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Journal

American Journal of Human Genetics, 107(5)

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Publication Date

2020-11-05

DOI

10.1016/j.ajhg.2020.10.004

Peer reviewed

A Prospective Study of Parental Perceptions of Rapid Whole-Genome and -Exome Sequencing among Seriously Ill Infants

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Summary

Rapid diagnostic genomic sequencing recently became feasible for infants in intensive care units (ICUs). However, research regarding parents' perceived utility, adequacy of consent, and potential harms and benefits is lacking. Herein we report results of parental surveys of these domains from the second Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT2) study, a randomized, controlled trial of rapid diagnostic genomic sequencing of infants in regional ICUs. More than 90% of parents reported feeling adequately informed to consent to diagnostic genomic sequencing. Despite only 23% (27) of 117 infants receiving genomic diagnoses, 97% (156) of 161 parents reported that testing was at least somewhat useful and 50.3% (88/161) reported no decisional regret (median 0, mean 10, range 0–100). Five of 117 families (4.3%) reported harm. Upon follow-up, one (1%) confirmed harm to child and parent related to negative results/no diagnosis, two (2%) reported stress or confusion, and two (2%) denied harm. In 81% (89) of 111 infants, families and clinicians agreed that genomic results were useful. Of the families for whom clinicians perceived harm from genomic testing, no parents reported harm. Positive tests/genomic diagnosis were more frequently perceived to be useful by parents, to benefit their infant, and to help manage potential symptoms ($p < .05$). In summary, the large majority of parents felt that first-tier, rapid, diagnostic genomic sequencing was beneficial for infants lacking etiologic diagnoses in ICUs. Most parents in this study perceived being adequately informed to consent, understood their child's results, and denied regret or harm from undergoing sequencing.

Introduction

It has been estimated that approximately 9%–16% of infants admitted to regional ICUs in the United States have a genetic disease.[1,2] Previously, we reported results from NSIGHT2 (ClinicalTrials.gov: NCT03211039) related to the analytic and diagnostic performance of singleton and trio rapid whole-exome sequencing (rWES), rapid whole-genome sequencing (rWGS), and ultra-rapid whole-genome sequencing (urWGS).[2] The accompanying article to this paper reports clinician perceptions of clinical utility, resultant changes in care and outcomes, and the safety or potential harms of testing.[3] However, it is essential to understand perceived benefit and harm from the parent perspective.[2,4–9] Prior research regarding parental perceptions of diagnostic genomic sequencing has focused on either hypothetical scenarios, older children suspected of a genetic condition and/or rare disease, and has only recently begun to include parents of acutely ill children and newborns.[10–14] Therefore, this study sought to build on prior work available at the launch of this study to assess perceived utility, harms, and benefits as reported by parents of acutely ill newborns who received diagnostic genomic sequencing.[13,15–18] We were able to then directly compare the perceptions of parents with those of their infants' medical providers. In addition to assessing perceived utility, benefits, and harms of genomic testing, this study also assessed the adequacy of informed consent for symptom-driven genomic testing in the ICU setting, as well as decisional regret.

Subjects and Methods

Subjects and Study Design

NSIGHT2 was a prospective, randomized, controlled, blinded trial in infants recruited from the NICU (67%; 143/213), PICU (5%; 11/213), and CVICU (27%; 57/213) at Rady Children's Hospital, San Diego (RCHSD) that compared rWGS and rWES, with analysis as singleton probands and reflex to familial trios (ClinicalTrials.gov: NCT03211039, Figure S1).[2] NSIGHT2 was approved by the local institutional review board, was designated non-significant risk by the Food and Drug Administration, and was performed in accordance with the Declaration of Helsinki. From June 2017 to October 2018, eligible ICU patients were identified by daily census review. Other inpatient infants were nominated by their physicians. Informed consent was obtained by research nurses from at least one parent or guardian. The inclusion criteria were age <4 months and <96 h elapsed since admission or development of a new feature that changed the differential diagnosis to include a genetic condition.[2] Infants with a previously confirmed genetic diagnosis or clinical presentation of isolated prematurity, transient

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https://doi.org/10.1016/j.ajhg.2020.10.004.

tachypnea of the newborn, isolated unconjugated hyperbilirubinemia, sepsis with a normal response to therapy, or hypoxic ischemic encephalopathy with a clear precipitating event were excluded.[2] Infants who were gravely ill with presentations that included differential diagnoses with a potential change in management were excluded from randomization and received urWGS, with fastest possible time to diagnosis.[2] All other infants were randomized to receive either rWES or rWGS.[2]

Rapid Whole-Genome and -Exome Sequencing, Analysis, and Interpretation

Clinical urWGS, rWGS, and rWES methods used in NSIGHT2 have been published in detail.[2] In brief, experts selected clinical features representative of each child's illness from the Electronic Health Record (EHR).[2] Provisional genomic diagnoses for which specific treatments had potential to prevent morbidity or mortality were immediately conveyed to the clinical team.[2] All causative variants were confirmed by Sanger sequencing, multiplex ligation-dependent probe amplification, or chromosomal microarray, as appropriate.[2] Secondary findings (genomic results sought out by the laboratory due to being known disease-causing variants regardless of symptomology) were not reported, but medically actionable incidental findings (genomic results related to the presenting symptoms but not believed to be causing the current disease state) were reported if families consented to receiving this information.[2]

Parent Surveys and Data Collection

Parents of enrolled infants were asked to take brief surveys (5–10 min) immediately following enrollment and within a week of the return of genomic results. Surveys were administered by email, phone, or in-person. We did not require parents to complete surveys in order to participate in NSIGHT2. Data were collected in REDCap.[19,20] The newborn's race and ethnicity were extracted from the EHR. As part of the survey, parents self-reported educational attainment, primary spoken language, and relationship to the infant/proband. Primary language spoken was categorized as English, Spanish, bilingual, and other. Educational attainment categories were: "Up to a high school degree" (completed 11 or fewer years or graduated from high school or GED completed), "Up to a four year degree" (graduated from 2-year college or graduated from 4-year college), and "Up to graduate degree" (completed some post-college education, completed master's degree, or completed professional or PhD). For analysis of the 1-week post-results survey, it was necessary to use demographic descriptors at the level of the household, and thus, we used the following approach to identify these descriptors when both parents responded to the survey. The highest educational attainment of individual parents in the enrollment survey was used to represent the household in the 1-week post-results surveys. Likewise, the primary spoken language was categorized as bilingual in 1-week post-results survey analyses in households where more than one language was reported by the parents at enrollment. Where there were discrepancies between parental responses in a household on survey items describing response to sequencing, we used the lower (more negative toward sequencing) response for categorical variables and the mean for analysis of continuous variables. Since none of the parents of the three families who received incidental findings responded to the 1-week post-results survey, type of test results was limited to either positive (receipt of a symptom-driven genomic diagnosis) or negative (no symptom-driven genomic diagnosis) results.

A total of 13 5-point Likert questions and 2 free-text questions were used to assess adequacy of consent, harms, and benefits. Perceived adequacy of information provided in the informed consent process was assessed with an item from the Holmes-Rovner measure, Patient Satisfaction with Health Care Decisions.[18] The perceived utility and benefits of genomic sequencing were assessed by questions adapted from Cacioppo et al. regarding utility of genetic research results in pediatric rare disease research.[13] Decisional regret was assessed using Brehaut's scale with additional questions added to address surrogate decision makers and benefits of testing.[17] Families who responded that they did not feel that enough information was provided in the informed consent process or who perceived that genomic sequencing was associated with harms after the return of genomic results were followed up and re-contacted by research nurses to offer additional information and resources.

The full methods and results of surveys administered to clinicians 1 week after results are reported in the accompanying manuscript.[3] Herein we endeavored to assess the degree of consistency between parents' perceived utility and clinicians' perceptions of clinical utility; however, the scales and items used to assess perceived utility of the sequencing were different for parents (three possible responses) and clinicians (five possible responses). Thus, in the analyses herein, to compare clinicians' and families' perceptions of genomic test results, parent responses were collapsed from a 3-point Likert scale to two responses—useful (useful or somewhat) and not useful (not useful)—and clinician responses were collapsed from a 5-point Likert scale to two responses—useful (very useful or useful) and not useful (neutral, not very useful, or not useful at all). When more than one clinician responded for a newborn, the lower (more negative toward sequencing) response was used.

Statistical Methods

Rates were compared between groups with Fisher's exact or the χ^2 test as appropriate. Multiple logistic regression was used to evaluate potential variables associated with decisional regret. Odds ratios and 95% confidence intervals are reported. A significance cutoff of $\alpha < 0.05$ was used for all analyses. Analyses were conducted in Microsoft Excel or R v3.6.2.[21]

Results

Survey Respondent Demographics

The NSIGHT2 enrollment survey was completed by 312 parents of 83% (176) of 213 enrolled infants (Figure 1; Table S1). Of the parent respondents, 84% (262) completed the survey independently on paper and 2% (7) were completed with staff present. Of parent respondents, 46% (142) were fathers, 39% (120) self-reported as Hispanic, and 41% (129) as non-Hispanic white (Figure 1; Table S1). 74% (230) of enrollment survey respondents reported English and 20% (61) Spanish as their primary spoken language. 46% (142) reported educational attainment up to a high school degree or equivalent and 26% (82) some post-college education (Table S1). The median age of infants of enrollment survey respondents was 4 days at time of enrollment (range 1–121 days). The infants of 42% (132) of parents who completed the enrollment survey were

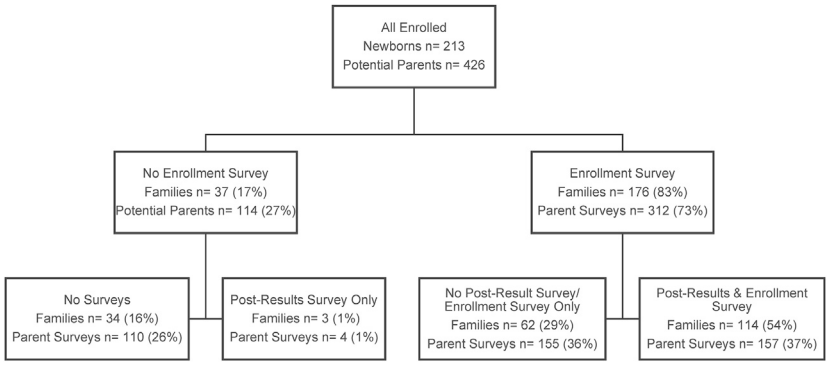

Figure 1. Survey Response Rates at Study Time Points for Parents and Families

randomized to rWGS and 46% (142) to rWES.[2] 12% (38) were not randomized and received urWGS (Table S1).[2]

The 1-week post-results survey was completed by 161 parents of 55% (117 of 213 enrolled) infants (Figure 1; Table 1). Of the parent respondents, 82% (132) completed the survey independently either on paper (31%; 50) or via email (34%; 55), and 4% (7) were completed with staff present: 0.6% (1) with an interpreter and 4% (6) either on paper or via telephone with research staff. Among these, median time to result (10 days, range 1–49 days), and proportion of infants receiving diagnoses (23%) did not significantly differ from all 213 enrollees (Table 1). Race/ethnicity differed between respondents and non-respondents at 1 week post results ($p = 0.001$) but not between enrolled infants and respondents at enrollment, nor between respondents at enrollment and respondents at 1 week post results (Table S1). There were not significant differences in household race/ethnicity, spoken language, educational attainment, and median age of infants at enrollment between the three study arms: rWGS, rWES, and urWGS.

Parental Survey Responses

91% of parents reported perceiving that they received adequate information at consent (284 of 312 at enrollment [data not shown] and 147 of 161 at 1 week after return of results; Table 2). Among 161 parents who completed the 1-week post-results survey, 79% (127) reported that they felt they understood the results 1 week after their return (Table 2). Parent-reported understanding of rWGS and rWES results was not significantly different. However, more parents reporting feeling they understood rWGS and rWES results than urWGS results ($p = 0.04$) and more reported understanding negative results than positive results ($p < .001$). These findings overlap since positive results were more common among infants receiving urWGS than rWGS or rWES.[2]

97% (156) of parents reported perceiving that their child's genomic sequencing results were either useful or somewhat useful (Table 2). This result was striking since only 23% (27) of the corresponding 117 infants received a genetic disease diagnosis (Table 1).[2] Parents' perceived utility of testing did not differ significantly by test method (rWGS versus rWES, or rWGS and rWES versus urWGS). However, more parents who received positive results (i.e., a genomic diagnosis) perceived sequencing to be useful relative to those who received negative results ($p = 0.004$; Table 2).

At 1 week after return of results, 76% (121) of parents reported feeling that the choice to have their infants' genome sequenced did their child a lot of good and 70% (112) that it did themselves a lot of good (Table 2). Parental perception of test benefit did not differ significantly by test method (rWGS versus rWES, or rWGS and rWES versus urWGS). However, more parents (90%) who received a positive genomic diagnosis perceived the test to be beneficial to their child relative to those who received negative results (70%, $p = 0.03$; Table 2).

At 1 week post results, 80% (129) of parents reported that diagnostic genomic sequencing made them more knowledgeable about their child's future health, 66% (106) reported feeling better able to manage their child's potential symptoms, and 76% (121) reported feeling better able to make informed reproductive planning decisions or care for other family members (Table 2). Perceived knowledge of their child's future health, ability to manage potential symptoms, and ability to make informed reproductive planning decisions did not differ by test method nor between those who received positive versus negative results, with one exception: more parents (83%) felt better able to manage potential symptoms when infants received positive results versus negative results (60%, $p = 0.03$).

As a measure of the potential harm of diagnostic genomic sequencing of infants in ICUs, parents were asked 1 week after return of results whether they regretted their decision to have their infant's genome sequenced. On a continuous scale (range 0–100, where 0 was no regret), household and individual parental regret were very low (household median 2.5, mean 6.7, range 0–50, $n = 117$ and parental median 0, mean 10.0, range 0–100, $n = 161$; Table 3), with 50.3% (81/161) of parents reporting no regret.

In the 1-week post-results survey, 4 families (3% of 117) reported that diagnostic genomic sequencing resulted in harm either to themselves or their child (Tables 2 and S2). Three parents reported harm to their child and three reported harm to the parent (Tables 2 and S2). These responses were followed up by a member of the research team. In family 225, one Spanish-speaking parent confirmed their perception of harm to self and child. The corresponding infant had a negative result. Further inquiry revealed that the nature of the perceived harm was that

Table 1. Demographics of 161 Parents of 117 Infants Who Responded to the Survey 1 Week after Return of Results

	Total (n, %)	rWES (n, %)	rWGS (n, %)	urWGS (n, %)
Parents	161 (100.0%)	71 (44.1%)	70 (43.5%)	20 (12.4%)
Race/Ethnicity				
Hispanic	47 (29.2%)	26 (36.6%)	16 (22.9%)	5 (25.0%)
Caucasian/white	79 (49.1%)	32 (45.1%)	34 (48.6%)	13 (65.0%)
Asian	2 (1.2%)	–	2 (2.9%)	–
African American/Black	3 (1.9%)	1 (1.4%)	2 (2.9%)	–
Native Hawaiian/Pacific Islander	8 (5.0%)	4 (5.6%)	4 (5.7%)	–
Other	17 (10.6%)	7 (9.9%)	8 (11.4%)	2 (10.0%)
Unknown	5 (3.1%)	1 (1.4%)	4 (5.7%)	–
Total households/probands	117 (100.0%)	54 (46.2%)	49 (41.9%)	14 (12.0%)
Parent/Families' Primary Spoken Language				
English	84 (71.8%)	37 (68.5%)	37 (75.5%)	10 (71.4%)
Spanish	21 (17.9%)	11 (20.4%)	7 (14.3%)	3 (21.4%)
Bilingual	6 (5.1%)	3 (5.6%)	2 (4.1%)	1 (7.1%)
Other	3 (2.6%)	1 (1.9%)	2 (4.1%)	–
Highest Educational Attainment				
Up to high school diploma	38 (32.5%)	17 (31.5%)	13 (26.5%)	8 (57.1%)
Up to four year college degree	29 (24.8%)	13 (24.1%)	13 (26.5%)	3 (21.4%)
Up to graduate degree	47 (40.2%)	22 (40.7%)	22 (44.9%)	3 (21.4%)
Result of Test				
No diagnosis	90 (76.9%)	44 (81.5%)	39 (79.6%)	7 (50.0%)
Positive	27 (23.1%)	10 (18.5%)	10 (20.4%)	7 (50.0%)
Age at consent (days, median, range)	4 (1–115)	4 (1–115)	4 (1–105)	6 (2–67)
Time to results (days, median, range)	10.1 (1.1–49.1)	11.2 (6.5–38.6)	10.8 (3.9–49.1)	2.3 (1.1–10.0)

Race/ethnicity was from the infants' EHRs. Highest educational attainment is for the household.

diagnostic genomic sequencing had failed to provide a diagnosis or parental incidental findings. When followed up later, another parent (family 210; P1) reported testing left the family with "a lot of unknowns," but denied that harm was experienced. In the remaining two families, who were also Spanish speaking (families 223 and 211, Table S2), the parents later denied harm to themselves or their child at the time of follow up. In a fifth family (family 256), a parent indicated that they experienced "a little bit of mental stress" (Table S2). There did not appear to be any association between test method or type of result and perceived harm to child or parent (Table 2). Thus, although 3% of families endorsed harm at 1-week post-results, when followed up later, half denied that they had ever experience harm, and among those that did, the harm was confusion regarding the results or perceived harm due to failure of the sequencing to provide a diagnosis.

Where both parents responded to survey questions, we evaluated response concurrence. Of 117 family responses to the 1-week post-results survey, 44 (38%) included responses from both parents. Of these 44 families with two responses, 33 (75%) families showed discord, but 25 (57%) families only varied in the strength of their response, not the direction. In the remaining eight families (18%), the two parents disagreed in response to a total of 16 of the 128 (13%) survey questions, excluding the decisional regret score (data not shown; available upon request). However, in only one family (211), did the two parents differ in responses to more than one question. Where both parents responded with regard to decisional regret, the mean difference was 8.1 (household mean 6.9, median 0, scale 0–100). In only one family (211) did one parent report no regret (score 0) and the other full regret (score 100; data not shown; available upon request), and this family is described above.

Predictors of Parental Regret

We used multiple logistic regression to evaluate potential variables believed to be associated with parental regret

Table 2. Parental Responses to Ten Questions from the 1-Week Post-Return of Results Survey

	Total (n, %)	rWES (n, %)	rWGS (n, %)	rWES versus rWGS p Value	urWGS (n, %)	urWGS versus rWES + rWGS p Value	Positive Tests (n, %)	Negative Tests (n, %)	Positive versus Negative p Value
Total Parents	161 (100%)	71 (44.1%)	70 (43.5%)	–	20 (12.4%)	–	41 (25.5%)	120 (74.5%)	–
Q1. Adequately Informed									
Agree	147 (91.3%)	63 (88.8%)	65 (92.9%)		19 (95%)		38 (92.7%)	109 (90.8%)	
Neutral	4 (2.5%)	4 (5.6%)	–	0.16	–	1	2 (4.9%)	2 (1.7%)	0.24
Disagree	10 (6.2%)	4 (5.6%)	5 (7.1%)		1 (5.0%)		1 (2.4%)	9 (7.5%)	
Q2. Understand Results									
Yes	127 (78.9%)	55 (77.5%)	60 (85.7%)		12 (60.0%)		23 (56.1%)	104 (86.7%)	
Somewhat	34 (21.1%)	16 (22.5%)	10 (14.3%)	0.28	8 (40.0%)	0.04	18 (43.9%)	16 (13.3%)	<0.001
No	–	–	–		–		–	–	
Q3. Results Useful									
Yes	124 (77.0%)	55 (77.5%)	54 (77.1%)		15 (75%)		39 (95.1%)	85 (70.8%)	
Somewhat	32 (19.9%)	14 (19.7%)	13 (18.6%)	1	5 (25%)	0.78	2 (4.9%)	30 (25.0%)	0.004
No	5 (3.1%)	2 (2.8%)	3 (4.3%)		–		–	5 (4.2%)	
Q4. More Knowledgeable about Child's Future Health									
Agree	129 (80.1%)	58 (81.7%)	57 (81.4%)		14 (70.0%)		33 (80.5%	96 (80.0%)	
Neutral	23 (14.3%)	12 (16.9%)	8 (11.4%)	0.18	3 (15%)	0.16	5 (12.2%)	18 (15.0%)	0.78
Disagree	9 (5.6%)	1 (1.4%)	5 (7.1%)		3 (15%)		3 (7.3%)	6 (5.0%)	
Q5. Better Able to Manage Potential Symptoms									
Agree	106 (66.2%)	46 (65.7%)	47 (67.1%)		13 (65%)		34 (82.9%)	72 (60.0%)	
Neutral	44 (27.5%)	21 (30.0%)	18 (25.7%)	0.71	5 (25%)	0.72	6 (14.6%)	38 (31.7%)	0.03
Disagree	10 (6.3%)	3 (4.3%)	5 (7.1%)		2 (10%)		1 (2.4%)	9 (7.5%)	
Q6. Able to Make Informed Reproductive Planning or Care for Other Family Members									
Agree	121 (75.6%)	51 (72.9%)	57 (81.4%)		13 (65.0%)		33 (80.5%)	88 (73.3%)	
Neutral	34 (21.3%)	17 (24.3%)	11 (15.7%)	0.43	6 (30.0%)	0.33	7 (17.1%)	27 (22.5%)	0.81
Disagree	5 (3.1%)	2 (2.9%)	2 (2.9%)		1 (5%)		1 (2.4%)	4 (3.3%)	
Q7. Benefit to Child									
Agree	121 (75.6%)	50 (71.4%)	58 (82.9%)		13 (65%)		37 (90.2%)	84 (70.0%)	
Neutral	35 (21.9%)	19 (27.1%)	9 (12.9%)	0.06	7 (35%)	0.30	4 (9.8%)	31 (25.8%)	0.03
Disagree	4 (2.5%)	1 (1.4%)	3 (4.3%)		–		–	4 (3.3%)	

(*Continued on next page*)

Table 2. *Continued*

	Total (n, %)	rWES (n, %)	rWGS (n, %)	rWES versus rWGS p Value	urWGS (n, %)	urWGS versus rWES + rWGS p Value	Positive Tests (n, %)	Negative Tests (n, %)	Positive versus Negative p Value
Q8. Benefit to Parent									
Agree	112 (70%)	47 (67.1%)	53 (75.7%)		12 (60%)		34 (82.9%)	78 (65.0%)	
Neutral	45 (28.1%)	22 (31.4%)	15 (21.4%)	0.43	8 (40%)	0.53	7 (17.1%)	38 (31.7%)	0.10
Disagree	3 (1.9%)	1 (1.4%)	2 (2.9%)		–		–	3 (2.5%)	
Q9. Harm to Child									
Agree	3 (1.9%)	3 (4.2%)	–		–		1 (2.4%)	2 (1.7%)	
Neutral	–	–	–	0.25	–	1	–	–	
Disagree	157 (97.5%)	67 (94.4%)	70 (100%)		20 (100%)		40 (97.6%)	117 (97.5%)	
Q10. Harm to Parent									
Agree	3 (1.9%)	2 (2.9%)	1 (1.4%)		–		1 (2.4%)	2 (1.7%)	
Neutral	6 (3.8%)	4 (5.7%)	2 (2.9%)	0.67	–	1	4 (9.8%)	2 (1.7%)	0.04
Disagree	150 (94.3%)	64 (91.4%)	66 (95.7%)		20 (100%)		36 (87.8%)	114 (95.0%	

regarding their decision to have their infant's genome sequenced (Table 4). After accounting for race/ethnicity, educational attainment, type of test, test result, time to diagnosis, and age of newborn at consent, we found that Spanish-speaking households had significantly higher regret scores than English-speaking households (mean 7.2 points, $p = 0.02$; Table 4). There were no significant differences in decisional regret for test method (rWGS, rWES, or urWGS), result type (positive or negative), or time to test results (Table 4).

Comparison of Parental and Clinician Survey Responses

The accompanying manuscript describes clinician perceptions of the clinical utility and changes in management associated with diagnostic genomic sequencing in the NSIGHT2 cohort.[3] We examined concordance between perceptions of parents (the focus of this manuscript) with those of clinicians (the focus of Dimmock et al.[3]). Of 111 infants with 1-week post-results survey responses from at least one parent and one clinician, perceived utility of genomic results was concordant in 81% (90), of which 80% (89) perceived that that diagnostic genomic sequencing was useful (Table S3). Among the 19% (21) of infants with discordant perceived utility by parents and clinicians, in 15% (17/111), parents reported that diagnostic genomic sequencing was useful (Table S3). Only 4% (4/111) of clinicians reporting testing was useful when the family did not (Table S3). No differences in perceived utility were observed by test type or test result for parents or clinicians (Table S4). As reported in the accompanying manuscript, the only harm that clinicians perceived was that genomic test results had increased stress in six families and increased confusion in one of those families.[3] Of those six families, 1-week post-result parent surveys were available for four, none of whom reported an increase in stress or confusion (Table S2).

Discussion

This study sought to assess parental perceptions of rapid genomic testing in the NICU setting. Overall, most families reported feeling that genomic sequencing benefitted their child and themselves. Specifically, most families reported having more knowledge about their child's future health, feeling able to make informed reproductive planning decisions or care for other family members, feeling better able to manage their child's potential symptoms, and having little decisional regret. Parents reported testing and study participation to be less stressful or confusing than clinicians perceived it to be for the families. Consistent with physician perceptions in the companion paper,[3] parents also placed strong value on negative test results, emphasizing that diagnostic yield is not a good proxy for parental perceived utility. Although 28-day mortality and illness acuity were higher in the non-randomized urWGS arm, this study found no significant differences by test types, indicating the type of technology

Table 3. Parent and Household Regret of Infant Genomic Sequencing 1 Week after Return of Results

	Total	rWES	rWGS	urWGS
Number of parents	161	71	70	20
Median parental regret (range)	0.0 (0–100)	0.0 (0–100)	5.0 (0–60)	15.0 (0–30)
Mean parent regret (SD)	10.0 (14.0)	9.2 (16.3)	9.6 (12.0)	14.0 (11.8)
Number of households	117	54	49	14
Median household regret (range)	2.5 (0–50)	0.0 (0–50)	5.0 (0–33)	8.8 (0–30)
Mean household regret (SD)	6.7 (9.3)	6.1 (10.5)	6.8 (7.9)	10.0 (9.6)

used did not impact perceptions of the test and results.[2] It is also noteworthy that only a single family that did confirm that the parent and child were harmed as a result of not receiving positive or incidental results also reported that both the parent and child received benefits from the testing and that they would make the same decision again. Similarly, stress and confusion were observed in two parents' responses, but both denied harm to either the parent or child upon follow up and reported they would make the same decision again.

Most families reported little to no decisional regret related to having genomic sequencing for their newborns, but it was observed that households whose primary spoken language was Spanish reported, on average, higher decisional regret. Of those families that also reported harm, a review showed the majority were Spanish-speaking parents. The study team had limited fluency in Spanish, and interpreters were used by research staff during consent and follow-up calls to the families. Additionally, the survey was translated but not validated in Spanish. These two factors potentially confounded both the consent process and the ability to accurately assess decisional regret. Such challenges make performing genomic research in diverse communities a challenge and require ongoing investment to validate tools specific to local context.

Although there were clinician reports of perceived stress and confusion in six families, parental survey responses for the four families who responded 1 week after results did not align with clinicians' perceptions. Unfortunately, this study did not include qualitative family follow up, but review of the 1-week post-result survey responses did not identify signs of confusion or stress from the parents' self-reported perception of the results. It is unclear to what extent this reflects differences in stress (that may fluctuate by day), differences in attribution of stress (testing versus the clinical state of their child or other testing uncertainty), and/or temporal changes (e.g., further clinician discussions after the clinician survey was completed prior to parental survey completion). Additional research should be considered to assess alignment and discord between clinician and parent perceptions of stress and confusion regarding genomic results.

This study did find that parents and clinicians agreed about the perceived utility of test results more than 80% of the time, suggesting that questionnaires with one group might be a reasonable proxy for the other group's perception of benefit. The concordance on the perceived utility of diagnostic testing that yields a negative result is intriguing. However, previous research indicates that negative results may be overinterpreted by participants as either providing more certainty of a true negative than the test can provide, also referred to as the "nuanced negative," or potentially providing a false sense of hope and/or relief that a genetic disorder is not present.[22–26] Although the results report we provided to study participants with negative findings stated that "no symptom-related results were found *at this time*," additional qualitative research is recommended to better understand how these findings are interpreted by clinicians and parents. For instance, it would be worthwhile to explore the degree to which clinicians emphasize the uncertainty of negative results, as well as the ways in which parents make meaning of negative results. Nonetheless, future research of genomic sequencing should consider focusing on perceived utility as a primary outcome alongside or in place of diagnostic rates.

Overall, 91% of families reported feeling that they received adequate information at the time of consent despite not receiving formal pre-test genetic counselling. Families advised that they felt comfortable with the information provided by the research nurses to make an informed decision to enroll for symptom-driven diagnoses and whether to opt in for incidental results. These findings are especially important as genomic testing is in its infancy, and its use in the intensive care setting has been somewhat controversial.[27–29] Of note, this study did not return variants of unknown significance (VUSs) or perform analyses to identify secondary findings. This decision was due in large part to the acute nature of the patients' conditions, the psychological distress of the intensive care setting, and the previously unmeasured risk of possible harm to the newborns related to disclosure of later-onset conditions (such as adult-onset conditions) at the launch of this study.[30] Families were given the option to opt in for the return of incidental findings for themselves and/or their child. Similarly, clinical and research genetic counselling was available for all families prior to consent, which may have impacted perceptions of adequacy of information by potentially giving families additional information

Table 4. Linear Regression of Household Decisional Regret after Return of Results

Variables	Estimate	95% Confidence Interval	p Value
Type of Genomic Test			
rWES	−5.66	−13.62–2.29	0.16
rWGS	−4.08	−12.18–4.02	0.32
urWGS	1.00	–	–
Type of Genomic Result			
Positive	3.44	−2.19–9.07	0.23
Negative	1.00	–	–
Time to results	0.12	−0.24–0.48	0.51
Newborn's age at consent	−0.01	−0.08–0.07	0.84
Highest Household Education			
Up to high school diploma	4.51	−0.25–9.28	0.06
Up to four year college degree	1.93	−2.69–6.56	0.41
Up to graduate degree	1.00	–	–
Household Primary Spoken Language			
Spanish	7.18	1.11–13.25	0.02
Bilingual	1.75	−6.40–9.89	0.67
Other language	−1.86	−13.98–10.26	0.76
English	1.00	–	–

Estimates reported after controlling for race/ethnicity and other listed variables

regarding genomic testing and identifying patient-specific potential benefits to genomic testing that would not have been provided in the informed consent process. These limitations on approach restrict the generalizability of these findings beyond symptom-driven, first-tier testing in the intensive care setting. However, parents in this setting appear to require less tailored pre-test counselling than has previously been thought, and thus, symptom-driven genomic testing may not be any more challenging to implement in the intensive care setting than other next generation sequencing.[31] Although pre-test counseling is still recommended for genomic testing, physicians in the neonatal and pediatric intensive care units are frequently ordering and consenting families to genetic tests, such as panel next generation sequencing or microarrays (both of which may return results unrelated to the patient's current phenotype), so we posit that genomic testing that is limited to identifying diagnoses related to the patient's current symptoms may be no more complicated to order than these other frequently used tests.[32]

This study was limited by the availability of validated measures in this population. Therefore, it is possible that parents included the benefits of usual care in their responses to questions of perceived utility and management. We note that while all results were returned by a clinician, the study did not track and account for what type of clinician returned results, nor the duration of time spent discussing the results with families. Therefore, our results cannot completely parse out whether parents reported feeling more knowledgeable due to the test results or as a result of consulting with a clinician (or some combination of both). Future research could inform this by capturing details about the types of consultations (e.g., intensivist, clinical geneticist, research genetic counsellor, etc.) families receive, in addition to the amount of time spent and quality of the explanation related to genomic test results given. Similarly, the translated version of the decisional regret measure was not validated for Spanish speakers and may have impacted the study's results related to perceived harms and decisional regret.[17] Reports of harm may also be understated due to the process of following up with families as parents may have denied harm to the research team despite perceiving harm. Furthermore, following the 6-month audit, the research workflow was changed to include follow-up post-results to all families by research genetic counsellors, which may have impacted initial perceptions prior to the administration of the post-results survey. Future research may benefit from validated measures specific to the impact of genomic testing during the newborn period. This study may also have been affected by response bias if families who were more satisfied with testing self-selected to respond to surveys. However, given that the diagnostic rate of the families that responded was similar to the overall diagnostic rate of the study, we believe this is unlikely.

This study was not well powered to observe differences between types of tests, so additional research regarding parental perceptions in a larger study may identify differences that were not detected as a part of this study. Similarly, this study was not powered to identify differences by method of survey administration (i.e., with staff present or completed independently). However, most parents completed the survey independently, and generally, there was very little variation in the results. The parental survey 1-week post results revealed lower rates of Hispanic families and households with at most a high school diploma participating in surveys. The different socio-demographic composition at the return of results time period may have affected the overall results. Furthermore, while we included covariates such as age of the newborn at consent, time to results, and demographic characteristics in our analyses, we were not powered to examine differences as a function of parents' perceived utility, benefits, and harms. A larger, multi-site study is recommended to determine what other factors may impact parental perceptions. Similarly, other unmeasured clinical variables, such as length of hospital stay and patient acuity, may impact the follow-up rates for these groups. Additional research is needed to assess access disparities related to availability of transportation and access to the hospital, cellular service, and email to determine how to ensure families are not lost to follow up.

This study did not adjust significance levels for multiple comparisons, and therefore, nominally significant results should be interpreted cautiously. Lastly, the results of this study are based on the voluntary response of parents at two survey time points (following enrollment and return of results), and it is possible that response bias may have affected the overall results of this study.

Conclusion

Overall, families reported a wide range of benefits from having symptom-driven genomic testing of their newborn in the intensive care setting. The primary report of harm was related to not receiving a diagnosis; this parent indicated that the testing was beneficial and if given the chance, would make the same decision again. Many factors need to be considered when implementing genomic testing in the newborn period, and parent-reported outcomes and opinions should weigh heavily on this process. Furthermore, this study has shown that this approach in this setting was acceptable to families with acutely ill newborns and did not cause perceived harm or decisional regret among families. These findings, coupled with clinician-reported clinical utility, changes in long-term outcomes, and cost effectiveness of genomic testing indicate that genomic testing of newborns in the intensive care setting is not only acceptable but perceived as beneficial by most families and clinicians.[2,5,6,8,33]

Data and Material Availability

Genotype and phenotype data associated with this study are available at the Longitudinal Pediatric Data Resource (LPDR) under a data use agreement and subject to the limitations of the informed consent documents for each subject (NBSTRN: nbs000003.v1.p). The full dataset supporting the current study have not been deposited in a public repository because of the potential of re-identification related to rare disease conditions previously reported but are available from Rady Children's Institute for Genomic Medicine via the corresponding author upon written request. There are restrictions to the availability of the parent survey dataset due to the potential for re-identification when demographic information is combined with previously published phenotypic and genotypic data. The research team at Rady Children's Institute for Genomic Medicine will review all requests and release all data that cannot be used to re-identify subjects.

Supplemental Data

Supplemental Data can be found online at https://doi.org/10.1016/j.ajhg.2020.10.004.

Acknowledgments

We thank Michele Feddock, Christian Hansen, Josh Braun, and the staff at Rady Children's Institute for Genomic Medicine. This study was supported by grant U19HD077693 from Eunice Kennedy Shriver NICHD and NHGRI to S.F.K., grant UL1TR002550 from NCATS to E.J. Topol, grant HG008753 from NHGRI to C.S.B., and gifts from the Liguori Family, John Motter and Effie Simanikas, Ernest and Evelyn Rady, and RCHSD.

Declaration of Interests

D.D. received funding from Biomarin (consultant for Pegvaliase trials), Audentes Therapeutics (Scientific Advisory Board), and Ichorion Therapeutics (consultant for mitochondrial disease drugs).

Received: July 31, 2020
Accepted: October 12, 2020
Published: November 5, 2020

Web Resources

ClinicalTrials.gov, https://clinicaltrials.gov
LPDR, http://www.nbscn.org/longitudinal-pediatric-data-resource.htm

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