Genetics in Medicine (2021) ■■, 1–10

ELSEVIER

Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

ARTICLE

Cost-effectiveness of genome sequencing for diagnosing patients with undiagnosed rare genetic diseases

Devin Incerti[1], Xiang-Ming Xu[1], Jacquelyn W. Chou[1], Nina Gonzaludo[2], John W. Belmont[2], Brock E. Schroeder[2,*]

[1]*PRECISIONheor, Los Angeles, CA;* [2]*Illumina, Inc, San Diego, CA*

ARTICLE INFO

Article history:
Received 6 January 2020
Revised 26 June 2020
Accepted 25 August 2021
Available online xxxx

Keywords:
Cost-effectiveness
Genetic disease
Genome sequencing
Rare disease

ABSTRACT

Purpose: To estimate the cost-effectiveness of genome sequencing (GS) for diagnosing critically ill infants and noncritically ill pediatric patients (children) with suspected rare genetic diseases from a United States health sector perspective.

Methods: A decision-analytic model was developed to simulate the diagnostic trajectory of patients. Parameter estimates were derived from a targeted literature review and meta-analysis. The model simulated clinical and economic outcomes associated with 3 diagnostic pathways: (1) standard diagnostic care, (2) GS, and (3) standard diagnostic care followed by GS.

Results: For children, costs of GS ($7284) were similar to that of standard care ($7355) and lower than that of standard care followed by GS pathways ($12,030). In critically ill infants, when cost estimates were based on the length of stay in the neonatal intensive care unit, the lowest cost pathway was GS ($209,472). When only diagnostic test costs were included, the cost per diagnosis was $17,940 for standard, $17,019 for GS, and $20,255 for standard care followed by GS.

Conclusion: The results of this economic model suggest that GS may be cost neutral or possibly cost saving as a first line diagnostic tool for children and critically ill infants.

Introduction

There are an estimated 6000 to 7000 distinct diseases that meet the definition of rare disease—a number that is growing as new diseases are identified.[1-3] Epidemiologic studies have estimated the prevalence of rare diseases to be between 2% to 6.2% of the population.[1-3] Although the precise prevalence of patients with rare genetic diseases is not well established, 2 recent analyses of the Orphanet database have estimated that between 70% and 80% of rare diseases are either exclusively genetic or have significant genetic forms that account for ≥10% of patients with those disorders.[2,4] Genetic diseases typically manifest either at birth (often in critically ill patients) or during childhood and

*Correspondence and requests for materials should be addressed to Brock E. Schroeder, Illumina Inc, 5200 Illumina Way, San Diego, CA 92122. *E-mail address:* bschroeder1@illumina.com

doi: https://doi.org/10.1016/j.gim.2021.08.015

represent a significant clinical and economic burden. For example, estimated total costs for suspected pediatric genetic diseases are between $4.6 billion and $17.5 billion—approximately 12% to 47% of the national bill for pediatric inpatient care.[5] Furthermore, in the National Vital Statistics Report, "congenital malformations, deformations, and chromosomal abnormalities"—which could be considered a proxy for a subset of genetic disease—were the leading cause of death among infants in 2016 and 2017, contributing to over 20% of total deaths.[6]

Compounding the burden of rare genetic diseases, with the exception of the subset of rare genetic diseases that are typically diagnosed through prenatal or newborn screening, these conditions are challenging to diagnose because of nonspecific clinical presentation and physician unfamiliarity.[7] These challenges are compounded by traditional diagnostic approaches, which focus on subjective assessment and iterative application of single gene tests. In recent years, multi-gene panels have been implemented for distinct classes of clinical presentations (eg, epilepsy) along with genome-wide approaches using chromosomal microarray (CMA) to detect copy number variations. Because of the vast number of genes with pathogenic variants (>4000), different types of genetic variations, disease heterogeneity, and iterative approaches on which time-to-diagnosis based,[8] rare genetic diseases are commonly associated with long diagnostic odysseys.[9] This delay can result in significant health and financial burden, including missed opportunities for critical intervention, unnecessary procedures, treatments, and specialist visits, and a financial and emotional toll for families.[10,11] Average costs of the diagnostic workup for children with suspected rare genetic diseases are frequently reported to be in the range of $3000 to $8000.[11-17] However, costs can be substantially higher for patients whose diagnostic workups include imaging or biopsies that require anesthesia.

Next-generation sequencing (NGS) technology has helped in increasing ability to sequence larger stretches of the genome to diagnose genetic diseases.[18] Although NGS can be used for investigating single genes or multi-gene panels, 2 newer applications of NGS are exome sequencing (ES), which sequences protein coding regions of the genome, and genome sequencing (GS), which assesses both coding and noncoding regions.[18] Both ES and GS have shown improvements in diagnostic yield compared with standard genetic testing approaches (including CMA) and have higher rates of clinical actionability.[12,15,19-21] In a head-to-head analysis, GS has been shown to have increased diagnostic yield compared with ES and to have diagnostic yield of 17% to 42% in patients who had previously undergone ES with no diagnosis.[12,14,22,23]

Several economic analyses of ES have been published.[15,20] In these studies, use of ES as a first-tier test was shown to be cost-effective vs standard genetic testing, eg, lowering the cost per diagnosis from >$20,000 to approximately $4000 in the model for critically ill infants.[15]

As GS investigates more of the genome than ES and more comprehensively detects different variant types, we sought to specifically evaluate the cost-effectiveness of GS compared with standard genetic testing. This study synthesized clinical and economic evidence and developed a decision-analytic model to estimate the cost-effectiveness of GS for diagnosing critically ill infants and pediatric outpatient population suspected of having a rare genetic disease.

Materials and Methods

Overview

We developed a decision-analytic model to simulate the diagnostic trajectory of patients with undiagnosed rare genetic diseases and to assess the cost-effectiveness of GS (incremental cost per diagnosis). Parameter estimates were based on a synthesis of available evidence from a range of sources. Outcomes were simulated over a time horizon of 5 years for infants and 15 years for children. The model used a time-to-event individual patient approach to simulate the diagnostic trajectory. Additional details are provided in the Supplemental Online Appendix. The model will be publicly available at https://wgscosteffectiveness.shinyapps.io/geneticdisease for 24 months.

Diagnostic pathways

Three diagnostic pathways were considered: (1) standard diagnostic care (Standard), (2) GS, and (3) Standard followed by GS (Standard → GS). For the purposes of this study, Standard refers to the combination of standard genetic tests and diagnostic investigations typically included in routine clinical practice, including single gene panels, multi-gene panels, CMA, and karyotype. ES is not included as part of Standard workup. Standard diagnostic investigations also include common non-genetic investigations performed during the diagnostic odyssey, such as medical appointments, imaging, and pathology.

Population

The target population consisted of undiagnosed patients presenting for medical genetics workup for a suspected genetic disease. The focus of the model was on patients with diagnostically challenging conditions. Clinical presentations were heterogeneous but typically included multiple congenital anomalies, epilepsy, intellectual disability, developmental delay, and other nonspecific presentations suspected of having genetic etiology (see Supplemental Online Appendix).[12,15,24] The model excluded patients with disorders identified using prenatal (eg, Trisomy 21) or newborn screening (eg, cystic fibrosis) as well as disorders

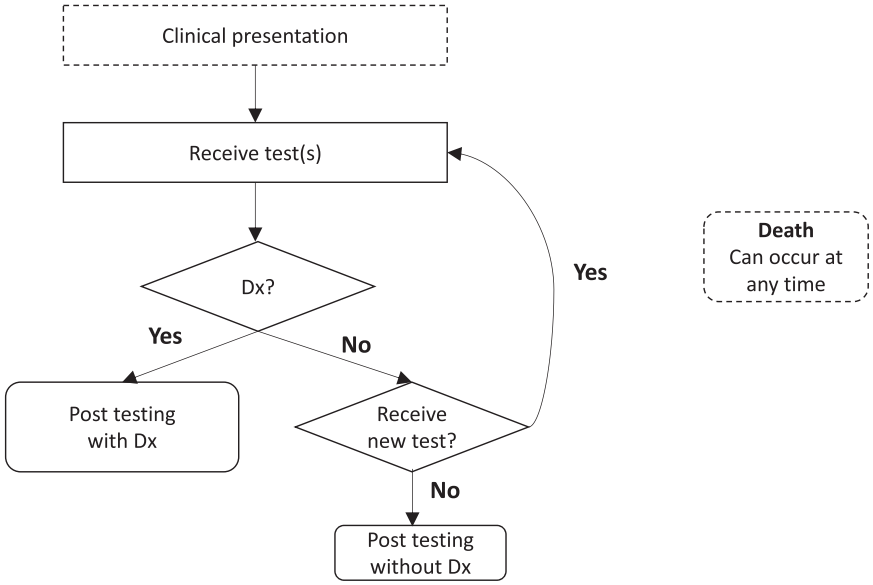

Figure 1 Flow diagram of the simulation for a single patient. Dx, Diagnosis; LOS, length of stay.

for which there were clear clinical criteria and single gene testing was indicated (eg, neurofibromatosis types I and II, achondroplasia). Finally, 2 groups were evaluated: critically ill infants aged > 1 year (infants) with suspected genetic diseases and noncritically ill pediatric patients aged >18 years (children) (at the time of presentation) with clinical phenotypes of suspected genetic origin.

Model structure

The diagnostic trajectory for a patient in the simulation moving between events, including genetic testing, a post–genetic testing phase, and death, is described in Figure 1 and Supplemental Figure A1. After undergoing a genetic test, patients may be diagnosed with a rare genetic disease or remain undiagnosed. If diagnosed, the patient entered the post–genetic testing phase; if undiagnosed, the patient either underwent the next genetic test or, if there was no next genetic test available, enters the post–genetic testing phase. Patients remained in the post–genetic testing phase until the end of the time horizon or death. Death could occur at any time during the model simulation. See Supplemental Online Appendix for additional details.

In our baseline models evaluating the impact of GS on both populations, costs were computed on the basis of diagnostic investigations during the diagnostic trajectory. Other costs such as those incurred for prescription drugs, surgeries, or hospitalizations were not included. For critically ill infants, we additionally evaluated the impact of GS on the basis of costs associated with length of stay (LOS) in the neonatal intensive care unit (NICU). This approach was incorporated because NICU LOS is a key driver of overall cost of care and rapid diagnosis in the NICU setting has been reported to decrease LOS in a subset of patients.[10,25] In this case, the model simulated time in the NICU and outpatient settings.

Model inputs

Parameter estimates were derived from a targeted review of peer-reviewed published studies (Table 1 and 2). Literature searches were not restricted to specific subpopulations. When multiple estimates were available for a single parameter, meta-analytic techniques were used to synthesize the available evidence and compute a pooled estimate. All costs were inflated to 2020 US dollars using the Consumer Price Index. Additional details are available in the Supplemental Online Appendix; Supplemental Tables A1-A12.

Diagnostic yield

The diagnostic yield (probability that a genetic test yields a diagnosis) for Standard was estimated using a meta-analysis of available studies. Although we relied on absolute effects for Standard, we used relative effects to estimate the diagnostic yield for GS—estimating the odds ratio of the probability of a diagnosis with GS relative to Standard and then applying the odds ratio to the diagnostic yield for Standard. We estimated separate diagnostic yields for GS depending on whether testing replaced most standard care and occurred at first line (1L) or whether it occurred after Standard at second line.

Duration of the diagnostic trajectory

The duration of testing for GS was measured using expected test turnaround times: 2 months for children and 14 days for critically ill infants (reflecting the higher likelihood that rapid testing is used). The duration of

Table 1 Summary of input parameters for outpatients

Parameter	Standard	GS
Clinical parameters (Pediatric)		
Baseline diagnostic yield (Standard), %	18 (10-32)[a]	-
Odds ratio of diagnostic yield 1L (GS vs Standard)	-	2.61 (1.65-4.13)
Odds ratio of reduction in diagnostic yield at 2L relative to 1L	-	0.7 (0.39-1.23)
Time until diagnosis, start of next test, or end of genetic testing for diagnosed patients	0.50 (0.32-0.71) y[a]	61 d[a]
Time until diagnosis, start of next test, or end of genetic testing for undiagnosed patients	6.50 (4.214-9.28) y	61 d[a]
% Diagnosed with a change in clinical management	60 (26-87)[a]	60 (26-87)[a]
Log mortality rate	–9.28	–9.28
Resource use and costs (pediatric)		
Annualized costs of standard diagnostic care, $	825.45 (622.29-1056.87)[b]	-
One-time upfront costs of standard diagnostic care, $	3877.53 (1992.43-6379.73)	
Cost of GS, $	-	5500[c]
One-time upfront cost of standard diagnostic care not replaced by GS, $	-	1783.66
Clinical parameters (infant)		
Baseline diagnostic yield (Standard), %	12 (9-18)[a]	
Odds ratio of diagnostic yield at 1L (GS vs Standard)	-	9.43 (4.11-21.62)
Odds ratio of reduction in diagnostic yield at 2L relative to 1L		0.69 (0.21-2.27)
Time until diagnosis, start of next test, or end of genetic testing, d	257 (59-598)	14[a]
Percent diagnosed with a change in clinical management, %	54 (46-62)[a]	54 (46-62)[a]
Log mortality rate (before diagnosis)	–0.30 (–1.04 to 0.44)	–0.30 (–1.04 to 0.44)
Log mortality rate (after diagnosis)	0.54 (–0.81 to 1.89)	0.54 (–0.81 to 1.89)
Resource use and costs (infant)		
Cost of rapid GS, $	-	8500[c]
Annualized cost of standard diagnostic care, $	2056.48	-
One-time upfront costs for standard diagnostic care, $	1205.37	
One-time costs of standard diagnostic care not replaced by GS, $	-	689
NICU LOS (standard), d	56	-
Reduction in NICU LOS with GS (relative to standard), d	-	2.95 (0.80-6.47)
Cost per day in the NICU, $	4145.02	4145.02
Cost per day in outpatient setting after discharge (infant), $	12.33	12.33

Please see Supplemental Online Appendix for references and additional details.

Data in parentheses have 95% confidence interval and computed using the distribution used for the probabilistic sensitivity analysis.

1L, first line; *2L*, second line; *GS*, genome sequencing; *LOS*, length of stay; *NICU*, neonatal intensive care unit.

[a]Estimate pooled based on a synthesis of available data. See Supplemental online appendix for details.

[b]Costs include those accrued for standard genetic tests and diagnostic investigations. Estimate pooled based on a synthesis of available data. See Supplemental online appendix for details.

[c]Costs associated with GS are assumed to include labor, supplies, follow-up testing, bioinformatics, and equipment as well as consultations with clinical geneticists and genetic counselors.

diagnostic testing for Standard was estimated from analysis of peer-reviewed studies (see Supplemental Online Appendix).[15,20,26-32]

Change in clinical management

The probability that a diagnosis resulted in a change in clinical management was estimated with a meta-analysis of published studies.

Mortality

The mortality rate for children was estimated by converting 1-year death probabilities from US life tables to (log) rates.[33] Mortality rates for infants varied before and after diagnosis and were predicted by fitting an exponential survival model with a time-varying covariate for diagnosis to the data reported by Petrikin et al.[26]

Costs of diagnostic care

The costs of standard diagnostic care for children were estimated by pooling estimates from studies that evaluated ES in patients without a diagnosis after standard workup and reported mean follow up of standard diagnosis.[20,32,34,35]

Costs for infants were based on the study by Stark et al[15] and were converted to US dollars from Australian dollars or Euros. In both cases, we assumed that patients would continue to receive diagnostic tests as long as they were undiagnosed. As such, we converted cumulative costs into upfront and annualized costs on the basis of the duration of standard diagnostic care as reported (see Supplemental Online Appendix).

Estimated costs for GS were based on a health sector perspective in the US health system and were assumed to include labor, supplies, bioinformatics, equipment, and

Table 2 Expected clinical and economic outcomes, children

Outcome	Standard	GS	Standard → GS
Clinical utility			
% Diagnosed	19 (9-33)	37 (20-58)	38 (18-63)
Duration of the diagnostic trajectory, y	4.18 (3.08-5.17)	0.17 (0.16-0.17)	4.28 (3.17-5.30)
Change in clinical management, %	10 (5-18)	19 (10-32)	20 (9-34)
Resource use and costs			
Cost per patient, $	7355 (5166-9988)	7284 (7284-7284)	12,030 (9631-14,704)
Cost per diagnosis, $	43,834 (19,359-90,168)	21,281 (12,454-37,291)	35,580 (15,935-70,226)
Cost-effectiveness			
Incremental cost-effectiveness ratio relative to standard additional diagnosis (diagnostic costs model, per patient cost)	-	Dominates	$24,178

The duration of the diagnostic trajectory is measured from the start of the model until whichever of the following occurs first: (1) diagnosis, (2) death, (3) the completion of genetic testing, or (4) the end of the model's time horizon.

GS, genome sequencing.

confirmatory testing. Costs were intended to reflect trio testing in most cases (although in practice this is not always possible). To inform our parameter estimates, we used the Medicare Clinical Laboratory Fee Schedule,[37] published microcosting studies,[36,37] and publicly available pricing from reference laboratories (see Supplemental Online Appendix). On the basis of consultation with experts and in accordance with other models, we also assumed that GS was used in conjunction with some diagnostic tests typically used in standard care (eg, biochemical, imaging), providing the evidence that leads to the suspicion of a genetic disorder and indicating a need for genetic testing.[15,17,20,38]

Cost of stay in the NICU

LOS with Standard was based on the estimates in Petrikin et al.[26] The difference in LOS between Standard and GS was derived from Farnaes et al[10] and comparable to the data reported by Stark et al[25] with rapid ES. The cost per day in an NICU was estimated to be $4145.02 and costs in an outpatient setting were estimated to be $12.33 per day (see Supplemental Online Appendix).[39]

Model outcomes

Clinical outcomes included the proportion of patients with a diagnosis, duration of the diagnostic trajectory, and the proportion of patients who had a change in clinical management. The duration of the diagnostic trajectory was measured until the first diagnosis, death, the end of genetic testing, or end of the time horizon. The primary economic outcome was total costs per patient. The cost-effectiveness of GS and Standard → GS were estimated by computing the incremental cost per diagnosis with Standard as the comparator.

Simulation and uncertainty analysis

Parameter uncertainty was quantified using probabilistic sensitivity analysis with 1000 Monte Carlo simulations. For each simulation, we calculated mean outcomes by simulating 10,000 patients and averaging the results. Additional details of the probabilistic sensitivity analysis, including probability distributions for each parameter, are provided in the Supplemental Online Appendix.

Scenarios

We considered a number of scenarios to test the sensitivity of the model to selected modeling assumptions and parameters. For children, these included standard testing costs, duration of diagnostic odyssey, mortality, post–genetic testing costs, and time horizon. For infants in the NICU LOS scenario, we tested mortality rate, inpatient and outpatient costs, and time horizon. For each parameter, except for mortality and time horizon, we varied the input value by ± 30%. For mortality, we tested a range of 0% to 30%, and for time horizon, we tested a range of 1 to 9 years for infants and 1 to 15 years for children. For post–genetic testing costs, including costs of additional or repeat diagnostic tests for undiagnosed patients and costs associated with treatment or palliative care for diagnosed patients, we estimated an upper bound of $172, annually, for diagnosed patients and $317, annually, for undiagnosed patients. See Supplemental Online Appendix for additional details.

Results

Clinical outcomes and costs in children (noncritically ill)

Expected clinical and economic outcomes from the simulation for children is shown in Table 2. The diagnostic pathways, including GS, increased the probabilities of a diagnosis and a change in clinical management and decreased the duration of the diagnostic trajectory. The percentage of patients diagnosed was estimated to be 37%

Table 3 Expected clinical and economic outcomes, critically ill infants

Outcome	Standard	GS	Standard → GS
Clinical utility			
% Diagnosed	12 (8-18)	57 (34-77)	41 (21-66)
Mean duration of the diagnostic trajectory, d	169.69 (74.52-281.14)	13.81 (13.39-14.21)	177.75 (84.49-287.55)
% Diagnosed with change in clinical management	7 (4-10)	31 (18-43)	22 (11-36)
Resource use and costs			
Model based on diagnostic costs			
Cost per patient, $	2156 (1388-3094)	9189 (9189-9189)	7540 (5323-9204)
Cost per diagnosis, $	17,940 (10,119-29,703)	17,019 (11,853-27,365)	20,255 (12,034-38,991)
Model based on NICU LOS costs			
Cost per patient, $	227,973 (163,094-308,846)	209,472 (150,459-284,616)	226,444 (164,827-304,122)
Cost per diagnosis, $	1,892,968 (1,091,800-2,957,262)	386,904 (235,115-663,297)	607,089 (317,541-1,110,349)
Cost-effectiveness			
Incremental cost-effectiveness ratio relative to standard of additional diagnosis (diagnostic costs model, per patient cost), $		15,904	19,071
Incremental cost-effectiveness ratio relative to standard of additional diagnosis (NICU LOS costs model)		Dominates	Dominates

The duration of the diagnostic trajectory is measured from the start of the model till whichever of the following occurs first: (1) diagnosis, (2) death, or (3) the end of the model's time horizon.

GS, genome sequencing; *LOS*, length of stay; *NICU*, neonatal intensive care unit.

(20%-58%) for GS compared with 19% (9%-33%) for Standard and 38% (18%-63%) for Standard → GS. The duration of the diagnostic odyssey was estimated to be significantly shortened for GS (0.17 years) compared with Standard (4.18 years) or Standard → GS (4.28 years).

Cost per patient was similar ($7284) for GS and Standard ($7355) and lower than Standard → GS ($12,030). Cost-effectiveness was assessed by evaluating cost per diagnosis using Standard as the comparator. GS as a replacement for Standard increased the probability of a diagnosis and slightly reduced costs indicating that it was a dominant strategy. The incremental cost per diagnosis was $24,178 for Standard → GS compared with Standard alone. The cost per diagnosis was $43,834 for Standard, $21,281 for GS, and $35,580 for Standard → GS.

Clinical outcomes and costs for critically ill infants

Expected clinical and economic outcomes from the simulation for critically ill infants is shown in Table 3. The percentage of diagnosed patients were estimated to be 12% (8%-18%) for the Standard workup, 41% (21%-66%) for Standard → GS, and 57% (34%-77%) for GS only. The average length of the diagnostic odyssey was shortest for GS (13.81 days) compared with Standard (169.69 days) and Standard → GS (177.75 days).

When evaluating the economic impact on the basis of diagnostic workup costs only, cost per patient was lowest for the Standard approach. The cost per patient was $2156 for Standard, $9189 for GS, and $7540 for Standard → GS. The cost per diagnosis was lowest for GS ($17,019) than for Standard ($17,940) or Standard → GS ($20,255). The incremental cost per diagnosis was $15,904 for the GS pathway and $19,071 for the Standard → GS pathway.

Because cost of care in the intensive care setting is driven by LOS, we also evaluated the cost impact of GS considering NICU LOS alone. The incremental costs of GS relative to Standard based on different reductions in LOS is shown in Figure 2. The dotted red line is the central estimate of the reduction in the LOS (a mean of 3 days); however, we varied the in LOS to assess the sensitivity of our results. All estimates were based on the LOS for Standard as shown in Table 1. The gray shaded region represents 95% confidence interval based on uncertainty in the cost, duration of the diagnostic trajectory, mortality, and LOS parameters.

Considering the central estimate in which GS decreased LOS by a mean of 3 days for the cohort, GS decreased costs per patient by $18,472, although the confidence interval included 0. Incremental costs decreased in a linear fashion as the effect of GS on LOS grew. When LOS was reduced by 1 day, incremental costs were –$11,516, and when LOS was reduced by 10 days, incremental costs were –$40,039. In this analysis, costs per patient were lowest for the GS pathway ($227,973 for Standard; $209,472 for GS; $226,444 Standard → GS). Cost per diagnosis was also lowest for the GS pathway ($1,892,968 for Standard; $386,904 for GS; and $607,089 for Standard → GS).

Scenario analyses

Sensitivity analyses were conducted to test the degree of uncertainty in key parameters (Supplemental

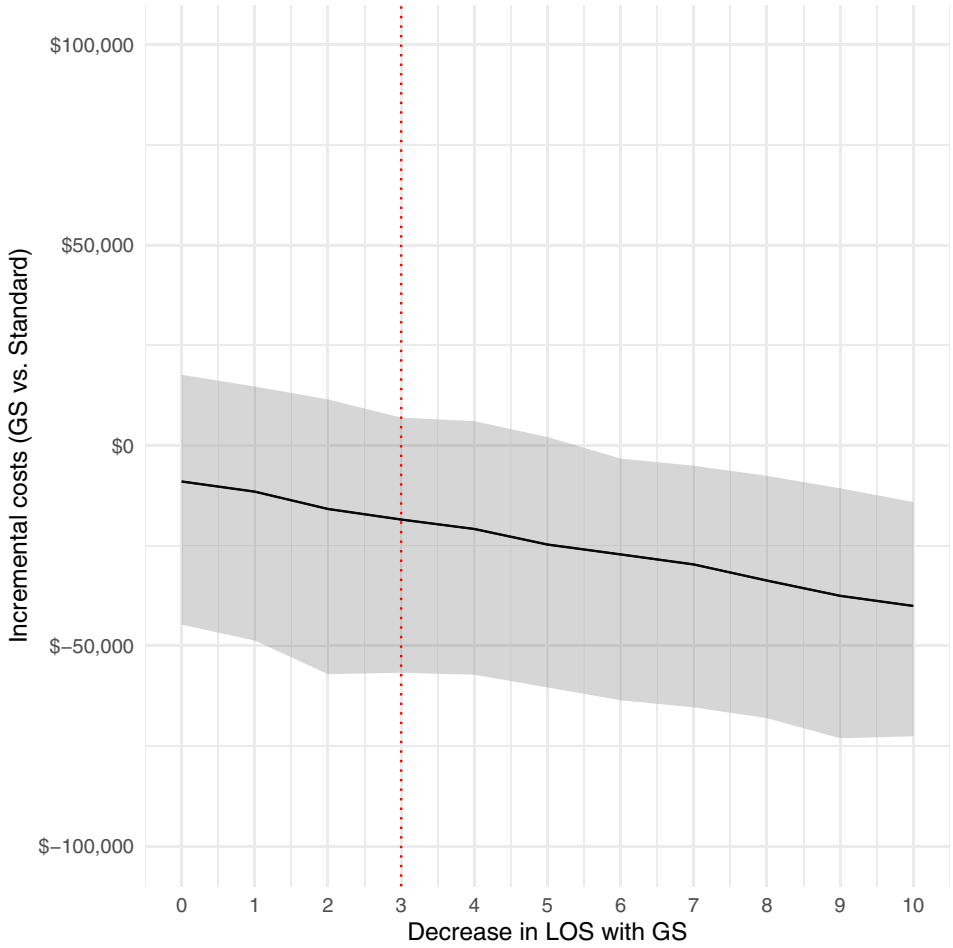

Figure 2 The impact of LOS on the costs of GS compared with standard care for infants in the NICU LOS–based model. GS, genome sequencing; LOS, length of stay; NICU, neonatal intensive care unit.

Figures A2-A4). For children, the most impactful parameters were costs of standard care, duration of the diagnostic trajectory, and time horizon. Lowering the costs of standard care (by 30%) or reducing the duration of the diagnostic trajectory (by 30%) would result in Standard having a lower cost per patient, and GS would have a lower cost per diagnosis (with 30% reduction in cost of standard care, cost per diagnosis was $32,875 for Standard and $19,262 for GS; with 30% reduction in trajectory, cost per diagnosis was $34,091 for Standard and $19,124 for GS). In varying the time horizon, GS would be shown to be cost saving in scenarios with a time horizon ≥9 years.

In critically ill infants, the most impactful drivers of costs were mortality rate and costs of standard care. Reducing the mortality rate to 0 led to an increase in costs (base-case: $2156, 0 mortality: $2602) in the Standard strategy but did not change GS costs because GS only generated costs in the beginning of the simulation. The NICU LOS–based model was most sensitive to mortality rate, inpatient costs, and time horizon. Setting the mortality rate to 0 had the largest impact, increasing costs for all diagnostic pathways; however, GS was still cost saving compared with Standard. A shorter time horizon also reduced the incremental costs of GS because patients spent less time in the NICU. Finally, the model was sensitive to daily NICU cost; however, GS was still cost saving when reducing daily costs by 30%.

Discussion

This study aimed to synthesize the available clinical and economic evidence for GS and assess its cost-effectiveness compared with conventional diagnostic approaches. Our study provides evidence that GS provides clinical utility as it increases the probability of a diagnosis, shortens the duration of the diagnostic trajectory, and increases the likelihood of a change in clinical management. Our model shows that implementing GS as a first-tier genetic test will be cost neutral or will potentially decrease costs relative to standard testing in children with suspected genetic diseases. In infants, implementing GS is not shown to save costs when diagnostic testing alone is considered; however, when potential cost savings from reduced LOS are considered, GS becomes a cost saving approach.

The implications of the model can be demonstrated with a hypothetical 1-million-member health care plan with 10,000 births per year. Assuming approximately 1% of newborns (100 infants) will present to the NICU with suspected genetic disorders, the standard diagnostic strategies would result in 13 diagnoses, 7 changes in clinical management, and $215,600 in diagnostic costs. First line GS would improve the diagnostic rate, resulting in 57 diagnoses and a change in care management in 31 patients costing $918,900. However, if we consider costs based on NICU LOS, GS would result in cost savings of approximately $1.9 million. Using the model of noncritically ill pediatric patients, approximately 2% of children (200 new patients per year) will at some point seek pediatric care for suspected genetic diseases; in such cases, employing standard diagnostic care would yield 38 diagnoses, 20 changes in clinical management, and $1.47 million in diagnostic workup costs. Employing GS as a 1L test would yield 74 diagnoses, 38 changes in clinical management, and $1.46 million in diagnostic workup costs.

Previous studies have assessed the cost-effectiveness of ES in the Australian and Dutch settings.[15,17,20,34,38] Similar to our findings, both studies found ES to be cost-effective compared with standard diagnostic care (and potentially cost saving), especially when used earlier in the diagnostic odyssey.[15,20] Furthermore, Farnaes et al[10] assessed the impact of rapid GS on clinical and economic outcomes among 42 inpatient infants in the United States, and reported cost savings of $3060 per infant tested.

Our estimates of the diagnostic yield are similar to a recent meta-analysis by Clark et al[21] in which the diagnostic yield of GS was higher than the diagnostic yield of ES and CMA, but there are some important differences. First, Clark et al[21] pooled data across both infants and children, whereas we estimated parameters separately. Second, Clark et al[21] estimated the absolute diagnostic yield separately for different genetic tests. We estimated the absolute diagnostic yield for Standard but computed the diagnostic yield for GS relative to Standard using direct comparisons (ie, studies that included both). We believe this approach allowed us to reduce the bias caused by population differences across studies. Finally, we estimated the diagnostic yield for a broad range of investigations and genetic tests encompassing standard diagnostic care, whereas Clark et al[21] limited their analysis to CMA. Our sensitivity analyses suggest implications for stakeholders weighing the decision to incorporate GS into standard care pathways and/or provide coverage and reimbursement. First, in noncritically ill children, the model was most sensitive to time horizon. Diagnostic workup costs accrue overtime during a diagnostic odyssey; thus, an appropriate time horizon is an important consideration for payers. GS is shown to be cost saving in scenarios with a time horizon ≥9 years. The model was also sensitive to costs of the Standard pathway. These costs will vary on the basis clinical presentation, severity of disease, availability of health care resources, subjective physician decision-making, and standard practices in different markets (among other factors). Our sensitivity analysis showed that with 30% lower costs in the Standard arm, GS was no longer cost saving but still resulted in a substantially lower cost per diagnosis. In critically ill infants, the model was most sensitive to mortality rate. However, even varying the mortality rate to 0 did not change the overall implications of the model.

Strengths and limitations

A primary strength of our study is the use of evidence synthesis techniques (ie, meta-analysis) to incorporate data from multiple studies and conduct a simulation model–based cost-effectiveness analysis for GS. One implication of this model-based approach is that we were able to extrapolate outcomes over different time horizons. Furthermore, because we combined evidence from multiple studies, our results were not subject to any specific study population.

There are limitations to this study. First, we acknowledge a challenge with precision in describing the population—a heterogeneous group with diagnostically challenging conditions. However, we believe that the description represents a typical cohort presenting to Medical Genetics on the basis of patient characteristics across published literature. Second, evidence was limited for a number of model parameters, particularly in the areas of the short- and long-term costs of conventional genetic workup, downstream costs (after the diagnostic workup), the typical length of the diagnostic odyssey, and the impact of GS on LOS. Third, given the limited data availability, this model did not use patient-level data but relied on aggregate data from published studies. Fourth, use of GS in the inpatient setting occurs in different health care settings in the United States with different reimbursement schemes, affecting the payer cost estimates in a given setting. This was evident in our study as estimates of costs based on LOS in the NICU were higher than estimates of costs based on diagnostic investigations alone. In addition, for critically ill infants, we focused on either diagnostic costs alone or on costs related to NICU LOS, although additional savings may accrue from reductions in procedures and professional fees.[10] Fifth, some diagnostic costs were converted to US dollars from Australian dollars or Euros and might be conservative estimates of actual costs in the United States.[15] Sixth, our evaluation compared GS with conventional testing strategies and did not evaluate ES separately. Finally, our cost-effectiveness analysis (using cost per diagnosis) represents a partial economic evaluation rather than a full evaluation. Although there are limitations for policymakers in defining acceptable values per diagnosis, we believe this analysis captures a key clinical benefit relevant to patients and providers at this stage of their diagnostic journey (see Supplemental Online Appendix). However, this approach does not capture the burden of the diagnostic trajectory on

caregivers, including emotional distress or lost productivity.[40,41]

Future considerations

NGS-based genome-wide diagnostic approaches are increasingly being used in clinical practice. Adoption of these technologies requires robust clinical and economic evidence of their benefits. The simulation approach outlined here can support this assessment given the challenges associated with modeling the value of genomic interventions using traditional frameworks.[42] New studies should focus on estimating costs and use during the diagnostic trajectory, downstream costs, and impact of NGS on the duration of the diagnostic trajectory. Although additional research would be helpful, evidence suggests that GS provides clinical utility, may be cost neutral or possibly cost saving, and is most cost-effective when used as a IL diagnostic investigation.

Data Availability

The authors of this manuscript are willing to share all data sets and protocols used in the development of the economic model. Much of this information is shared in the Supplemental Online Appendix. In addition, the model itself will be publicly available at https://wgscosteffectiveness.shinyapps.io/geneticdisease for 24 months. After that time, please contact the corresponding author (B.E.S.).

Acknowledgments

The work described in this manuscript was funded by Illumina, Inc.

Author Information

Conceptualization: D.I., X.M.X., J.W.C., N.G., J.W.B., B.E.S.; Formal Analysis: D.I., X.M.X., J.W.C., N.G., J.W.B., B.E.S.; Investigation: D.I., X.M.X., J.W.C., N.G., J.W.B., B.E.S.; Methodology: D.I., X.M.X., J.W.C., N.G., J.W.B., B.E.S.; Project Administration: D.I., X.M.X., J.W.C., B.E.S.; Supervision: D.I., X.M.X., B.E.S.; Writing-original draft: D.I., X-M.X., J.W.C., N.G., J.W.B., B.E.S.; Writing-review and editing: D.I., X.M.X., J.W.C., N.G., J.W.B., B.E.S.

Conflict of Interest

Brock E. Schroeder, Nina Gonzaludo, John W. Belmont are employees and stockholders of Illumina, Inc. Devin Incerti, Xiang-Ming Xi, and Jacquelyn W. Chou are employed by Precision Health Economics, a health economics and outcomes research consultancy. The work described in this manuscript was funded by Illumina, Inc.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2021.08.015) contains supplementary material, which is available to authorized users.

References

1. Ferreira CR. The burden of rare diseases. *Am J Med Genet A*. 2019;179(6):885–892. http://doi.org/10.1002/ajmg.a.61124.
2. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet*. 2020;28(2):165–173. http://doi.org/10.1038/s41431-019-0508-0.
3. Walker CE, Mahede T, Davis G, et al. The collective impact of rare diseases in Western Australia: an estimate using a population-based cohort. *Genet Med*. 2017;19(5):546–552. http://doi.org/10.1038/gim.2016.143.
4. Bick D, Jones M, Taylor SL, Taft RJ, Belmont J. Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases. *J Med Genet*. 2019;56(12):783–791. http://doi.org/10.1136/jmedgenet-2019-106111.
5. Gonzaludo N, Belmont JW, Gainullin VG, Taft RJ. Estimating the burden and economic impact of pediatric genetic disease. *Genet Med*. 2019;21(8):1781–1789. Published correction appears in *Genet Med*. 2019;21(9):2161. https://doi.org/10.1038/s41436-018-0398-5.
6. Heron M. Deaths: leading causes for 2017. *Natl Vital Stat Rep*. 2019;68(6):1–77.
7. Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. *Lancet*. 2008;371(9629):2039–2041. http://doi.org/10.1016/S0140-6736(08)60872-7.
8. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med*. 2015;3(5):377–387. http://doi.org/10.1016/S2213-2600(15)00139-3.
9. Shire Human Genetic Therapies. Rare disease impact report: insights from patients and the medical community. 2013. https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf. Accessed May 31, 2020.
10. Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med*. 2018;3:10. http://doi.org/10.1038/s41525-018-0049-4.
11. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med*. 2014;6(265):265ra168. http://doi.org/10.1126/scitranslmed.3010076.
12. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med*. 2018;20(4):435–443. http://doi.org/10.1038/gim.2017.119.
13. Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med*. 2014;16(2):176–182. Published correction appears in *Genet Med*. 2013;15(10):849. https://doi.org/10.1038/gim.2013.99.
14. Splinter K, Adams DR, Bacino CA, et al. Effect of genetic diagnosis on patients with previously undiagnosed disease. *N Engl J Med*. 2018;379(22):2131–2139. http://doi.org/10.1056/NEJMoa1714458.
15. Stark Z, Schofield D, Alam K, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of

usual care overwhelmingly supports early use and reimbursement. *Genet Med*. 2017;19(8):867–874. http://doi.org/10.1038/gim.2016.221.
16. U.S. Centers for Medicare & Medicaid Services. Clinical laboratory fee schedule. U.S. Centers for Medicare & Medicaid Services. Updated 2019. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.htmls. Accessed August 3, 2019.
17. Vissers LELM, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med*. 2017;19(9):1055–1063. http://doi.org/10.1038/gim.2017.1.
18. US National Library of Medicine. Help me understand Genetrics. *Genet Test*; 2018. https://medlineplus.gov/genetics/understanding/. Accessed July 1, 2021.
19. Stavropoulos DJ, Merico D, Jobling R, et al. Whole genome sequencing expands diagnostic utility and improves clinical management in pediatric medicine. *NPJ Genom Med*. 2016;1:15012. http://doi.org/10.1038/npjgenmed.2015.12.
20. Tan TY, Dillon OJ, Stark Z, et al. Diagnostic impact and cost-effectiveness of whole-exome sequencing for ambulant children with suspected monogenic conditions. *JAMA Pediatr*. 2017;171(9):855–862. http://doi.org/10.1001/jamapediatrics.2017.1755.
21. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med*. 2018;3:16. http://doi.org/10.1038/s41525-018-0053-8.
22. Shashi V, Schoch K, Spillmann R, et al. A comprehensive iterative approach is highly effective in diagnosing individuals who are exome negative. *Genet Med*. 2019;21(1):161–172. http://doi.org/10.1038/s41436-018-0044-2.
23. Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. *Nature*. 2014;511(7509):344–347. http://doi.org/10.1038/nature13394.
24. Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet Med*. 2016;18(11):1090–1096. http://doi.org/10.1038/gim.2016.1.
25. Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. *Genet Med*. 2018;20(12):1554–1563. http://doi.org/10.1038/gim.2018.37.
26. Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. *NPJ Genom Med*. 2018;3:6. http://doi.org/10.1038/s41525-018-0045-8.
27. Valencia CA, Husami A, Holle J, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. *Front Pediatr*. 2015;3:67. http://doi.org/10.3389/fped.2015.00067.
28. Global Commission. Ending the diagnostic odyssey for children with a rare disease: global commission year one report. Published 2019. https://www.globalrarediseasecommission.com/Report/assets/static/documents/GlobalCommission-print-021919-a68c8ce2a5.pdf. Accessed February 20, 2019.
29. Critical Care Services Ontario. Rare diseases working group report: final report to the Ministry of Health and Long-Term Care. Published March 10, 2017 http://www.health.gov.on.ca/en/common/ministry/publications/reports/rare_diseases_2017/rare_diseases_report_2017.pdf. Accessed January 18, 2021.
30. Macnamara EF, Schoch K, Kelley EG, et al. Cases from the undiagnosed diseases network: the continued value of counseling skills in a new genomic era. *J Genet Couns*. 2019;28(2):194–201. http://doi.org/10.1002/jgc4.1091.
31. Global Genes. Rare facts. Global Genes. Updated 2021 https://globalgenes.org/rare-facts/. Accessed January 18, 2021.
32. Dragojlovic N, van Karnebeek CDM, Ghani A, et al. The cost trajectory of the diagnostic care pathway for children with suspected genetic disorders. *Genet Med*. 2020;22(2):292–300. http://doi.org/10.1038/s41436-019-0635-6.
33. Arias E, Heron M, Xu J. United States life tables, 2014. *Natl Vital Stat Rep*. 2017;66(4):1–64.
34. Vrijenhoek T, Middelburg EM, Monroe GR, et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. *Eur J Hum Genet*. 2018;26(11):1566–1571. http://doi.org/10.1038/s41431-018-0203-6.
35. Yeung A, Tan NB, Tan TY, et al. A cost-effectiveness analysis of genomic sequencing in a prospective versus historical cohort of complex pediatric patients. *Genet Med*. 2020;22(12):1986–1993. http://doi.org/10.1038/s41436-020-0929-8.
36. Schwarze K, Buchanan J, Fermont JM, et al. The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom. *Genet Med*. 2020;22(1):85–94. http://doi.org/10.1038/s41436-019-0618-7.
37. Jegathisawaran J, Tsiplova K, Hayeems R, Ungar WJ. Determining accurate costs for genomic sequencing technologies-a necessary prerequisite. *J Community Genet*. 2020;11(2):235–238. http://doi.org/10.1007/s12687-019-00442-7.
38. van Nimwegen KJ, Schieving JH, Willemsen MA, et al. The diagnostic pathway in complex paediatric neurology: a cost analysis. *Eur J Paediatr Neurol*. 2015;19(2):233–239. http://doi.org/10.1016/j.ejpn.2014.12.014.
39. US Centers for Medicare & Medicaid Services. National health expenditures 2017 highlights. US Centers for Medicare & Medicaid Services. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/highlights.pdf. Accessed January 18, 2021.
40. Graungaard AH, Skov L. Why do we need a diagnosis? A qualitative study of parents' experiences, coping and needs, when the newborn child is severely disabled. *Child Care Health Dev*. 2007;33(3):296–307. http://doi.org/10.1111/j.1365-2214.2006.00666.x.
41. Genetic Alliance UK. The hidden costs of rare diseases. Genetic Alliance, UK. Published September 2016. https://www.geneticalliance.org.uk/media/2502/hidden-costs-full-report_21916-v2-1.pdf. Accessed January 18, 2021.
42. Khoury MJ, Feero WG, Chambers DA, et al. A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health. *PLoS Med*. 2018;15(8), e1002631. Published correction appears in *PLoS Med*. 2018;15(8):e1002650. https://doi.org/10.1371/journal.pmed.1002631.