



Rapid Genome Sequencing Compared with a Gene Panel in Critically Ill Infants with a Suspected Genetic Disorder: An Economic Evaluation

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Objective To compare 1-year health care costs and quality-adjusted life years (QALYs) for 2 diagnostic strategies in critically ill infants with suspected genetic disorders: 1) early rapid genome sequencing (rGS; within 7 days of admission) for all infants, and 2) early targeted neonatal gene sequencing (NewbornDx) for all infants, followed by later rGS (after 7 days) for undiagnosed infants.

Study design The Genomic Medicine for Ill Neonates and Infants study was a multicenter, prospective study that enrolled 400 hospitalized infants under 1 year of age with suspected genetic disorders. All participants underwent both rGS and NewbornDx. Using patient-level Genomic Medicine for Ill Neonates and Infants data and 2023 Medicare rates, we developed a decision tree to compare total costs and QALYs over a 1-year period for these 2 hypothetical testing strategies.

Results The diagnostic yield and upfront testing costs were higher for rGS (49%; \$12,297) than NewbornDx (27%; \$2449; $P < .05$). As neither early testing nor diagnosis significantly affected QALYs, we conducted a cost-minimization analysis, focusing solely on cost differences between strategies. Over 1 year, early rGS was estimated to save \$158,592 per patient (95% CI: \$63,701–\$253,292) compared with early NewbornDx with later rGS if necessary.

Conclusions Early rGS results in substantial health care cost savings, highlighting the need to expand reimbursement to improve access early in a hospitalization for critically ill infants. (*J Pediatr* 2026;289:114889).

Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: [NCT03890679](https://clinicaltrials.gov/ct2/show/study/NCT03890679).

Genetic disorders are a major cause of infant mortality in the US.¹ For critically ill infants with suspected genetic disorders, traditional genetic tests are often ordered serially, have low diagnostic yields, and have slow turnaround times, which can delay informed care management. In the US, rapid genome sequencing (rGS) can generally provide results within 7 days and offers higher diagnostic yields, but higher upfront costs have limited its widespread use.^{2,3} Previous US economic evaluations of rGS in critically ill infants that included upfront and downstream costs have demonstrated that rGS is cost-effective or cost-saving when used as a first-line diagnostic approach.^{2,4} However, these studies have relied on data from restricted geographic areas, limited follow-up duration, or decision analytic models developed without empirical data.²

The Genomic Medicine for Ill Neonates and Infants (GEMINI) study was the first multistate US prospective study of rGS in hospitalized, critically ill infants (age <1 year) with suspected genetic disorders ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03890679) Identifier: [NCT03890679](https://clinicaltrials.gov/ct2/show/study/NCT03890679)).⁵ The study has been described in detail elsewhere.⁵ In summary, from June 2019 to November 2021, 400 hospitalized infants (93% admitted to an intensive care unit) underwent simultaneous testing with rGS (Rady Laboratory) and NewbornDx (Athena Diagnostics), a commercial targeted neonatal gene-sequencing panel that can identify variants across 1722 genes linked to infant-onset disorders. The GEMINI study compared the two tests in terms of time to result, diagnostic yield, and clinical utility. Although enrollment depended on the proband, trio testing was preferred. Participants were followed from

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CGA	Corrected gestational age
GEMINI	Genomic Medicine for Ill Neonates and Infants
HRQOL	Health-related quality of life
IRB	Institutional Review Board
QALYs	Quality-adjusted life years
rGS	Rapid genome sequencing
VUS	Variant of uncertain significance

enrollment until 1 year corrected gestational age (CGA). Although NewbornDx offered a faster median time to return of results (4.2 vs 6.1 days for rGS), rGS had a significantly higher diagnostic yield (49% vs 27%; $P < .05$).^{2,3}

The GEMINI study also aimed to conduct the first evidence-based US economic evaluation comparing rGS to NewbornDx in a diverse cohort of critically ill hospitalized infants with suspected genetic disorders. In GEMINI, all enrolled infants underwent both rGS and NewbornDx concurrently, which provided patient-level clinical and cost data from the study. These data were then used to parameterize a decision model comparing 2 hypothetical testing strategies (not actually implemented in the study): 1) early rGS for all hospitalized infants, and 2) early NewbornDx for all hospitalized infants followed later by rGS for undiagnosed infants. The goal of the study was to compare costs and quality-adjusted life years (QALYs) between the 2 modeled strategies over the 1-year study period from the US health care perspective.

Methods

Overview

This study was conducted in several stages: 1) collection of data during the GEMINI study, including diagnostic yield, health-related quality of life (HRQOL), and health care utilization that could be used for the model-based economic evaluation comparing 2 hypothetical strategies; 2) analysis of these patient-level data to generate model parameters; and 3) development of a decision tree model informed by these empirical inputs.

The study received approval from the Johns Hopkins Single Institutional Review Board (IRB; JHUSIRB0000007) and all participating site IRBs. The IRB submission included an economic evaluation study protocol in addition to the clinical study protocol. The economic evaluation study protocol is not publicly available. Parents of all participants provided informed consent.

Data Collection

Study site coordinators collected baseline data, including the infant's gestational age, birth weight, enrollment age, sex, race and ethnicity, and residential ZIP code to match to median household income.⁶ Caregivers reported infant health-care utilization and HRQOL data through 1-year CGA. After discharge, monthly caregiver health resource utilization surveys captured infant hospitalizations, physician visits, laboratory tests, imaging, procedures, home services, allied health professional visits, and medications (**Supplemental Methods 1**; available at www.jpeds.com). Parents/caregivers also rated their infant's HRQOL on a visual analog scale (0-100) and their own HRQOL using the 12-item Short-Form Health Survey at discharge and every 3 months (**Supplemental Methods 2-3**; available at www.jpeds.com).⁷ If surveys were incomplete, coordinators abstracted utilization data from electronic medical records but left HRQOL surveys blank. For each parent/caregiver-reported

hospitalization at the enrolling hospital, coordinators obtained deidentified hospital billing charges and Current Procedural Terminology/Healthcare Common Procedure Coding System codes and uploaded these into REDCap. These data allowed us to estimate both facility and professional fees for services used.^{8,9}

Estimating Resource Utilization and Costs

All reported health care utilization and hospital charge data were converted into costs using Centers for Medicare & Medicaid Services fee schedules and hospital cost-to-charge ratios.^{10,11} We reviewed all outpatient medications and excluded their costs from the analysis because they were relatively inexpensive generics, which had minimal annual costs. Costs were adjusted to 2023 US dollars using the US medical care consumer price index.¹² Due to the study's short time horizon, we did not discount costs or health utility values.

Estimating Health Utility

The results of 12-item Short-Form Health Survey were converted into Short Form 6-Dimensions utility values, ranging from 0 (dead) to 1 (perfect health). We divided visual analog scale scores by 100 to estimate utility scores. We assigned a utility value of 0 to deceased infants and 0.64 to bereaved caregivers.¹³ We calculated accrued QALYs for infants and parents/caregivers from enrollment through 1 year CGA by weighting time spent in each health state by its utility value.¹⁴

Addressing Missing Data

The analysis used multiple imputation by chained equations to impute missing observations for health care resource use, nonenrolling hospitalization costs, utility values, and baseline demographic variables. The R package procedure generated 30 imputed datasets.^{15,16} **Supplemental Methods 4**; available at www.jpeds.com, provides the detailed methods.

Statistical Analysis

We stratified infants by timing of rGS and NewbornDx after admission: 1) early testing (≤ 7 days after admission) and 2) later testing (> 7 days after admission). This 7-day cutoff reflected both the cohort's median testing time and clinical agreement that testing within the first week is critical for clinical management. Baseline characteristics and study outcomes were reported for the entire cohort and for each test group. Categorical variables were reported as frequencies, continuous variables as means (SD) or medians (IQR), and group comparisons used t-tests, Kruskal-Wallis, or Fisher exact and chi-square tests (2-sided, 5% significance level).

Identifying Factors Influencing Utilization, Costs, and QALYs. We used multivariable regression models to assess the impact of early testing without later testing vs strategies that required later testing and the impact of diagnosis vs no diagnosis on health care costs, length of stay, and QALYs for infants and caregivers. Models adjusted for relevant demographic and clinical covariates, with sensitivity analyses

addressing death and illness severity. Full model specifications, variable definitions, and statistical procedures are provided in **Supplemental Methods 5**; available at www.jpeds.com.

Economic Evaluation. We used the empirical data collected in GEMINI, including diagnostic yield, HRQOL, and health care utilization, to populate a decision tree model comparing 2 hypothetical testing strategies: 1) early rGS and 2) early NewbornDx followed by later rGS for undiagnosed infants (early NewbornDx/late rGS). Strategies were selected to address whether less expensive tests should be used prior to rGS. We used a decision tree model (**Figure**) due to the short time horizon of the study and obtained data inputs from several sources (**Table I**).

Diagnostic Rates. We obtained diagnostic rates from GEMINI study variant result classifications.⁵ Infants were classified as having a diagnosis if they had a diplotype that fit the pattern of inheritance of a disorder that comprised a variant or variants classified as pathogenic, likely pathogenic, or of uncertain significance (VUS) only if associated with genes that fit the infant's phenotype. All NewbornDx diagnoses were confirmed through rGS, except for 9 cases unique to NewbornDx. We used this partial overlap to estimate the diagnostic rate for later rGS following a negative early NewbornDx result in the decision model.

Test Costs. We used Current Procedural Terminology codes and 2023 Medicare reimbursement rates to estimate the costs of NewbornDx and rGS, accounting for whether rGS was performed as a proband, duo, or trio.

Other Healthcare Costs during the Study Period. The decision model includes 4 unique pathways (**Figure**). Both rGS and NewbornDx strategies include pathways for early testing with a diagnosis (no later testing). The early rGS strategy also includes a pathway for early testing without a diagnosis (no later testing). The NewbornDx strategy

includes 2 pathways not included in the rGS strategy: 1) early testing without a diagnosis, followed by later testing with a diagnosis, and 2) early testing without a diagnosis, followed by later testing without a diagnosis. We used multivariable regression models to predict total health care costs for these 4 pathways, excluding the costs of rGS and NewbornDx.

To account for uncertainty, we performed a probabilistic sensitivity analysis with 10 000 iterations to construct 95% uncertainty intervals around our mean expected values. Deterministic sensitivity analyses varied test costs. In 2 scenario analyses we: 1) assumed that VUS results were nondiagnostic; and 2) did not trim total costs during the study period. Analyses were conducted using R4.3.0 (R Core Team, 2023).¹⁷

Results

Sample Characteristics

Table II presents baseline demographic and clinical characteristics of infants and families, comparing those tested early vs later. The median infant age at enrollment was 18.0 days (IQR: 8.0-66.2) with 58% male and 57% with public insurance. Early and later testers differences included their median age at enrollment (8.0 days [IQR: 4.0-65.0] vs 32.0 [IQR: 13.0-68.5]; $P < .01$), mean gestational age (37.2 weeks [SD: 3.1] vs 36.0 [SD: 4.0]; $P < .01$), and birth weight (2809 g [SD: 817] vs 2596 [SD: 989], $P = .02$).

Survey Response Rates

A parent/caregiver or study coordinator completed 98% of health care utilization surveys. Forty-four percent of parents/caregivers completed all child and parent HRQOL surveys, with 93% completing at least 1 survey. **Supplemental Table 1**; available at www.jpeds.com, displays characteristics of infants and families with and without missing HRQOL data.

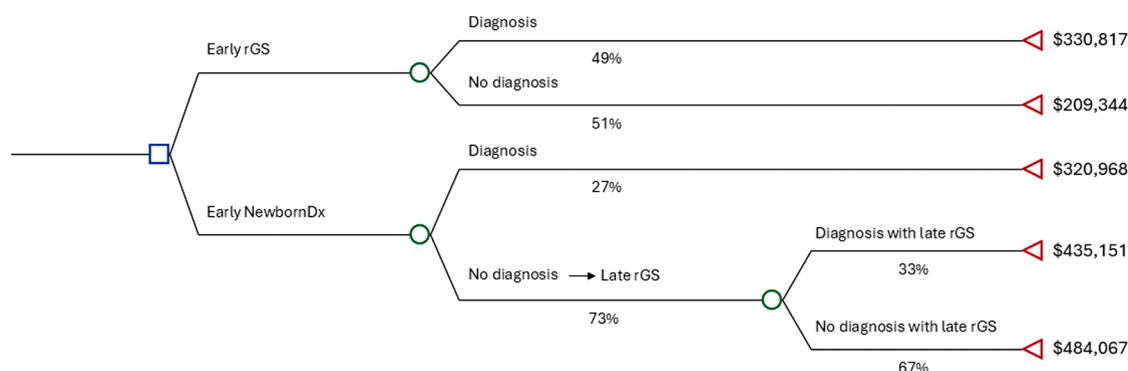


Figure. Decision analytic model comparing 2 hypothetical testing strategies for critically ill hospitalized infants with suspected genetic conditions.

Table I. Decision analytic model inputs and ranges used in probabilistic and deterministic sensitivity analyses

Decision analytic model input	Mean*	Distributions used in probabilistic sensitivity analysis	95% CI of distributions used in probabilistic sensitivity analysis	Ranges used in deterministic sensitivity analyses
Diagnostic rates				
Early rGS	0.49 [†]	Binomial	(0.44, 0.54)	-
Early NewbornDx	0.27	Binomial	(0.23, 0.32)	-
Later rGS, following NewbornDx for undiagnosed infants	0.33	Binomial	(0.28, 0.39)	-
Costs of rGS and NewbornDx*				
rGS	\$12,297		-	\$1000-\$12,297
NewbornDx	\$2449		-	\$100-\$2449
Other healthcare costs during the study period for 4 model pathways [‡]				
For both rGS and Newborn Dx strategies in the model: Early testing with a diagnosis, and no later testing	\$318,520	Sampling distribution from GEMINI data	(\$220,108, \$429,139)	-
For rGS strategy: Early rGS testing without a diagnosis and no later testing	\$197,046	Sampling distribution from GEMINI data	(\$138,211, \$263,891)	-
For Newborn Dx strategy: Early Newborn Dx testing without a diagnosis, followed by later rGS testing with a diagnosis	\$420,405	Sampling distribution from GEMINI data	(\$285,019, \$572,058)	-
For Newborn Dx strategy: Early Newborn Dx testing without a diagnosis, followed by later rGS testing without a diagnosis	\$469,321	Sampling distribution from GEMINI data	(\$358,768, \$587,167)	-

CPT, Current Procedural Terminology.

*All model inputs were derived from GEMINI study data, except for (1) rGS cost, which was derived using a weighted average of 2023 Medicare reimbursement rates for the CPT codes 0094U (proband) and 81 426 (duo and trio) based on the rates of proband/duo/trio utilization in GEMINI, and (2) NewbornDx, which was based on the 2023 Medicare reimbursement rate for the CPT code 81 443.

[†]In the model, we changed the rGS diagnostic status of the 1 participant with Prader-Willi syndrome from nondiagnostic to diagnostic. We made this adjustment because the current diagnostic capabilities of rGS now can identify mutations associated with Prader-Willi syndrome. As such, the diagnostic rate for rGS changed from 48.75% to 49.00%.

[‡]The expected costs for the four model pathways are based on the predicted costs generated by the multivariable regression model shown in Table IV, which uses total cost over the study period (excluding rGS and NewbornDx costs) as the dependent variable.

Unadjusted Resource Utilization and Costs during the Enrolling Hospitalization

Most infants (78%) received trio rGS, 18% infant-mother duo, and 4% proband. Fifty-one percent of infants underwent early testing. The mean enrolling hospitalization cost was \$295,835 (SD: \$25,770) per patient, with a median of \$115,401 (IQR: \$109,225-\$123,038). The mean enrolling hospitalization length of stay was 60.8 days (SD: 74.3) with a median of 33.0 days (IQR: 14.0-79.0). Additional resource utilization is shown in Table III and Supplemental Table 2; available at www.jpeds.com.

Unadjusted Resource Utilization and Costs during Follow-Up and Total Study Period

The mean follow-up period from enrolling hospitalization discharge to 1 year CGA was 270.2 days (SD: 139.1) with a median of 339.0 days (IQR: 153.0-363.0). During this period, infants had a mean of 2.9 subsequent hospitalizations (SD: 2.4), 7.6 primary care visits (SD: 0.2), and 11.4 specialty outpatient visits (SD: 0.6). The mean follow-up cost per patient was \$92,912 (SD: \$15,681) with a median of \$45,350 (IQR: \$40,509-\$47,564). For the total study period, the mean total cost per patient was \$388,572 (SD: \$31,271) with a median of \$169,990 (IQR: \$156,216-\$179,758) (Table III).

Adjusted Cost and Length of Stay Analyses

In multivariable regression analyses adjusting for baseline characteristics, early testing without later testing (irrespective

of platform) was associated with significantly reduced costs and length of stay during the enrolling hospitalization vs strategies that required later testing (mean per patient reduction of \$189,719 and 54 days, respectively; $P < .01$ for both estimates, Tables IV and V). Over the entire study period, early testing without later testing was associated with a mean cost savings of \$272,275 per patient ($P < .01$) vs strategies that required later testing (Tables I and IV). Diagnosis and its interaction with early testing was not significantly associated with enrolling hospital costs, length of stay, or total costs (Table IV). Adjusting for infant death with and without withdrawal of care did not alter the findings (Supplemental Table 3; available at www.jpeds.com). This indicates that after adjusting for other characteristics, enrolling hospitalization costs, length of stay, and total costs were not significantly different between infants who died and those who survived. Adjusting for urgent testing, which was more common within the early testing period (69% of early testers were urgent cases vs 13% of later testers, $P < .05$ for difference), also did not alter the findings (Supplemental Table 4; available at www.jpeds.com).

Based on the multivariable regression model, the expected mean per patient costs over the total study period, excluding testing costs, were 1) early testing with a diagnosis and no late testing: \$318,520 (95% CI: \$220,108-\$429,139), 2) early testing without a diagnosis and no late testing: \$197,046 (95% CI: \$138,211-\$263,891), 3) early testing without a diagnosis followed by later testing with a diagnosis: \$420,405

Table II. Infant and family baseline characteristics

Sample characteristics	Infants with early testing (≤7 days after admission) (n = 205)	Infants with later testing (>7 days after admission) (n = 195)	P value for difference between early and later testers*	Entire cohort (n = 400)
Infant characteristics				
Age at enrollment (d), median (IQR)	8.0 (4.0-65.0)	32.0 (13.0-68.5)	P < .01	18.0 (8.0-66.5)
Sex, n (%)			P = .94	
Male	118 (57.6)	113 (57.9)		231 (57.8)
Female	87 (42.4)	82 (42.1)		169 (42.2)
Race, n (%)†	[n = 180]	[n = 167]	P = .04	[n = 347]
American Indian	2 (1.1)	2 (1.2)		4 (1.2)
Asian	16 (8.9)	6 (3.6)		22 (6.3)
Black	14 (7.8)	29 (17.4)		43 (12.4)
Multiracial	35 (19.4)	28 (16.8)		63 (18.2)
White	110 (61.1)	98 (58.7)		208 (59.9)
Other	3 (1.7)	4 (2.4)		7 (2.0)
Hispanic ethnicity, n (%)‡	[n = 195]	[n = 177]	P = .69	[n = 372]
Yes	62 (31.8)	52 (29.4)		114 (30.6)
Infant insurance, n (%)			P = .02	
Public insurance§	105 (51.2)	124 (63.6)		229 (57.3)
Private insurance	100 (48.8)	71 (36.4)		171 (42.8)
Gestational age (wks), mean (SD)	37.2 (3.1)	36.0 (4.0)	P < .01	36.6 (3.6)
Birth weight (grams), mean (SD)	2809.4 (817) [n = 202]	2596.0 (988.9) [n = 195]	P = .02	2704.6 (910.7) [n = 397]
Household characteristics				
Median household income in participant's zip code, n (%)	[n = 202]	[n = 193]	P = .76	[n = 395]
<\$50,000	33 (16.3)	37 (19.2)		70 (17.7)
\$50,000-\$74,999	84 (41.6)	79 (40.9)		163 (41.3)
\$75,000-\$99,999	59 (29.2)	49 (25.4)		108 (27.3)
>\$100,000	26 (12.9)	28 (14.5)		54 (13.7)
Maternal characteristics				
Age (y), mean (SD)	30.0 (5.7) [n = 205]	30.5 (5.8) [n = 193]	P = .39	30.2 (5.7) [n = 398]
Race, n (%)	[n = 180]	[n = 167]	P = .01	[n = 347]
American Indian	2 (1.1)	3 (1.8)		5 (1.4)
Asian	19 (10.6)	9 (5.4)		28 (8.1)
Black	17 (9.4)	33 (19.8)		50 (14.4)
Multiracial	15 (8.3)	5 (3.0)		20 (5.8)
White	124 (68.9)	111 (66.5)		235 (67.7)
Other¶	3 (1.7)	6 (3.6)		9 (2.6)
Hispanic ethnicity, n (%)	[n = 198]	[n = 187]	P = .64	[n = 385]
Yes	56 (28.3)	48 (25.7)		104 (27.0)
Paternal characteristics				
Race, n (%)	[n = 177]	[n = 162]	P = .08	[n = 339]
American Indian	3 (1.7)	3 (1.9)		6 (1.8)
Asian	16 (9.0)	8 (4.9)		24 (7.1)
Black	20 (11.3)	35 (21.6)		55 (16.2)
Multiracial	10 (5.6)	4 (2.5)		14 (4.1)
White	122 (68.9)	107 (66.0)		229 (67.6)
Pacific Islander	1 (0.6)	0 (0)		1 (0.3)
Other**	5 (2.8)	5 (3.1)		10 (2.9)
Hispanic ethnicity, n (%)	[n = 193]	[n = 178]	P = .79	[n = 371]
Yes	50 (25.9)	43 (24.2)		93 (25.1)

All P-values < .05 are bolded.

*We used ANOVA to compare the difference between groups in terms of gestational age, birth weight, and maternal age; we used Kruskal-Wallis test for age at enrollment; we used chi-square test for ethnicity, infant insurance, and household income; and we used Fisher's exact test for race.

†Infant race is derived from mother and father race. If mother's or father's race did not match, then the infant was categorized as multiracial. If mother's or father's race was categorized as "Other," the infant's race was categorized as "Other."

‡If either the mother or father reported their ethnicity to be Hispanic, the infant was categorized as Hispanic.

§Infants reported as not having insurance were reclassified as having public insurance.

¶Mothers who reported their race as "Other" reported their race to be Amish, Bangladeshi, Cape Verdean, Dominican, Malian, Puerto Rican, or Puerto Rican/Taino.

**Fathers who reported their race as "Other" reported their race to be Amish, Asian Black, Bangladeshi, Black African American, White Caucasian, Cape Verdean, Dominican, Egyptian, or Puerto Rican.

(95% CI: \$285,019-\$572,058), and 4) early testing without a diagnosis followed by later testing without a diagnosis: \$469,321 (95% CI: \$358,768-\$587,167) (Table I). As noted

with the 95% CIs, these results are consistent with the regression findings that cost differences were significant between those that required later testing and those that did

Table III. Unadjusted study outcomes: diagnostic rates, resource utilization and costs

Unadjusted study outcomes	Infants with early testing (≤7 days after admission) (n = 205)	Infants with late testing (>7 days after admission) (n = 195)	Entire cohort (n = 400)
Diagnostic rates*			
Rapid genome sequencing (rGS)	0.55	0.43	0.49
NewbornDx	0.32	0.22	0.27
rGS and NewbornDx (used sequentially)	0.57	0.46	0.51
Enrolling hospitalization testing and length of stay			
Type of rGS, n (%)			
Proband	5 (2.4)	11 (5.6)	16 (4.0)
Duo	30 (14.6)	42 (21.5)	72 (18.0)
Trio	170 (82.9)	142 (72.8)	312 (78.0)
Total length of stay for enrolling hospitalization (days)†			
Mean (SD)	36.4 (48.8)	86.5 (87.0)	60.8 (74.3)
Median (IQR)	20.0 (9.0-40.0)	58.0 (25.5-119.5)	33.0 (14.0-79.0)
ICU length of stay for enrolling hospitalization (days)†			
Mean (SD)	31.2 (43.3)	71.6 (68.8)	50.9 (60.6)
Median (IQR)	17.0 (5.0-36.0)	52.5 (21.0-103.0)	29.0 (10.0-69.0)
At least 1 night at ICU, n (%)	186 (91) [n = 205]	187 (96) [n = 194]	373 (93) [n = 399]
Discharge location‡, n (%)			
Home	166 (81.0)	147 (75.4)	313 (78.3)
Another inpatient hospital (transfer)	6 (2.9)	11 (5.6)	17 (4.3)
Long-term care facility	0 (0.0)	3 (1.5)	3 (0.8)
Inpatient rehabilitation facility	2 (1.0)	5 (2.6)	7 (1.8)
Infant died prior to discharge	30 (14.6)	25 (12.8)	55 (13.8)
Hospitalized until 1 year corrected gestational age (CGA)§	1 (0.5)	4 (2.1)	5 (1.3)
Follow-up resource utilization: discharge from enrolling hospitalization to 1 year CGA			
Duration of follow-up period (d)			
Mean (SD)	260.5 (147.5)	280.4 (129.3)	270.2 (139.1)
Median (IQR)	336.0 (119.0-368.0)	339.0 (195.0-357.0)	339.0 (153.0-363.0)
Among infants who completed the study			
Mean (SD)	317.6 (108.0)	319.6 (97.4)	318.6 (102.6)
Median (IQR)	358.0 (264.8-380.0)	349.0 (301.2-370.8)	353.0 (290.5-375.0)
Among infants who were lost to follow-up			
Mean (SD)	254.9 (126.2)	222.0 (124.2)	244.8 (121.4)
Median (IQR)	274.0 (196.0-341.0)	231.5 (156.5-297.0)	274.0 (186.0-341.0)
Among infants who died during the study			
Mean (SD)	52.4 (71.1)	99.9 (108.4)	73.3 (91.9)
Median (IQR)	27.5 (10.0-66.2)	66.0 (22.0-138.0)	35.0 (12.0-96.0)
Subsequent hospitalizations§			
Mean (SD)	3.0 (2.6)	2.8 (2.2)	2.9 (2.4)
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
Emergency room visits, mean (SD)	1.8 (0.2)	1.6 (0.2)	1.71 (0.1)
Primary care visits**, mean (SD)	7.5 (0.3)	7.6 (0.4)	7.6 (0.2)
Specialist outpatient visits**, mean (SD)	10.3 (0.6)	12.6 (0.9)	11.4 (0.6)
Cardiologist	1.2 (0.2)	1.8 (0.4)	1.5 (0.2)
Gastrointestinal	0.9 (0.1)	1.5 (0.2)	1.2 (0.1)
Geneticist	0.7 (0.1)	0.6 (0.1)	0.6 (0.1)
Neurologist	1.3 (0.2)	0.8 (0.1)	1.1 (0.1)
Pulmonologist	0.5 (0.1)	1.0 (0.1)	0.8 (0.1)
Other, mean (SD)¶	5.6 (0.5)	6.8 (0.6)	6.2 (0.4)
Complex care clinic visits, mean (SD)	0.3 (0.1)	0.3 (0.1)	0.3 (0.04)
Outpatient labs, tests, or procedures, mean (SD)			
Blood work	4.7 (0.6)	3.5 (0.4)	4.1 (0.4)
Echocardiogram	1.8 (0.2)	1.6 (0.2)	1.7 (0.1)
Genetic test	0.9 (0.1)	0.6 (0.1)	0.8 (0.1)
MRI	0.7 (0.1)	0.6 (0.1)	0.7 (0.1)
Outpatient surgery	0.7 (0.1)	0.6 (0.1)	0.7 (0.1)
X-ray	1.3 (0.2)	1.1 (0.1)	1.2 (0.1)
Other¶	11.3 (1.0)	9.1 (0.8)	10.2 (0.6)
Occupational, physical, or speech therapy visits**, mean (SD)	22.3 (1.6)	24.6 (1.7)	23.4 (1.2)
Home nursing visits, mean (SD)	11.8 (2.7)	14.7 (2.8)	13.2 (2.0)
Home health aide visits, mean (SD)	2.1 (0.4)	2.2 (0.7)	2.1 (0.4)
Long-term care (LTC) admissions, mean (SD)	0.2 (0.2)	0.6 (0.5)	0.4 (0.2)
Inpatient rehabilitation admissions, mean (SD)	1.4 (1.4)	1.5 (1.1)	1.4 (0.9)
Total costs (2023 US\$)			
Enrolling hospitalization††			
Mean (SD)	\$194,072 (23 074)	\$402,990 (46 258)	\$295,835 (25 770)
Median (IQR)	\$77,934 (76 880-79 801)	\$191,117 (171 326-199 516)	\$115,401 (109 225-123 038)

(continued)

Table III. Continued

Unadjusted study outcomes	Infants with early testing (≤7 days after admission) (n = 205)	Infants with late testing (>7 days after admission) (n = 195)	Entire cohort (n = 400)
Postdischarge follow-up			
Mean (SD)	\$70,282 (19 463)	\$116,463 (24 629)	\$92,912 (15 681)
Median (IQR)	\$34,577 (28 620-45,859)	\$49,147 (44 482-64 869)	\$45,350 (40 509-47 564)
Total cost until infant's 1 year CGA [§]			
Mean (SD)	\$264,455 (29 615)	\$519,575 (54 436)	\$388,572 (31 271)
Median (IQR)	\$120,044 (106 951-130 492)	\$241,837 (217 103-262 902)	\$169,990 (156 216-179 758)

*The diagnosis rates include variants categorized as pathogenic, likely pathogenic, or variants of uncertain significance.

†Includes any additional days that may have resulted from transfers to acute-care hospitals.

‡From the enrolling hospital.

§Subsequent hospitalizations are any hospitalizations that occur after discharge from the enrolling hospitalization or after discharge from an acute-care hospital that the infant was transferred to from the enrolling hospital.

¶See [Supplemental Table 2](#); available at www.jpeds.com for details on "Other" resource utilization.

**At home, in person, or through telehealth.

††Includes any additional costs that may have resulted from direct transfers to acute-care hospitals.

not, but not between those who did or did not receive a diagnosis.

Adding testing costs to the expected mean per-patient costs over the study period allowed us to estimate the total expected costs for each arm of the decision tree: 1) \$330,817 for undergoing early rGS and receiving a diagnosis, 2) \$209,344 for undergoing early rGS without receiving a diagnosis, 3) \$320,968 for early NewbornDx with a diagnosis,

4) \$435,151 for early NewbornDx without a diagnosis, followed by rGS with a diagnosis, and 5) \$484,067 for early NewbornDx without a diagnosis, followed by rGS without a diagnosis ([Figure](#)).

Economic Evaluation

Because neither early testing nor diagnosis had a significant impact on QALYs ([Supplemental Table 5](#); available at

Table IV. Adjusted analyses: multivariable regression models with three dependent variables: 1) enrolling hospital cost, 2) enrolling hospital LOS, 3) total cost over the study period

Independent variables	Outcome variables					
	Model 1. Enrolling hospital cost		Model 2. Enrolling hospital LOS		Model 3. Total cost over study period	
	Exponentiated coefficient*	P value	Exponentiated coefficient*	P value	Exponentiated coefficient*	P value
Intercept	\$467,918	<0.001	110 days	<0.001	\$575,191	<0.001
Later testing (>7 days after admission) (ref)						
Early testing (≤7 days after admission)	0.46	0.002	0.35	<0.001	0.43	0.002
Infant did not receive a diagnosis (ref)						
Infant did receive a diagnosis	0.87	0.36	0.88	0.21	0.88	0.41
(Interaction): Early testing * with diagnosis	1.56	0.15	1.64	0.07	1.77	0.07
Normal or low birth weight (>1500g) (ref)						
Very low birth weight (≤1500g)	1.75	0.02	1.54	0.01	1.41	0.18
Gestational age at birth: >32 wks (ref)						
Gestational age at birth: ≤32 wks	0.91	0.69	0.93	0.70	0.97	0.91
Household income: <\$50,000 (ref)						
\$50,000-\$74,999	0.68	0.01	0.78	0.02	0.76	0.08
\$75,000-\$99,999	0.77	0.11	0.67	0.002	0.77	0.12
≥\$100,000	0.76	0.23	0.68	0.03	0.68	0.14
Infant race and ethnicity: White, non-Hispanic or Latino (ref)						
Black, non-Hispanic or Latino	1.15	0.42	1.09	0.46	1.40	0.06
Hispanic or Latino	0.95	0.74	0.93	0.51	1.04	0.81
Other race, non-Hispanic or Latino	0.63	0.11	0.92	0.62	0.75	0.30
Insurance: Public (ref)						
Private	0.85	0.26	0.89	0.25	0.91	0.54

LOS, length of stay.

*Coefficients have been exponentiated to show the multiplicative change in the outcome variable for different categories of the predictor variable relative to the reference category. The intercept represents the baseline outcome variable at the reference category of all predictors.

Table V. Expected enrolling hospital costs and length of stay for four different testing scenarios[†]

Enrolling hospital cost and length of stay	Enrolling hospital cost		Enrolling hospital length of stay (days)	
	Mean	95% uncertainty intervals	Mean	95% uncertainty intervals
Early testing with a diagnosis and no later testing	\$215,220	(\$143,519, \$295,565)	42	(31, 55)
Early testing without a diagnosis and no later testing	\$154,259	(\$106,851, \$214,076)	29	(22, 35)
Early testing without a diagnosis followed by later testing with a diagnosis	\$304,098	(\$217,283, \$405,325)	73	(60, 88)
Early testing without a diagnosis followed by later testing without a diagnosis	\$343,978	(\$265,584, \$426,800)	83	(70, 97)

†As indicated by the 95% CIs, the results align with the regression findings: cost and LOS differences were statistically significant between strategies that required later testing and those that did not, but not between groups that did or did not receive a diagnosis.

www.jpeds.com), we conducted a cost-minimization analysis, focusing solely on cost differences between strategies rather than differences in health outcomes.

The expected total costs per patient over the study period are \$269,566 (95% CI: \$211,194-\$332,326) for early rGS and \$428,158 (95% CI: \$358,729-\$503,403) for early NewbornDx/later rGS. Early rGS is expected to save \$158,592 (95% CI: \$63,701-\$253,292) in health care costs per patient over the study period compared with NewbornDx/later rGS (Table VI, Supplemental Figures 1-3; available at www.jpeds.com. for sampling distributions).

The observed cost savings are primarily driven by the efficiency of testing all infants early in the hospitalization with rGS, which eliminates the need for subsequent reflex testing. In contrast, beginning with NewbornDx often necessitates later rGS when no diagnosis is achieved, substantially increasing the overall duration of the hospitalization and associated costs.

Sensitivity analyses showed that varying the testing costs minimally affected results (Supplemental Figures 4-5; available at www.jpeds.com). When VUS results were considered nondiagnostic, early rGS saved an estimated \$186,816 (95% CI: \$11,945-\$373,887) compared with early NewbornDx/later rGS over the study period (Supplemental Table 6; available at www.jpeds.com). Without cost trimming in our regression models, early rGS

saved \$185,221 (95% CI: \$47,677-\$321,086) compared with early NewbornDx/later rGS over the study period (Supplemental Table 6).

Discussion

Our decision analytic model demonstrates that performing early rGS for critically ill infants in the US with suspected genetic disorders could save over \$150,000 in health care costs during an infant's first year of life compared with early NewbornDx followed by rGS (if needed). The cost savings stemmed primarily from shorter length of stay if later rGS was avoided. These results are consistent with prior studies showing that rGS is most cost-effective when used early in a hospitalization of critically ill infants as a first-line test.^{2,4} By delivering timely results, rGS can guide management decisions sooner and shorten hospital stays, leading to favorable economic value.^{2,4} Our economic data are unique in their direct derivation from this particular clinical trial and testing approach. Importantly, our study leverages empirical evidence from GEMINI's 400 infants and offers insights into resource utilization for this population in the US health care system, spanning from the enrolling hospitalization through 1 year of follow-up, a timeframe pertinent for US payer decision-making.

Our study highlights the economic value of ordering rGS early in a hospitalization, regardless of diagnostic outcome. This result aligns with GEMINI, in which physicians rated rGS very useful/useful in 87% of diagnosed and 65% of undiagnosed cases.⁵ One benefit of early rGS is that it permits physicians to make timely and informed care management decisions based on the presence or absence of genetic diagnosis.

Currently, most state Medicaid programs (covering approximately 40% of US children) and private insurers do not routinely reimburse hospitals for inpatient rGS.¹⁸ Our findings are timely as more payers are considering or are being required by new legislation to establish supplemental payments to hospitals for inpatient rGS.² Separate reimbursement for rGS will enable all eligible patients to access rGS early in a hospitalization, maximizing clinical and economic benefits of rGS while minimizing health disparities.

Table VI. Expected total cost over the study period, estimated from the decision model that compared 2 hypothetical testing strategies for critically ill hospitalized infants with suspected genetic conditions

Strategy	Cost	95% uncertainty interval
Early rapid genome sequencing (rGS) (≤7 days after hospital admission)	\$269,566	(\$211,194, \$332,326)
Early NewbornDx (≤7 days after hospital admission), followed by later (>7 days following admission) rGS for undiagnosed infants	\$428,158	(\$358,729, \$503,403)
Difference	-\$158,592	(-\$253,292, -\$63,701)

Other important factors related to the appropriate utilization of rGS are also noteworthy, and economic value is only one of many considerations.¹⁹ Ethical, legal, and social implications also play a critical role in determining the appropriateness and impact of rGS.^{20,21} For example, ethical concerns include issues of equity and access to early rGS. Legal factors include the implementation of laws to protect the privacy of genetic information. Social implications include the psychological impact of testing and diagnoses on families and children as they age. These factors, in combination with health economic data, should be considered to make informed, responsible decisions about the appropriate implementation of rGS in clinical practice.¹⁹

This study has several limitations. In our model, we evaluated 2 hypothetical testing strategies that differed by the timing of rGS: 1) early rGS and 2) early NewbornDx and later rGS if no diagnosis was achieved. However, because testing time was not randomized in GEMINI, we used regression models to evaluate the independent effects of test timing and diagnosis on costs, length of stay, and QALYs, adjusting for all available baseline infant and household demographic and clinical characteristics. We also conducted sensitivity analyses that adjusted for infant death and urgent testing, which demonstrated that these variables were not confounders. However, unobserved or unrecorded data that may be associated with early testing, diagnosis, and outcomes could lead to potential confounding and bias in our estimates.

Second, health outcomes after testing were not routinely measured, aside from self-reported infant and caregiver HRQOL used to estimate accrued QALYs. Although QALYs are standard in health economic evaluations, they may not adequately capture the benefit of rGS in infants with suspected genetic disorders. One goal of rGS is to identify genetic disorders for which therapeutic interventions may extend life and improve HRQOL. Another goal is to provide parents with prognostic information that may lead to the withdrawal of life-sustaining support, reducing QALYs. Given these limitations, we recommend that future economic evaluations of rGS also use objective health outcome measures post-testing. These measures are crucial for understanding the clinical implications of molecular diagnoses and assessing the economic impact of subsequent treatments and management strategies. Future studies should also extend follow-up periods to evaluate whether evolving phenotypic data can influence diagnostic yield and economic impact. Extended time horizons are also needed to capture long-term clinical outcomes, HRQOL, and the full economic value of genomic testing as its impact unfolds over time.

Third, we relied primarily on parent-reported health care utilization, as infants could receive care outside the enrolling hospital system, and electronic medical record review alone would not capture all services. Parent reports may be subject to recall bias. For families who could not be reached, we abstracted utilization from medical records, recognizing that these data may not reflect care received outside the enrolling hospital.

Fourth, we combined “partial” and “full” diagnoses into a single “diagnosis” category in the model. This simplification provides conservative cost estimates for early NewbornDx, as infants partially diagnosed by NewbornDx were classified as “diagnosed” and thus were assumed not to require later rGS. If, in practice, infants with partial diagnoses from NewbornDx still undergo later rGS, this would increase the overall costs of the early NewbornDx strategy, thereby further highlighting the cost savings associated with early rGS.

Fifth, the model did not include comparisons with exome sequencing (ES) or other clinically available genetic tests besides NewbornDx. Previous studies have shown that genome sequencing has a higher diagnostic rate and is more cost-effective than ES or other genetic tests when it is used as a first-line test.^{2,22,23} In the absence of rGS or ES, infants in the US have typically undergone sequential karyotyping, chromosomal microarray, and targeted single-gene or small-panel tests. These approaches have a low cumulative diagnostic yield and often lead to a costly “diagnostic odyssey.” The total US costs of this pathway are difficult to quantify in a way directly comparable with our sample, as available estimates come from heterogeneous studies with varying designs, follow-up periods, and populations. Nonetheless, published comparisons consistently show that rGS is more cost-effective than standard sequential testing when used as a first-line test in ill infants with suspected genetic conditions.^{2,4}

Sixth, we conducted this analysis from the US health care system perspective to inform payer coverage decisions for rGS. However, this approach does not capture broader societal costs and benefits associated with rGS, such as caregiver productivity, family out-of-pocket expenses for non-health care utilization, and personal utility, which is the utility associated with testing that is not health related. Personal utility may be influenced by the perceived benefits of receiving rGS results, such as improved coping, feeling a sense of control, and the ability to plan for the future.²⁰ Conversely, personal utility may also be affected by concerns about rGS, including potential discrimination and privacy risks.²⁴⁻²⁹ Although societal costs and benefits could affect the overall economic value of rGS, they were outside the scope of this study and should be considered in future economic evaluations.

Finally, our analysis could not determine whether certain categories of genetic disorders were associated with higher health care costs. The infants in GEMINI had a wide variety of genetic and suspected genetic conditions, but small sample sizes within each category, coupled with heterogeneity in disease presentation and severity, limited our ability to examine cost differences. Larger studies or pooled datasets will be needed to evaluate whether particular genetic disorder categories are linked to higher expenditures.

In conclusion, critically ill infants with suspected genetic disorders who undergo early rGS have significantly lower costs compared with those who receive early NewbornDx, primarily due to the frequent reflex to rGS. This observation underscores an urgent need for payers to ensure timely and equitable access to rGS for all eligible infants, thereby

improving access to this important diagnostic tool, maximizing clinical and economic benefits, and reducing health disparities.

Ethics Declaration

This study was approved by the Johns Hopkins Single Institutional Review Board (IRB; JHUSIRB00000007), which served as the central IRB for all participating institutions in the Genomic Medicine for Ill Neonates and Infants (GEMINI) study. All institutions involved in the research received IRB approval for the study. Informed consent was obtained from all participants or their legal guardians, as required by the IRB. The data collected for this study were deidentified to protect participant confidentiality. The study adhered to the principles outlined in the Declaration of Helsinki. ■

CRedit authorship contribution statement

Tara A. Lavelle: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Jill L. Maron:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Stephen F. Kingsmore:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Ching-Hsuan Lin:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Yingying Zhu:** Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Benjamin Sweigart:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Dallas Reed:** Writing – review & editing, Methodology, Investigation. **Bruce D. Gelb:** Writing – review & editing, Investigation. **Jerry Vockley:** Writing – review & editing, Investigation. **Jonathan M. Davis:** Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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Data Statement

Data sharing statement available at www.jpeds.com.

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