

Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project

A Randomized Clinical Trial

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IMPORTANCE Newborn genomic sequencing (nGS) may provide health benefits throughout the life span, but there are concerns that it could also have an unfavorable (ie, negative) psychosocial effect on families.

OBJECTIVE To assess the psychosocial effect of nGS on families from the BabySeq Project, a randomized clinical trial evaluating the effect of nGS on the clinical care of newborns from well-baby nurseries and intensive care units.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial conducted from May 14, 2015, to May 21, 2019, at well-baby nurseries and intensive care units at 3 Boston, Massachusetts, area hospitals, 519 parents of 325 infants completed surveys at enrollment, immediately after disclosure of nGS results, and 3 and 10 months after results disclosure. Statistical analysis was performed on a per-protocol basis from January 16, 2019, to December 1, 2019.

INTERVENTION Newborns were randomized to receive either standard newborn screening and a family history report (control group) or the same plus an nGS report of childhood-onset conditions and highly actionable adult-onset conditions (nGS group).

MAIN OUTCOMES AND MEASURES Mean responses were compared between groups and, within the nGS group, between parents of children who received a monogenic disease risk finding and those who did not in 3 domains of psychosocial impact: parent-child relationship (Mother-to-Infant Bonding Scale), parents' relationship (Kansas Marital Satisfaction Scale), and parents' psychological distress (Edinburgh Postnatal Depression Scale anxiety subscale).

RESULTS A total of 519 parents (275 women [53.0%]; mean [SD] age, 35.1 [4.5] years) were included in this study. Although mean scores differed for some outcomes at singular time points, generalized estimating equations models did not show meaningful differences in parent-child relationship (between-group difference in adjusted mean [SE] Mother-to-Infant Bonding Scale scores: postdisclosure, 0.04 [0.15]; 3 months, -0.18 [0.18]; 10 months, -0.07 [0.20]; joint $P = .57$) or parents' psychological distress (between-group ratio of adjusted mean [SE] Edinburgh Postnatal Depression Scale anxiety subscale scores: postdisclosure, 1.04 [0.08]; 3 months, 1.07 [0.11]; joint $P = .80$) response patterns between study groups over time for any measures analyzed in these 2 domains. Response patterns on one parents' relationship measure differed between groups over time (between-group difference in adjusted mean [SE] Kansas Marital Satisfaction Scale scores: postdisclosure, -0.19 [0.07]; 3 months, -0.04 [0.07]; and 10 months, -0.01 [0.08]; joint $P = .02$), but the effect decreased over time and no difference was observed on the conflict measure responses over time. We found no evidence of persistent negative psychosocial effect in any domain.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of nGS, there was no persistent negative psychosocial effect on families among those who received nGS nor among those who received a monogenic disease risk finding for their infant.

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Advances in genomic sequencing technologies and interpretation alongside decreased costs have made genomic sequencing increasingly accessible. In clinical settings, genomic sequencing is currently used most often to diagnose and inform clinical management of rare disorders and cancer,¹⁻⁴ but wider clinical application is anticipated in the near future.⁵⁻⁸ For example, some have suggested that newborn genomic sequencing (nGS) may eventually complement existing state-run newborn screening (NBS) programs.⁹⁻¹¹ Application of nGS as a screening modality has the potential to provide health benefits throughout life by facilitating diagnoses at birth, identifying risk for future disease that could be prevented or mitigated, and serving as a resource for future health questions and family planning. Questions remain, however, about whether nGS could have a negative psychosocial effect on families.^{12,13} Professional guidelines underscore these concerns.¹⁴⁻¹⁷

Previous studies of the psychosocial effect of genetic or genomic testing results for adult patients generally found no evidence of harm.¹⁸⁻²² Receiving genetic testing results about one's child, however, may have a different effect and thus warrants investigation. Evidence from studies of parents' psychosocial response to expanded NBS results, for example, suggests that some parents experience psychological distress after receiving either true-positive or false-positive results from NBS²³⁻²⁷ or guilt and blame in response to learning their child's genetic information.²⁸⁻³⁰

Furthermore, disclosing nGS information to parents may have broad impacts beyond parents' psychological well-being. Health information can disrupt family systems,³¹ and disruptions in any family system may exacerbate issues across family domains.³² However, there is a dearth of evidence on the impact across such domains of learning genetic information. Although some studies have assessed the effect of expanded NBS on the parent-child relationship, they have yielded mixed findings.^{23,33-37} Similarly, although there is little evidence on how parents' relationships may be impacted by their child's NBS or genetic results, some unfavorable (ie, negative) impacts have been documented.^{28,36} Assessment across multiple domains of family impact is therefore crucial for a more complete understanding of the effect of nGS on families.

Herein we report on the psychosocial effect of returning nGS findings for more than 1000 childhood-onset and highly actionable adult-onset conditions across 3 family domains to parents of newborns enrolled in the BabySeq Project, a randomized clinical trial of nGS in newborns from both well-baby nurseries and intensive care units (ICUs).³⁸

Methods

Trial Design and Participants

The study methods have been described in detail elsewhere.³⁸ In brief, we enrolled newborns up to 42 days of age and their English-speaking parents from well-baby nurseries and ICUs at Boston Children's Hospital, Brigham and Women's Hospital, and Massachusetts General Hospital in Boston, Massachu-

Key Points

Question What is the psychosocial effect of newborn genomic sequencing results on families?

Findings In this randomized clinical trial that included 325 families, scores on measures of psychosocial impact in 3 family domains—parent-child relationship, parents' psychological distress, and parents' relationship—did not show sustained statistical differences between study groups over time.

Meaning This study found no evidence that returning newborn genomic sequencing information has an unfavorable psychosocial effect on families.

sets, from May 14, 2015, to May 21, 2019. Recruitment for this randomized clinical trial ended at a predetermined date to allow time for follow-up. Before randomization, DNA was collected from all newborns and their parents. We randomized newborns with simple 1:1 allocation using computer-generated randomization to receive either a family history assessment and review of standard NBS results (control group) or the same plus exome sequencing (nGS group). The nGS results reported to families in the nGS group included dominant or biallelic recessive variants in a single gene known to significantly increase the risk of developing a condition, referred to here as monogenic disease risk (MDR); recessive carrier variants; and select pharmacogenomic variants associated with medications used in pediatrics.³⁹ If an MDR variant was detected in the newborn, parental DNA was genotyped to determine if the variant was de novo or inherited; these results were included in the nGS report. Parents' DNA was not genotyped when carrier status or pharmacogenomic variants were found in the infant. Results for more than 1000 conditions that could present and/or for which surveillance was recommended before 18 years of age were reported.⁴⁰ Later, variants associated with a limited number of highly actionable adult-onset conditions were reported.⁴¹ Parents enrolled before the protocol change were offered the additional information and were reconsented if interested. Only 1 family (2 parents) completed surveys after receiving an nGS result for an adult-onset condition. Results for both groups were disclosed to parents at an in-person visit by a study genetic counselor and physician, sent to the infant's clinician(s), and entered into the infant's medical record. The Partners (now Mass General Brigham) Human Research Committee, the Boston Children's Hospital institutional review board, and the Baylor College of Medicine institutional review board approved this study. All participating parents provided written informed consent. Details of the trial protocol are available in [Supplement 1](#). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

We assessed outcomes using web-based longitudinal surveys. Hyperlinks to the surveys were emailed to both parents at 4 time points: enrollment, immediately after results disclosure, and 3 and 10 months after results disclosure. At least 1 parent from each family was required to complete a baseline survey before the family was considered fully enrolled and randomized.³⁸ Otherwise, participants could skip surveys or

Table 1. Primary and Secondary Psychosocial Outcomes by Family Impact Domain

Family impact domain and outcome	Measure	Score range	Administration time points			
			Baseline	After disclosure	3 mo After disclosure	10 mo After disclosure
Parent-child relationship						
Parent-child bonding ^a	Mother-to-Infant Bonding Scale ^{42,b}	0-24	Yes	Yes	Yes	Yes
Parents' perception of child's vulnerability	Vulnerable Baby Scale ^{43,c}	4-20	^d	Yes	^d	^d
Stress in parent-child system	Parenting Stress Index, 4th Edition Short Form ^{44,e}	36-180	No	No	No	Yes
Parents' relationship						
Relationship satisfaction ^a	Kansas Marital Satisfaction Scale ^{45,f,g}	1-5	^d	^d	Yes	^d
Relationship conflict	Novel item ^{f,h}	1-5	Yes	Yes	Yes	Yes
Partner blame	Novel item ⁱ	1-5	No	No	Yes	Yes
Parents' psychological distress						
Anxiety ^a	Edinburgh Postnatal Depression Scale anxiety subscale ^{46,j}	0-9	Yes	Yes	Yes	No
	Generalized Anxiety Disorder Scale-7 ^{47,k}	0-21	No	No	Yes	Yes
Depression	Edinburgh Postnatal Depression Scale ^{46,l}	0-30	Yes	Yes	Yes	No
	Patient Health Questionnaire-9 ^{48,m}	0-30	No	No	Yes	Yes
Self-blame	Novel item ⁿ	1-5	No	No	Yes	Yes

^a Denotes primary outcome for domain.

^b Lower scores indicate less negative feeling toward the new baby; measure was administered to all parents, not just mothers.⁴⁹

^c Lower scores indicate less perceived vulnerability.

^d Indicates that investigator-abbreviated version of the measure was used.

^e Lower scores indicate less parenting stress.

^f Only measured if the parent indicated he or she was currently in a committed relationship.

^g Lower scores indicate less relationship satisfaction.

^h Lower scores indicate less relationship conflict.

ⁱ Lower scores indicate less partner blame.

^j Lower scores indicate less postnatal anxiety.

^k Lower scores indicate fewer symptoms of generalized anxiety.

^l Lower scores indicate less postnatal depression.

^m Lower scores indicate fewer symptoms of depression.

ⁿ Lower scores indicate less self-blame.

individual questions. Both parents received all outcome measures. Follow-up was completed in May 2019.

Survey Measures

Primary and secondary outcomes and associated measures used to assess the 3 domains of family impact are shown in Table 1.⁴²⁻⁴⁹ We explored both the impact of receiving genomic results, and, within the nGS group, the impact of receiving an MDR finding.

Outcome measures were chosen based on psychometric properties according to the age of the infant at the time of survey administration (Table 1⁴²⁻⁴⁹). Accordingly, some outcomes were measured with different instruments over time. All published measures were used without modification except for the Vulnerable Baby Scale⁴³ and the Kansas Marital Satisfaction Scale,⁴⁵ which were shortened at some points to reduce survey burden (eMethods in Supplement 2). Novel items were used to assess relationship conflict, partner blame, and self-blame (eMethods in Supplement 2). Participants' self-reported age, educational level, income, race, and ethnicity were collected at study enrollment to characterize the sociodemographic makeup of the sample.

Statistical Analysis

Statistical analysis was performed on a per-protocol basis from January 16, 2019, to December 1, 2019. We tested for an effect

of nGS results and receipt of an MDR finding within the nGS group on each outcome. For outcomes with a clinically relevant cutoff score, we compared the proportion of parents below the cutoff in each study group. For constructs that were measured using more than one instrument, we analyzed each scale separately. Data from both parents were included in the analyses because there was weak or no correlation of partner scores within families (absolute value of Pearson $r < 0.145$ for all scales at all time points). To compare performance of investigator-abbreviated versions with full scales, we calculated the Pearson correlation coefficient between individual scores on each scale at the time the full scale was administered, which was 0.855 for the Vulnerable Baby Scale at post-disclosure and 0.961 for the modified Kansas Marital Satisfaction Scale at 3 months.

For each measure, we tested for differences in mean responses by study group and by MDR status group at each time point using 2-sided t tests with $\alpha = .05$. Nonparametric analyses were also conducted (eMethods in Supplement 2). We initially designed the protocol using a noninferiority framework, but given the evidence that information such as nGS can disrupt family systems,^{23,28,31-33,35,36} we concluded that our scientific aims would be best served by the use of nonequivalence comparisons. We did not adjust for multiple comparisons in order to maximize power to detect possible harms.⁵⁰

For each measure that was administered at 3 or more time points, we used repeated-measures analysis of longitudinal data within individuals. We used a generalized estimating equations approach to test for differences in population-averaged responses between groups or MDR groups and control for cohort (well-baby nursery vs ICU). We developed 2 models for each selected outcome: a primary model for all parents and an nGS-specific model for parents in the nGS group only to examine the impact of disclosing MDRs. The primary model included main effects for randomization group, cohort and time point (categorical variable with baseline or earliest time point that an instrument was administered as the reference category), and interactions of group with cohort and group with time. The nGS-specific model included main effects for cohort, time point, and MDR status (present or not) and an interaction term for cohort with MDR status and MDR status with time. Three-way interactions between group or MDR status (within the nGS group), cohort, and time were not statistically significant ($P > .10$ on triple interaction term in all models) and were omitted from final models.

To test whether the pattern of responses differed by study group or MDR status over time, we performed a joint contrast test of marginal linear predictions of the set of interaction terms of study group with time and MDR status with time. The threshold for statistical significance was $\alpha = .05$. We plotted model-predicted population mean outcome scores to illustrate response patterns. Mean imputation was used for missing data with a 75% rule for completion.⁵¹ Data analysis was performed using Stata/IC, version 15.1 (StataCorp LLC).

Results

Participant Characteristics and Genomic Findings

Figure 1 depicts numbers of families at each study step, beginning with recruitment. Of the 5002 families we approached, 510 (10.2%) agreed to hear about the study. Of those 510 families, 351 (68.8%) completed the consent process. We found no characteristics independently associated with consent, as previously reported.⁵² Of the 351 families that consented, at least 1 parent of 325 families responded to the baseline survey and thus were fully enrolled and randomized, for a total of 519 individual parents with a mean (SD) age of 35.1 (4.5) years (275 women [53.0%]) (Table 2). For all but 3 families, 2 parents enrolled, yet not all parents responded at any given survey time point.

Sequencing results were previously published.³⁹ In summary, 159 of the 325 enrolled newborns were randomized to the nGS group. Monogenic disease risks were found in 18 newborns, with risk for a childhood-onset disease identified in 15 of the 159 newborns (9.4%). Only one finding explained a child's clinical features. None of the rest of the findings were anticipated based on clinical presentation or family history. Carrier status for recessive disease was identified in 140 of 159 newborns (88.1%), and limited atypical pharmacogenomics variants associated with response to pediatric medications were identified in 8 of 159 newborns (5.0%). Risk of actionable adult-onset disease was found

in 3 of 85 newborns (3.5%) whose parents consented to receive such information about their infants.

Overview

We found no evidence of a persistent negative impact of nGS during the course of the study in any of the 3 family domains studied. Generalized estimating equations models taking into account whether the infant was in the well-baby nursery or an ICU showed no consistent or increasing negative effect on families over time associated with nGS. The proportion of parents with scores below measure cutoffs for clinical significance was no different between study groups for any scale at any time point (eTable 1 in Supplement 2). In single time-point analyses, conclusions from the parametric and nonparametric tests were consistent (Table 3 and eTables 2-10 in Supplement 2).

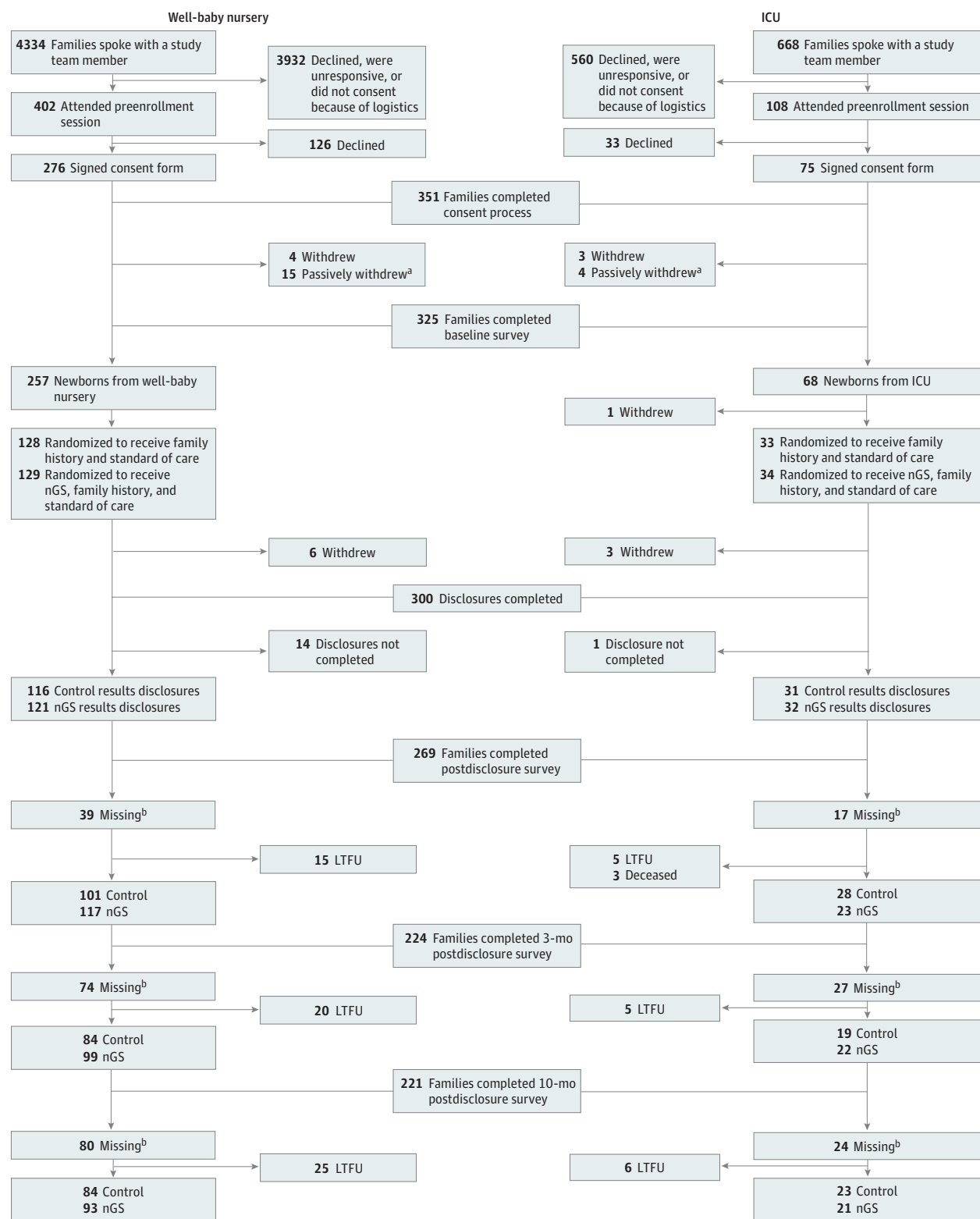
Parent-Child Relationship

Parent-child bonding did not differ between study groups (between-group difference in adjusted mean [SE] Mother-to-Infant Bonding Scale scores: postdisclosure, 0.04 [0.15]; 3 months, -0.18 [0.18]; 10 months, -0.07 [0.20]; joint $P = .57$) or by MDR status over time (between-group difference in adjusted mean [SE] Mother-to-Infant Bonding Scale scores over time: postdisclosure, -0.61 [0.55]; 3 months, 0.17 [0.64]; and 10 months, -0.57 [0.57]; joint $P = .10$) (eTables 11 and 12 and eFigures 1 and 2 in Supplement 2). Parents in the nGS group who received an MDR finding reported lower mean (SD) Mother-to-Infant Bonding Scale impairment scores (range, 0-24, with lower scores indicating less negative feeling toward the new baby) compared with controls (0.53 [1.14] vs 1.18 [1.42]; $P = .03$) after disclosure of results, but this effect was not observed at other time points. Perceived child vulnerability, measured by the short-form Vulnerable Baby Scale (score range, 4-20, with lower scores indicating less perceived vulnerability), did not differ by study group (between-group ratio of adjusted mean [SE] Vulnerable Baby Scale scores over time: postdisclosure, 1.04 [0.03]; 3 months, 0.99 [0.03]; and 10 months, 1.00 [0.03]; joint $P = .25$) or MDR status (between-group ratio of adjusted mean [SE] Vulnerable Baby Scale scores over time: postdisclosure, 1.10 [0.07]; 3 months, 1.03 [0.07]; and 10 months, 1.15 [0.08]; joint $P = .08$) (eTables 13 and 14 and eFigure 3 in Supplement 2; Figure 2a). Mean (SD) Vulnerable Baby Scale scores were higher after disclosure of results in the nGS group than the control group (9.16 [3.20] vs 8.49 [2.80]; $P = .02$; Figure 2a). No differences in vulnerability were observed by MDR status. No differences were observed in parent-child system stress measured on the Parenting Stress Index 4 Short Form (score range, 36-180, with lower scores indicating less parenting stress) at 10 months after disclosure by study group (mean [SD] score: nGS group, 60.77 [15.43]; control group, 62.01 [18.41]) or MDR status (mean [SD] score: no MDR, 61.12 [15.20]; MDR, 57.65 [17.53]) (Table 3).

Parents' Relationship

In generalized estimating equations models of the short-form Kansas Marital Satisfaction Scale (score range, 1-5, with

Figure 1. Study Flow Diagram



Families lost to follow-up (LTFU) submitted a survey for the immediately previous time point, did not submit a survey for this time point, and did not return to any subsequent time point. nGS indicates newborn genomic sequencing; ICU, intensive care unit.

^a Passive withdrawal: neither parent completed a baseline survey within 2 weeks of enrollment and the family was therefore withdrawn.

^b Missing: did not submit a survey for this time point but may have returned at a subsequent time point; includes LTFU.

Table 2. Demographic Characteristics of Parents at Baseline^a

Characteristic	Study group	
	Control (NBS and family history) (n = 255)	nGS (nGS with NBS and family history) (n = 264)
Place of enrollment		
Well-baby nursery	202 (79.2)	204 (77.3)
ICU	53 (20.8)	60 (22.7)
Gender		
Female	136 (53.3)	139 (52.7)
Male	119 (46.7)	125 (47.3)
Race		
White	194 (76.1)	201 (76.1)
Asian	21 (8.2)	24 (9.1)
Black or African American	10 (3.9)	6 (2.3)
Native Hawaiian or other Pacific Islander	0	2 (0.8)
More than 1 race	5 (2.0)	4 (1.5)
Other ^b	9 (3.5)	6 (2.3)
Missing	16 (6.3)	21 (8.0)
Ethnicity		
Non-Hispanic	201 (78.8)	224 (84.8)
Hispanic or Latino	21 (8.2)	8 (3.0)
Missing	33 (12.9)	32 (12.1)
Educational level		
Less than bachelor's degree	29 (11.4)	32 (12.1)
Bachelor's degree or higher	225 (88.2)	232 (87.9)
Missing	1 (0.4)	0
Household income ^c		
\$0-\$100 000	35/132 (26.5)	21/135 (15.6)
\$100 001-\$199 999	47/132 (35.6)	61/135 (45.2)
≥\$200 000	50/132 (37.8)	53/135 (39.3)
Married or in committed relationship		
Yes	239 (93.7)	242 (91.7)
No	15 (5.9)	22 (8.3)
Missing	1 (0.4)	0
Patient is parents' first child		
Yes	130 (51.0)	136 (51.5)
No	101 (39.6)	109 (41.3)
Missing	24 (9.4)	19 (7.2)
MDR finding ^d		
MDR	NA	29 (11.0)
No MDR	NA	232 (87.9)
Carrier status finding ^d		
Yes	NA	224 (85.8)
No	NA	37 (14.2)

Abbreviations: ICU, intensive care unit; MDR, monogenic disease risk; NA, not applicable; NBS, newborn screening; nGS, newborn genomic sequencing.

^a All randomized parents who submitted a baseline survey.

^b Race/ethnicity was self-reported and included, verbatim: Caucasian/Bulgarian, Caucasian/Russian, East Indian, El Salvadorian, Hispanic (n = 2), Indian (n = 2), Jewish, Latina, Latino, Portuguese, Puerto Rican, South American Native, and American Indian/Native Alaskan.

^c Household income as reported only by the parent who completed the enrollment survey on behalf of the family (most often, birth mother), total nonmissing n = 267.

^d Three parents withdrew from the study after submitting a baseline survey and before sequencing.

lower scores indicating lower relationship satisfaction), the pattern of responses over time differed by randomization group (between-group difference in adjusted mean [SE] scores: postdisclosure, -0.19 [0.07]; 3 months, -0.04 [0.07]; and 10 months, -0.01 [0.08]; joint $P = .02$; eTable 15 and eFigure 4 in Supplement 2), with lower relationship satisfaction in the nGS group than the control group. The magnitude of differences in mean scores decreased over time. Parents in the nGS group reported lower relationship satisfaction than control group parents immediately after disclosure (mean

[SD] score, 4.40 [0.79] vs 4.58 [0.66]; $P = .01$), but differences did not persist at later time points. Although parents of infants who later had an MDR reported lower relationship satisfaction compared with other nGS group parents (mean [SD] score, 4.20 [1.05] vs 4.71 [0.55]; $P < .001$) at baseline, modeled satisfaction did not differ by MDR status (eTable 16 and eFigure 5 in Supplement 2). There were no differences in reported satisfaction after result disclosure among these parents. Reported relationship conflict (measured with 1 novel item on a scale from 1-5, with lower scores indicating less

Table 3. Measures of Family Impact Administered After Disclosure of NBS and Family History (Control Group) or in Combination With nGS

Measure and survey time point	Score, mean (SD)					
	Study group			Within nGS group		
	Control	nGS	P value	No MDR	MDR	P value
Parent-child relationship						
PSI-4-SF, DC						
10 mo	20.99 (6.64)	20.94 (5.91)	.93	20.99 (5.87)	20.41 (6.47)	.70
No. of parents	158	172	NA	155	17	NA
PSI-4-SF, P-CDI						
10 mo	17.24 (6.07)	17.10 (4.65)	.82	17.12 (4.52)	16.94 (5.85)	.88
No. of parents	157	182	NA	164	18	NA
PSI-4-SF, PD						
10 mo	23.22 (8.07)	22.78 (7.50)	.61	23.02 (7.52)	20.67 (7.19)	.21
No. of parents	157	181	NA	163	18	NA
PSI-4-SF, total scale						
10 mo	62.01 (18.41)	60.77 (15.43)	.52	61.12 (15.20)	57.65 (17.53)	.38
No. of parents	148	169	NA	152	17	NA
Parents' relationship						
Partner blame						
3 mo	1.76 (0.70)	1.86 (0.79)	.23	1.84 (0.79)	2.00 (0.82)	.37
No. of parents	159	202	NA	180	22	NA
10 mo	1.93 (0.82)	1.71 (0.66)	.006	1.70 (0.69)	1.83 (0.38)	.42
No. of parents	170	189	NA	171	18	NA
Parents' distress						
Self-blame						
3 mo	1.86 (0.86)	1.97 (0.88)	.27	1.95 (0.90)	2.09 (0.75)	.48
No. of parents	160	202	NA	180	22	NA
10 mo	2.05 (0.96)	1.80 (0.83)	.009	1.77 (0.83)	2.11 (0.76)	.09
No. of parents	170	189	NA	171	18	NA

Abbreviations: DC, difficult child subscale; MDR, monogenic disease risk; NA, not applicable; NBS, newborn screening; nGS, newborn genomic sequencing; P-CDI, parent-child dysfunctional interaction; PD, parental distress subscale; PSI-4-SF, Parenting Stress Index 4 Short Form.

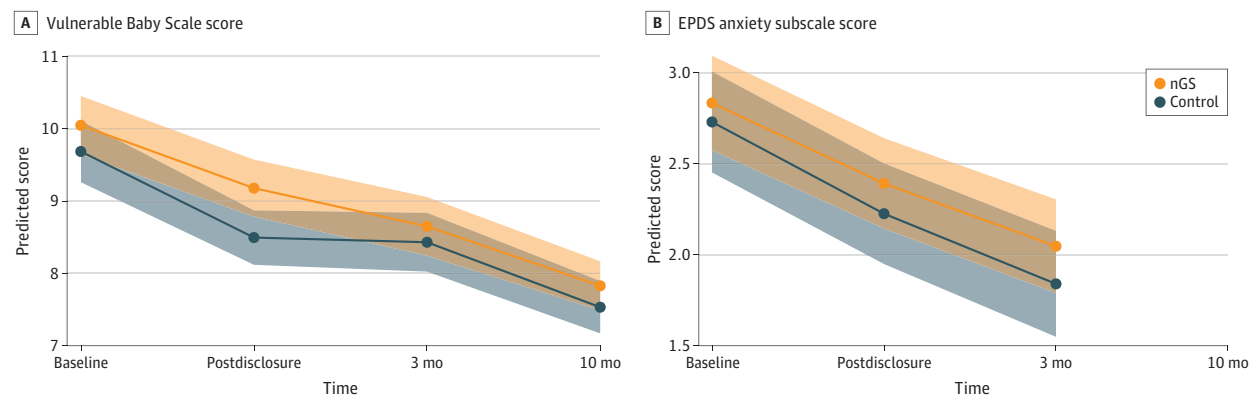
relationship conflict) did not differ by study group over time (between-group difference in adjusted mean [SE] scores: postdisclosure, 0.03 [0.06]; 3 months, 0.05 [0.07]; and 10 months, -0.01 [0.08]; joint $P = .84$; eTable 17 and eFigure 6 in Supplement 2) yet did differ by MDR status among nGS parents (between-group difference in adjusted mean [SE] scores: postdisclosure, -0.47 [0.17]; 3 months, -0.66 [0.23]; and 10 months, -0.51 [0.22]; joint $P = .02$; eTable 18 and eFigure 7 in Supplement 2). The MDR group reported more conflict at baseline, and between-group differences decreased after disclosure. On the partner blame measure (measured with 1 novel item scored from 1 to 5, with lower scores indicating less partner blame), no differences were observed at 3 months after disclosure (mean [SD] score: control group, 1.76 [0.70]; nGS group, 1.86 [0.79]; Table 3). Control group parents reported higher blame compared with parents in the nGS group at 10 months after disclosure (mean [SD] score, 1.93 [0.82] vs 1.71 [0.66]; $P = .006$).

Parents' Distress

Measured anxiety by the Edinburgh Postnatal Depression Scale Anxiety subscale (score range, 0-9, with lower scores indicating less postpartum anxiety) did not differ by study

group when modeled across time (between-group ratio of adjusted mean [SE] scores: postdisclosure, 1.04 [0.08]; 3 months, 1.07 [0.11]; joint $P = .80$) or when comparing mean group-level responses at any individual time point (eTable 19 in Supplement 2; Figure 2b). However, the response pattern on the anxiety measure differed significantly by MDR group. Although scores decreased for both groups after disclosure, the decrease was particularly large among the MDR group at 3 months; this variation reached significance (ratio of adjusted mean [SE] scores: postdisclosure, 1.09 [0.18]; 3 months, 0.64 [0.17]; joint $P = .046$; eTable 20 and eFigure 8 in Supplement 2). Depression measure scores did not differ by study group (ratio of adjusted mean [SE] scores: postdisclosure, 0.98 [0.08]; 3 months, 1.00 [0.10]; joint $P = .95$) or MDR status (ratio of adjusted mean [SE] scores: postdisclosure, 0.95 [0.20]; 3 months, 0.63 [0.16]; joint $P = .13$) (eTables 21 and 22 and eFigures 9 and 10 in Supplement 2). Mean (SD) self-blame scores were higher in parents of infants in the control group than those in the nGS group (2.05 [0.96] vs 1.80 [0.83]; $P = .009$) only at 10 months after disclosure (Table 3). Anxiety as measured by the Generalized Anxiety Disorder Scale-7 (score range, 0-21, with lower scores indicating fewer symptoms of generalized

Figure 2. Parents' Scores on Vulnerable Baby Scale and Edinburgh Postnatal Depression Scale (EPDS) by Study Group Over Time



A, Vulnerable Baby Scale score by study group over time. Group \times time interaction joint $P = .25$. See eTable 13 in Supplement 2 for generalized estimating equation results. Higher scores indicate greater concern or worry about a child's vulnerability and health. Shaded areas indicate pointwise 95% CIs. B, Edinburgh Postnatal Depression Scale, anxiety subscale by study group over time. Group \times time interaction joint $P = .80$. See eTable 19 in Supplement 2 for generalized estimating equation results. Higher numbers indicate more anxiety-related symptoms. Shaded areas indicate pointwise 95% CIs. nGS indicates newborn genomic sequencing.

anxiety) and depression as measured by the Patient Health Questionnaire-9 (score range, 0-30, with lower scores indicating fewer symptoms of depression) were not higher in the nGS group or MDR group than the respective reference group (eTables 5 and 6 in Supplement 2).

Discussion

In this randomized clinical trial of nGS and return of results for a large spectrum of conditions in newborns from well-baby nurseries and ICUs, nGS in general and nGS with MDR findings were not associated with negative psychosocial impacts compared with standard of care that persisted during the study period across 3 family domains: parent-child relationship, parents' relationship with each other, and parents' psychological distress. Even where differences between study groups reached statistical significance, the magnitude of the differences were small and decreased over time. Furthermore, we found no evidence of negative psychosocial effect on the subset of families who received an MDR result. The differences we did observe between those who did and did not receive an MDR result were already present at baseline (before receipt of an MDR result) and decreased over time.

Determining the harm-to-benefit balance of nGS is critical before considering whether nGS should be integrated into routine care. The BabySeq Project demonstrated that nGS can identify risk and carrier status for a broad range of disorders not currently detected in state NBS programs.^{11,39} The present study's findings, consistent with the return of genomic information to parents of newborns in other contexts,^{36,37} suggest that nGS is unlikely to cause harm to families who volunteer for such testing even when carrier status or MDR findings are disclosed to the parents. Although some studies have found evidence of psychosocial harms in response to expanded NBS,²³⁻²⁶ it may have been the timing of the result immediately after birth, uncertainty inherent in the testing process

and results, receipt of abnormal results from a clinical test (vs research study), or the nonelective nature of state NBS inducing parents' distress. We also found lower self-blame and partner blame in the nGS group compared with the control group possibly because nGS information provided some degree of peace of mind. Future research should explore the potential positive psychosocial impacts of nGS.

Limitations

This study has several limitations. First, because few families agreed to hear about the study, the parents who ultimately enrolled may have had more positive attitudes toward research. Second, although we found no evidence of negative psychosocial impact in this volunteer sample of families, our findings may not be generalizable to a scenario in which nGS was state mandated, as with NBS. Third, although we used validated instruments when available, it was necessary to adapt or develop novel measures for some outcomes, and surveys are generally less robust than direct observation for assessment of parent-child relationships. Fourth, the number of families who received an MDR was small, resulting in large 95% CIs for comparisons by MDR status. Fifth, because we collected data for only 10 months after results were disclosed to parents, we cannot draw conclusions about longer-term impacts. Nonetheless, our results suggest that any negative psychosocial effects on families are minor and subside over time.

Conclusions

In this randomized clinical trial of nGS, there was no persistent negative psychosocial effect on families among those who received nGS nor among those who received an MDR finding for their infant. Further research is necessary to explore the impact of nGS in a more diverse patient population and to evaluate potential longer-term effects on families and the children themselves.

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