7	11	23.4	15	10.1
Negative ES results	110	57.9	14	29.8	100	67.1

ES, exome sequencing; *SF*, secondary findings; *URM*, underrepresented minority.

[a]The total includes 6 families who completed both surveys and interviews. These include 3 pediatric and 3 prenatal families, who are also included in the respective columns for interviewed and surveyed families.

Table 2

SF acceptance

Population (*n*)	Accepted SF *n* (%)	Declined SF *n* (%)	*P* value[a]
Pediatric (*n* = 140)	112 (80)	28 (20)	.55
Prenatal (*n* = 50)	38 (76)	12 (24)	
URM (*n* = 143)	113 (79)	30 (21)	.96
White (*n* = 47)	37 (79)	10 (21)	

SF, secondary findings; *URM*, underrepresented minority.

[a] *P* value from χ^2 test.

Table 3

H-SF preference survey responses (n = 149)

Result recipient	Type of SF	Definitely or Maybe Yes[a] Overall, *n* (%)	Definitely or Maybe Yes[a] URM, *n* (%)	Definitely or Maybe Yes[a] White, *n* (%)	Definitely or Maybe No[a] Overall, *n* (%)	Definitely or Maybe No[a] URM, *n* (%)	Definitely or Maybe No[a] White, *n* (%)
Genetic changes in you	Genetic changes that could cause you to have a serious medical condition that can be treated or prevented. For example, cancer or heart problems.	127 (85.2)	87 (81.3)	40 (95.2)	22 (14.8)	20 (18.7)	2 (4.8)
	Genetic changes that could cause you to have a serious medical condition that cannot be prevented or treated. For example, Alzheimer disease.	117 (78.5)	83 (77.6)	34 (81.0)	32 (21.5)	24 (22.4)	8 (19.0)
	Genetic changes that the laboratory does not have enough information about to know if they cause medical conditions.	107 (71.8)	78 (72.9)	29 (69.0)	42 (28.2)	29 (27.1)	13 (31.0)
	Genetic changes that will not cause a medical condition in you but could cause one in future children. For example, being a carrier for a condition such as cystic fibrosis or sickle cell disease.	124 (83.2)	85 (79.4)	39 (92.9)	25 (16.8)	22 (20.6)	3 (7.1)
Genetic changes in your child/fetus	Genetic changes that could cause your child to have a serious medical condition while they are still young. The medical condition can be treated or prevented. For example, childhood cancer or heart problems.	134 (89.9)	93 (86.9)	41 (97.6)	15 (10.1)	14 (13.1)	1 (2.4)
	Genetic changes that could cause your child to have a serious medical condition while they are still young. The medical condition cannot be treated or prevented. For example, juvenile Parkinson disease.	125 (83.9)	86 (80.4)	39 (92.9)	24 (16.1)	21 (19.6)	3 (7.1)
	Genetic changes that could cause your child to have a serious medical condition when they grow up. The medical condition can be treated or prevented. For example, cancer or heart problems that happen in adulthood.	128 (85.9)	89 (83.2)	39 (92.9)	21 (14.1)	18 (16.8)	3 (7.1)
	Genetic changes that could cause your child to have a serious medical condition when they grow up. The medical condition cannot be treated or prevented. For example, Alzheimer disease.	122 (81.9)	86 (80.4)	36 (85.7)	27 (18.1)	21 (19.6)	6 (14.3)
	Genetic changes that could cause a mild health condition in your child.	122 (81.9)	87 (81.3)	35 (83.3)	27 (18.1)	20 (18.7)	7 (16.7)
	Genetic changes in your child that the laboratory does not have enough information about to know whether they cause medical conditions.	116 (77.9)	85 (79.4)	31 (73.8)	33 (22.1)	22 (20.6)	11 (26.2)
	Genetic changes in your child that will not cause medical conditions in your child but could cause one in their future children. For example, being a carrier for a condition such as cystic fibrosis or sickle cell disease.	120 (80.5)	84 (78.5)	36 (85.7)	29 (19.5)	23 (21.5)	6 (14.3)

H-SF, hypothetical categories of secondary findings; *SF*, secondary findings; *URM*, underrepresented minority.

[a]Survey responses indicating interest in receiving H-SF. "Definitely yes" and "maybe yes" categories were combined as were "definitely no" and "maybe no" categories.

Table 4

Major themes: Mixed-methods presentation

Major Themes	Quantitative	Qualitative	Interpretation
Qualified interest in receiving SF	• Of the 190 families, 150 accepted SF as part of their child/fetus's ES. • Most survey respondents (94/149, 63%) said "maybe yes" or "definitely yes" to receiving all categories of H-SF.	• Participants who accepted SF as part of ES described motivations, which included the following: ○ The desire for as much information as possible ○ The desire to prepare for the future, both psychologically and through early intervention.	• Qualitative and quantitative findings suggest that participants are interested in receiving SF, with qualitative findings adding depth of understanding around motivations such as desire to be proactive and receive as much information as possible.
Less desire for uncertain results	• Survey respondents were more likely to say "maybe no" or "definitely no" to uncertain (VUS) results in themselves (42/149, 28%) and their child (33/149, 22%) than any other categories of H-SF.	• Uncertain SF were not explicitly discussed in interviews, but uncertainty still factored heavily into interviews in other contexts, such as inconclusive primary results. Major themes surrounding uncertain results include stress and anxiety.	• Qualitative and quantitative findings suggest that uncertainty is a driving factor in decisions to decline SF, both in real life and hypothetically.
Concerns about receiving SF	• Of the 190 families, 40 (21%) declined SF as part of their child/fetus's ES. • Of the 149 families surveyed, 55 (37%) declined at least 1 category of H-SF.	• Participants who declined SF as part of ES described motivations, which included the following: ○ Psychological burden of knowing about a risk for a future illness ○ Concerns about insurance discrimination or a limiting of future opportunity.	• Although there was general interest in SF as suggested by qualitative and quantitative data, more participants declined at least 1 category of H-SF than previously reported, potentially because of the concerns interview participants reported about SF, including psychological burden and fear of discrimination.
Confusion about SF and/or context-specific decisions	• Discordance between parents' choices to receive SF as part of their child/fetus's ES and their survey responses regarding categories of H-SF similar to the ACMG 59™[a] ○ Most of the 31 survey respondents who declined SF as part of their child/fetus's ES said "maybe yes" or "definitely yes" to receiving H-SF related to adult-onset actionable conditions for themselves (22/31, 71%) and/or their child (21/31, 68%). ○ Of the 108 survey respondents who accepted SF as part of their child/fetus's ES, 11 (10%) said "maybe no" or "definitely no" to receiving H-SF related to adult-onset actionable conditions for themselves and 12 (11%) said "maybe no" or "definitely no" to receiving H-SF related to adult-onset actionable conditions for their child.	• Parents often did not recall discussing SF at consent or return of results. • Confusion about who was tested for what was common. • Confusion about what is included in SF was common. • Some parents misremembered whether they had consented to SF. • Parents expected to get their own report.	• Confusion and misremembering related to SF expressed during interviews were supported by quantitative data showing counterintuitive responses to survey questions on the basis of parents' real-life choices to accept or decline SF.

ACMG, American College of Medical Genetics and Genomics; *H-SF*, hypothetical categories of SF; *SF*, secondary findings; *URM*, underrepresented minority; *VUS*, variant of uncertain significance.

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