Supplementary Online Appendix
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A1: Introduction

The aim of this supplementary appendix is to provide detail on our modeling approach. The model is a continuous time patient-level simulation that simulates a diagnostic trajectory for individual patients. The model “jumps” from the time of one event to the time of the next event and tracks each patient’s history. We use a patient-level simulation to maximize flexibility and ensure that the model can make the best use of the available evidence.

The remainder of this document is organized as follows. Section A2 describes the aim of the model. Section A3 examines the populations that the model is parameterized to analyze. Section A4 outlines the diagnostic pathways that the model is capable of simulating. Section A5 describes the model structure and a patient’s trajectory through the model. Section A6 provides information on the clinical and economic outcomes that can be simulated. Section A7 details the statistical techniques and data sources used to estimate the model parameters. Section A8 provides an overview of the probabilistic sensitivity analysis (PSA) and the computational techniques used to implement the simulation. Finally, Section A9 contains supplemental figures for the manuscript.

A2: Decision problem

The model was designed to evaluate the cost-effectiveness of various genetic testing strategies for diagnosing patients with suspected rare genetic diseases. Analyses were conducted from a United States (US) health care sector perspective (Sanders et al., 2016). The populations analyzed are described in Section A3 and the diagnostic pathways that were modeled are described in Section A4.

A3: Population

We simulated outcomes for patients with suspected rare genetic diseases in two age groups:

1. Critically ill infants less than 1 year of age; and
2. Children less than 18 years of age presenting for medical genetics workup.

The target population consists of undiagnosed patients suspected of having a genetic disease and presenting for medical genetics workup. The focus of the model is on patients with diagnostically challenging conditions. Clinical presentations are heterogeneous, but would typically include multiple congenital anomalies, epilepsy, intellectual disability, and developmental delay, as well as other nonspecific presentations suspected of genetic etiology. While we recognize that there is a lack of precision in the definition of this population due to heterogeneity, we believe this description represents a typical cohort of patients presenting to medical genetics based on the
patient characteristics across the relevant literature that informed this model.2-7

**A4: Diagnostic pathways**

We used the model to simulate outcomes for 3 distinct diagnostic pathways:

1. Standard;
2. GS; and
3. Standard → GS.

“Standard” refers to standard diagnostic care, which is a catch-all term consisting of a series of standard genetic tests and related diagnostic investigations. Examples of standard genetic tests include single gene panels, multi-gene panels, chromosomal microarray, and karyotype, among others.

Diagnostic investigations frequently obtained alongside these genetic tests include medical appointments, pathology, and imaging. When modeling GS, we assumed that some, but not all, diagnostic investigations were replaced (see Section A7.4).

After completing a sequence of genetic tests (or after a diagnosis), a patient moves to a post genetic testing phase and remains there until death or until the completion of the time horizon of the simulation. For a patient who has been diagnosed, this post genetic testing phase might be thought of as representative of any downstream treatments obtained as a result of the diagnosis; for an undiagnosed patient, this phase would represent any additional diagnostic care obtained after failing to obtain a diagnosis with the modeled genetic testing sequence.

**A5: Model structure**

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. Decision-analytic modeling has been well-established as a method of evaluating cost-effectiveness of medical innovation, particularly where there is uncertainty in long-term outcomes.8-12 This technique is intended to help inform decision-makers by synthesizing information from multiple sources, such as clinical trials and estimates from the literature, to compare costs and outcomes of different policies or practices. The results from the decision-analytic model can provide more information about the long-term, population-wide clinical and economic impacts of a particular healthcare-related decision, than can say, one or even several clinical trials.8-10 When selecting the appropriate method for conducting the cost effectiveness analysis, it is important to consider two approaches to the
model: cohort vs. individual patient level simulation (or microsimulation). While the cohort model may be computationally simpler to perform, the patient level simulation can better capture heterogeneity of both patients and outcomes. Patient heterogeneity and outcome uncertainty are particularly key to incorporate when evaluating the potential of genomic sequencing diagnostic tools for rare diseases. Recent examples of decision analytic microsimulation models used to evaluate cost effectiveness have been conducted in treatment for nonsolid pulmonary nodules, immunoncology therapies in metastatic melanoma, screening strategies for fetal cardiac anomalies, treatment protocols in hemophilia patients, and intervention for dental caries. The cost effectiveness of diagnostic tools and test have also been evaluated using microsimulation decision analytic models, though calls for expanded evaluation remain particularly as new innovations come to market.

The model is an individual patient simulation that simulates a diagnostic journey for individual patients in continuous time. Patients move between discrete events and time to each event is sampled using an exponential distribution. Figure A1 describes the flow of a single patient through the simulation. The simulation begins at the time of clinical suspicion and ends either at death or at the end of the specified time horizon.

While receiving a genetic test (or a series of genetic tests), the model samples whether a patient is diagnosed (prior to death) from a binomial distribution based on a probability determined by the diagnostic yield. If a patient is diagnosed, the model samples time to diagnosis and time to death following diagnosis. Upon diagnosis, the patient moves to a post genetic testing phase and remains there until either death or the end of the time horizon. If a patient is not diagnosed, the model simultaneously samples (i) time until death, and (ii) time until either the next genetic test or, if there is no next genetic test, time until moving to the post genetic testing phase. If (i) is less than (ii), the patient dies and the simulation ends. If not, then there are two possibilities. First, if there is a subsequent genetic test in the genetic testing sequence, then the patient obtains the new test and the process repeats itself with the patient again being diagnosed with a probability based on the diagnostic yield. Second, if there is no subsequent genetic test, then the patient moves to the post genetic testing phase and remains there until either the sampled time of death or the end of the time horizon. In cases where a patient is ultimately diagnosed, the model samples whether the diagnosis leads to a change in clinical management from a binomial distribution.
Figure A1: Flow diagram of the simulation for a single patient
When infants are modeled, costs can be computed in two ways: first, based on diagnostic tests performed, and second, based on the costs of a stay in the Neonatal Intensive Care Unit (NICU). When costs are computed using the first method, the model proceeds as described above. However, when costs are computed using the second method, the model also simulates length of stay (LOS) in the NICU as a function of (i) the type of test (Standard or GS) and (ii) whether a patient is diagnosed by the initial genetic test. If the patient dies prior to the sampled discharge time, then LOS is set equal to the time of death; conversely, if the patient dies after discharge, then LOS is set equal to the sampled time until discharge. Costs are calculated as a function of sampled LOS as described in Section A6.

**A6: Model outcomes**

We used the model to simulate clinical and economic outcomes associated with a given diagnostic pathway. All model outcomes were summarized with mean values, which were calculated by averaging across simulated individuals. Clinical outcomes included the following:

- Proportion of patients diagnosed by any genetic test in a diagnostic pathway;
- Proportion of patients with a change in clinical management following diagnosis; and
- The duration of the diagnostic trajectory.

Both the proportion of patients diagnosed and the proportion of patients experiencing a change in clinical management are computed based on outcomes after completing all genetic tests associated with a diagnostic pathway. Economic outcomes are as follows:

- Total diagnostic costs per patient; and
- Cost-effectiveness (cost per diagnosis).

The proportion of patients diagnosed is just the number of simulated patients for whom a diagnosis is obtained prior to death or at the end of the model’s time horizon. Likewise, the proportion of patient with a change in clinical management is equal to the number of simulated patients whose clinical management changed following a diagnosis. The duration of the diagnostic trajectory is defined as the time from the start of the simulation until whichever of the following occurs first: (i) diagnosis, (ii) death, (iii) completion of genetic testing, or the (iv) end of the simulation.

For children, total diagnostic costs per patient are based on the costs of diagnostic tests performed; for infants, total diagnostic costs can either be based on the costs of diagnostic tests performed, or, if time in the NICU is modeled, costs based on length of stay in the NICU. The model accounts for two
types of costs. The first type of cost is a fixed up-front cost which occurs at a single point in time. The second type of cost is an annualized cost that accrues over time. The cost of GS is an example of a fixed cost because it does not depend on the duration of the diagnostic trajectory; on the other hand, clinical assessments might be considered annualized costs because patients will continue to be assessed by clinicians while they remain undiagnosed during the diagnostic trajectory. In addition, costs accrue during discrete phases within the model as patients jump between events. These phases are associated with the sequences of genetic tests described in Section A4, or, when time in the NICU is modeled, whether patients are in the NICU or an outpatient setting. For example, patients would accrue costs in up to 3 phases (standard diagnostic care, GS, post-genetic testing) when Standard → GS is modeled. Similarly, in a NICU based model, patients would accrue costs based on the (annualized) cost of the NICU during a first phase and based on (annualized) costs in an outpatient setting during a second phase. Mathematically, (discounted) costs during phase $j$ can be written as:

$$
costs_j = z_0 e^{-rt} + z_1 \int_{t_1}^{t_2} e^{-rt} dt = z_0 e^{-rt} + z_1 \left[ \frac{e^{-rt_1} - e^{-rt_2}}{r} \right],$$

where a patient enters phase $j$ at time $t_1$ and jumps to a new phase at time $t_2$, $r$ is the discount rate, $t$ is a continuous measure of time, $z_0$ is a fixed cost, and $z_1$ is an annualized cost. When, costs are not discounted so that $r = 0$, this simplifies to $z_0 + z_1 \ast (t_2 - t_1)$. Total diagnostic costs for a given simulated patient are:

$$
costs = \sum_{j=0}^{J} costs_j$$

(A2)

where $J$ denotes the number of phases that a given patient experiences, which will differ across patients depending on the time of diagnosis and the time of death.

Finally, cost-effectiveness is estimated using costs per diagnosis. Specifically, the incremental cost-effectiveness of an alternative to a comparator is:

$$
\frac{\text{costs}_1 - \text{costs}_0}{\text{diagnoses}_1 - \text{diagnoses}_0}
$$

(A3)

where 0 denotes the comparator and 1 denotes the alternative, $\text{costs}_1 - \text{costs}_0$ are mean incremental diagnostic costs, and $\text{diagnoses}_1 - \text{diagnoses}_0$ are the number of incremental diagnoses.

We chose to conduct a cost effectiveness analysis (incremental cost per diagnosis) rather than a cost utility analysis. While it is recommended to measure outcomes in quality-adjusted life years (QALYs)
when possible, there are a variety of reasons we chose to focus on cost per diagnosis—many of which have been well described in the peer-reviewed literature. First, it is challenging to estimate QALYs from GS because the technology does not influence outcomes directly; rather, the impact is through downstream management. This patient population itself is highly heterogeneous and the impact of changes in management is also highly heterogeneous. For example, some diagnoses may lead to reduced mortality or improved quality of life, while others may have no impact or in fact lead to an earlier determination for redirection to palliative care and shorter survival. There are challenges with trying to estimate QALYs from the broad range of results from GS. For example, one would either need to (i) model the health gains due to adoption of heterogeneous treatments as a result of the diagnosis or (ii) use/perform a study that links diagnosis to long-term outcomes. The first is impractical because the set of possible treatments is impractically large to model, and we are unaware of any studies large enough or with long enough follow up to support the second proposal. Second, it is well characterized that QALYs do not capture the impact of genomic interventions on family spillover effects or non-health outcomes. Finally, we believe that diagnostic outcome captures the most relevant clinical benefit to patients and providers during the diagnostic odyssey. Diagnostic yield is also a strong predictor of change in management (i.e., most changes in management are directly enabled by the molecular diagnosis). Diagnostic yield is the most common outcome measure across the clinical literature, and numerous publications in this field have utilized a similar approach for evaluating cost effectiveness analysis.

A7: Parameter estimation and data sources

A7.1 Diagnostic yield

The diagnostic yield is defined as the probability that a genetic test yields a diagnosis. We modeled the probability of such a diagnosis on the logit scale,

\[
\text{logit}(p) = \log \left( \frac{p}{1-p} \right) = \alpha + \beta \cdot 1(GS)
\]  

(A4)

where \(\alpha\) is the diagnostic yield on the logit scale with standard diagnostic care and \(\beta\) is the effect of GS on the diagnostic yield (i.e., the log odds ratio). The predicted diagnostic yields for standard care and GS are therefore \(\text{logit}^{-1}(\alpha)\) and \(\text{logit}^{-1}(\alpha+\beta)\), respectively, where \(\text{logit}^{-1}(\gamma) = 1/(1+\exp(-\gamma))\).
We estimated Equation A4 separately for infants and children and allowed the regression coefficients to vary by line of genetic testing. \( \alpha \) was estimated with a meta-analysis of the absolute diagnostic yield for standard care while \( \beta \) was estimated from studies directly comparing the diagnostic yield of GS to standard care (i.e., with a meta-analysis of the log odds ratio).

A summary of studies reporting the diagnostic yield for standard diagnostic care identified in the literature review is shown in Table A1. Overall, the diagnostic yield was considerably higher for children than infants, although the sample sizes were also much smaller. \( \alpha \) is simply the logit transformation of the pooled percentage estimate (e.g., for infants, \( \alpha = \logit(0.12) = -1.95 \)).

Studies directly comparing GS to standard care are shown in Table A2. The odds ratios were considerably higher for infants, although the sample sizes were also significantly smaller. Point estimates and 95% confidence intervals for the parameters from Equation A4 based on Table A1 and Table A2 for first line genetic testing are displayed in Table A3. All parameters are on a logit scale and can be transformed to generate probabilities of diagnosis using the logistic function.

**Table A1: Diagnostic yield with standard diagnostic care at first line**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnoses</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panel A. Infants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farnaes et al. (2018)</td>
<td>4</td>
<td>42</td>
<td>9.52%</td>
</tr>
<tr>
<td>Petrikin et al. (2018)</td>
<td>1</td>
<td>33</td>
<td>3.03%</td>
</tr>
<tr>
<td>Stark et al. (2016)</td>
<td>11</td>
<td>80</td>
<td>13.75%</td>
</tr>
<tr>
<td>Stark et al. (2017)</td>
<td>7</td>
<td>40</td>
<td>17.50%</td>
</tr>
<tr>
<td>Willig et al. (2015)</td>
<td>3</td>
<td>32</td>
<td>9.38%</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td><strong>12.44%</strong></td>
</tr>
<tr>
<td><strong>Panel B. Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lionel et al. (2017)</td>
<td>25</td>
<td>103</td>
<td>24.27%</td>
</tr>
<tr>
<td>Stavropoulos et al. (2016)</td>
<td>13</td>
<td>100</td>
<td>13.00%</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td><strong>18.30%</strong></td>
</tr>
</tbody>
</table>

Note: Pooled estimate based on random effects meta-analysis on logit scale.
Table A2: Odds ratio of diagnostic yield with GS vs. standard genetic testing at first line

<table>
<thead>
<tr>
<th>Study</th>
<th>Standard Diagnoses</th>
<th>GS Diagnoses</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Panel A. Infants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farnaes et al. (2018)</td>
<td>4</td>
<td>9.52%</td>
<td>18</td>
</tr>
<tr>
<td>Petrikin et al. (2018)</td>
<td>1</td>
<td>3.03%</td>
<td>8</td>
</tr>
<tr>
<td>Willig et al. (2015)</td>
<td>3</td>
<td>9.38%</td>
<td>20</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Panel B. Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lionel et al. (2017)</td>
<td>25</td>
<td>24.27%</td>
<td>42</td>
</tr>
<tr>
<td>Stavropoulos et al. (2016)</td>
<td>13</td>
<td>13.00%</td>
<td>34</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Pooled estimate based on random effects meta-analysis on logit scale. Diagnoses in Petrikin et al. (2018) were based on diagnosis within 28 days of test order/enrollment (as reported in the study) due to significant crossover from the control arm to the treatment arm. Since the treatment arm in Petrikin et al. (2018) assigned patients to both GS and standard testing, we only coded a patient as diagnosed with GS if a diagnosis was obtained with GS; as a result, 2 diagnoses that were obtained with standard genetic testing rather than GS were excluded, resulting in 8/32 diagnoses with GS.

Table A3: First line diagnostic yield parameter estimates on logit scale

<table>
<thead>
<tr>
<th>Parameter</th>
<th>95% Confidence Interval</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td><strong>Panel A. Infants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>-1.95</td>
<td>-2.36</td>
</tr>
<tr>
<td>β</td>
<td>2.24</td>
<td>1.41</td>
</tr>
<tr>
<td><strong>Panel B. Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>-1.50</td>
<td>-2.24</td>
</tr>
<tr>
<td>β</td>
<td>0.96</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Note: Pooled estimate based on random effects meta-analysis on logit scale.

Parameter estimates for second line genetic testing were calculated by estimating the expected reduction in the diagnostic yield after first line. To do so, we utilized studies that compared diagnostic yields between GS (or exome sequencing (ES) when required) and standard care. We inferred the reduction in the diagnostic yield with GS by comparing the diagnostic yield among all patients to the diagnostic yield among the subset of patients who were not diagnosed by standard diagnostic investigations.

For infants, we made this comparison using data from Petrikin et al. (2018). In the case cohort, 10/32 = 31% of patients were diagnosed by GS, but among patients not diagnosed by standard investigations, only 6/25 = 24% of patients were diagnosed. This implies an odds ratio of 0.69, although the confidence interval is large (0.21 to 2.27) due to the small sample size. We made a similar comparison for children using data from Stavropoulos et al. (2016) to estimate the reduction in diagnostic yield for GS. Specifically, in the Stavropoulos et al. (2016) study, 34/100 = 34% of
patients were diagnosed by GS and $23/87 = 26\%$ of patients who were not diagnosed by standard investigations were diagnosed. The implied odds ratio is 0.69 and the confidence interval is again fairly large (0.39 to 1.23).

Predicted diagnostic yields by age group, genetic testing approach, and line are shown in Table A4. Estimates for first line were calculated using the parameter values in Table A3, and parameters for second line were calculated using the estimated reductions in the yield after failing to obtain a diagnosis at first line as described in the preceding paragraph.

**Table A4: Predicted diagnostic yield by genetic test and line of testing**

<table>
<thead>
<tr>
<th>Line</th>
<th>Standard</th>
<th>GS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panel A. Infants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12.44%</td>
<td>57.24%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>48.19%</td>
</tr>
<tr>
<td><strong>Panel B. Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18.30%</td>
<td>36.89%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>28.97%</td>
</tr>
</tbody>
</table>

Note: The predicted probability was calculated by applying the logistic function to Equation A4.

**A7.2 Mortality**

Time to death was assumed to have an exponential distribution with a constant mortality rate. The mortality rate for infants differs pre- and post- diagnosis, while the rate for children was assumed to be the same during all time periods. The mortality rate for infants was estimated using patient-level data from Petrikin et al. (2018). An exponential survival model was used with a time-varying covariate indicating whether a patient had obtained a diagnosis. Coefficients transformed to the real line using the natural logarithm from the survival model are shown in Table A5. The regression suggests that the mortality rate increases after diagnosis, but the coefficient is estimated imprecisely. The point estimates imply that the mortality rate prior to diagnosis is 0.74 and that the rate after diagnosis increases to 1.71. For children, we assumed a mortality rate based on the 1-year probability of death, for a 9-year old child, 0.000092, using the 2014 US life tables for the general population (Arias et al., 2017) (the 1-year probability of death is converted to a rate using $r = -\log(1 - p)$ where $r$ is the rate and $p$ is the probability).

**Table A5: Exponential survival model for infants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.30</td>
<td>-1.04 to 0.44</td>
</tr>
<tr>
<td>Post diagnosis</td>
<td>0.84</td>
<td>-0.51 to 2.19</td>
</tr>
</tbody>
</table>

Note: Sample size of 65 infants. Coefficients are transformed to the real line using the natural logarithm.
A7.3 Duration of the diagnostic trajectory

Recall that after sampling whether a patient obtains a diagnosis with a given diagnostic approach, the model samples time to the next event. If a diagnosis is obtained, the next event is a diagnosis; if no diagnosis is obtained, the next event is either death, the start of the next genetic test, or (if there is no next genetic test), the start of the post genetic testing period as an undiagnosed patient.

When patients use GS, time to the next event is measured using expected turnaround times. For children, we used a turnaround time of 2 months; for infants, we used a turnaround time of 14 days since rapid testing is more likely to be used with infants. Turnaround times do not depend on whether a diagnosis is obtained. We modeled the duration of the diagnostic trajectory with standard care separately for children and infants. For children, the duration of standard testing depended on whether a patient was ultimately diagnosed; for infants, it did not (i.e., a single estimate was used regardless of whether a patient was diagnosed).

For diagnosed children, our estimate of the mean duration of the trajectory—0.5 years—was based on expert opinion and published literature. We assumed that some patients with standard care will be diagnosed after the first visit and test(s), some will remain undiagnosed but will be diagnosed after a second visit/tests(s), and the remainder will be diagnosed after a third visit/tests(s). Each visit & associated testing will take ~4 months. Approximately 2/3 of patients will be diagnosed in the first visit. Of the remaining, approximately 2/3 will be diagnosed after the second visit, and 1/3 after the third visit. This estimate was generally consistent with published studies. For instance, Shashi et al. (2013)\textsuperscript{33} reported that the average time from initial evaluation to diagnosis was 0.63 years and Oei et al. (2017)\textsuperscript{34} estimated that the median duration of the testing period among diagnosed patients was 0.35 years. After that, we calibrated our overall trajectory for children by varying the trajectory for undiagnosed children based on the average trajectory reported by Dragojlovic et al.\textsuperscript{35} Dragojlovic et al followed an unselected cohort of children with unexplained intellectual disability referred to an academic medical center and reported a mean diagnostic trajectory of 4.2 years from the first genetic clinical evaluation. Since the duration of the diagnostic odyssey in our model is a combination of the outcomes among those diagnosed and undiagnosed, a trajectory of 6.5 years for undiagnosed children gave us an overall average trajectory of 4.18 years in the mixed cohort in our model (see Table 2). This estimate is also in line with several publications—informe in part through patient/family surveys—which have reported estimates of the diagnostic odyssey between 5-8 years.\textsuperscript{38-41} In addition to the aforementioned studies, we also considered a few other others, but believe they are generally less reliable. For example, while Tan et al.\textsuperscript{2} reported that a mean “duration
of the diagnostic odyssey” of 6 years that is consistent with our estimate, they did not specify how they measured the diagnostic odyssey. Furthermore, while there are published clinical studies of undiagnosed patients recruited for clinical studies of ES or GS which report estimates in the range of 2.55 to 3.33 years from first presentation to specialists to study enrollment, these studies may underestimate the true diagnostic odyssey as reported estimates reflect patients that were recruited into studies.\textsuperscript{2,36-38} For example, Vrijenhoek et al. reported the time since the first visit to the Wilhelmina Children’s Hospital, but diagnosis procedures prior to that were not included in the analysis. Still, we acknowledge that the source data have limitations and consequently evaluated alternative estimates in our scenario analyses. A limitation of the evidence base is that the duration of standard care is not consistently defined or modeled. It would ideally be measured within a competing risk framework with three competing events (diagnosis, time at which families stop seeking diagnostic evaluations, and death).

For infants, we used a pooled estimate based on Stark et al. (2017) and Petrikin et al. (2018).\textsuperscript{3,6} Stark et al. reported the “duration of the diagnostic trajectory”, which was measured from the age of onset of symptoms until either a diagnosis was established or an uninformative ES report was issued (which was given in parallel to standard diagnostic care). In contrast, Petrikin et al. used the Kaplan-Meier estimator to estimate time to diagnosis, with patients right censored at the end of follow-up. However, we chose not to use these estimates directly because they include patients diagnosed during the model’s post genetic testing phase and would consequently overestimate the diagnostic trajectory. Instead, we used the data from Petrikin et al. to conservatively estimate time to diagnosis among diagnosed patients only.

### Table A6: Duration of standard diagnostic care

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrikin et al. (2018)\textsuperscript{6}</td>
<td>USA</td>
<td>8</td>
<td>0.309</td>
<td>0.137</td>
</tr>
<tr>
<td>Stark et al. (2017)\textsuperscript{3}</td>
<td>Australia</td>
<td>40</td>
<td>1.081</td>
<td>0.072</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td>0.704</td>
<td>0.386</td>
</tr>
</tbody>
</table>

Note: Pooled estimate based on random effects meta-analysis of means.

### A7.4 Cost of diagnostic care

Estimated costs for GS (Table A7) were based on a health sector perspective in the US health system in USD and are assumed to include labor, supplies, bioinformatics, equipment, and confirmatory testing. Costs are intended to reflect trio testing in most cases (though in practice this is not always possible which would reduce costs). To inform our parameter estimates, we assessed the Medicare Clinical Laboratory Fee Schedule (CLFS)\textsuperscript{44}, published microcosting studies\textsuperscript{45,46}, and pricing from
reference laboratories that have made pricing publicly available. For example


Based on our analysis, we used the point estimates shown in Table A7 for the base case analysis. Costs in the economic model were considered to be fixed costs (see Section A6 for a discussion of the distinction between fixed and annualized costs).

**Table A7: Cost of GS**

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS</td>
<td>$5500</td>
<td>$8500</td>
</tr>
</tbody>
</table>

Note: Costs in the model for children represent standard turnaround time; Costs for critically ill infants are based on rapid turnaround.

The costs of standard diagnostic care for children were estimated by pooling estimates from studies that evaluated WES in patients without a diagnosis following standard workup and reported mean follow-up of standard diagnosis.\(^2,^3,^6,^37\) Tables A8 and A9 summarize the evidence used to estimate the costs of standard diagnostic care as well as the pooled estimates used in the model. Costs from Australian and Netherlands studies were converted into USD using the exchange rate at the time of the study and all costs were converted to 2020 dollars using the US consumer price index (CPI). Based on a published study from Dragojlovic et al\(^35\) (and supported by our own as-yet unpublished study of costs in a large US insurance claims database), costs of a standard diagnostic pathway are highest in the first two years (the higher cost period) then drop down to a relatively constant level thereafter (the lower cost period). For each study included in Table A10 we assumed the same ratio of the higher cost period ($3252 in total) vs. the lower cost period ($441 annually) as Dragojlovic et al. As an example, in Table A9, the mean total costs reported by Vrijenhoek et al were $8453.62 over 2.55 years. We assumed that if we followed patients from Dragojlovic’s study for 2.55 years, we would observe total costs of $3252 + $441 * (2.55-2) = 3494.55. Therefore for the Vrijenhoek et al study, the higher costs period total costs would be 8453.62 * (3252/3494.55) = 7865.21 as we assumed the same ratio of the higher costs period costs over total costs, and the annualized costs during the lower
costs period would be \((8453.62 - 7865.21)/0.55 = $1066.59\). The same calculation was applied to all studies in Table A9 below to split the total mean costs into the total higher costs period costs and the annualized lower costs period costs. We then pooled the higher costs period costs and lower costs period costs separately and used the annualized lower costs period costs as the annualized costs in the model ($825.45) directly. The upfront costs were then estimated using the higher costs period total costs minus the annualized costs for the first two years, giving a parameter estimate of $3877.53.

An important question when evaluating the cost impact of GS relative to standard diagnostic care is the extent to which GS might replace genetic and non-genetic diagnostic investigations typically obtained with standard care. To generate estimates for this quantity, we required studies that (i) considered costs for GS when replacing some standard investigations and (ii) estimated costs by category. Since there were—to our knowledge—no studies analyzing GS that provided this information, we used studies examining ES. Furthermore, we communicated with the authors of the relevant articles to ensure that our estimates were reasonable. Our estimates are reported in Table A9.

For infants, we assumed that diagnostic costs that would be accrued in addition to first-tier GS were similar to those reported with ES by Stark et al (2017). In the first scenario ("Model 2"), ES replaced some investigations and in the second scenario ("Model 3"), ES was used as a first-line test. In Model 2, the authors estimated that $2,160 AUD were incurred in addition to ES; in Model 3, ES replaced all costs except microarray, which was estimated to cost $597 AUD. To convert from AUD to USD, we used the exchange rate on January 30, 2015 as reported in the paper ($1 AUD = $0.78 USD) and converted costs (from 2015) to 2020 USD using the CPI yielded an estimate of $1,205.37. We assumed that microarray would not be incurred for GS, yielding an estimate of $800 in 2015 AUD, or $688.79 in 2020 USD.

For children, we again assumed that some standard diagnostic costs would be accrued in addition to first-tier GS. In Tan et al (2017), the authors modeled standard diagnostic costs that would remain if ES was introduced at either first tertiary presentation or first genetics presentation. These costs represented between 11% and 30% of the total standard workup costs (between $913 and $2,491 in 2020 USD). Van Nimwegen et al (2015) reported a similar analysis, finding that with earlier use of ES, 46% of standard costs would remain. By applying that percentage to mean costs during the initial 2-year high cost period, remaining standard costs are $1,783.66. To be conservative, we used $1,783.66 in the model.

For the standard diagnostic pathway, for infants we assumed patients incurred the same upfront
costs but included the cost of the microarray, yielding estimates of $1,205.37. For children, we estimated the upfront costs by taking two years worth of yearly costs from the higher cost period total which give us $4,790 (6572.88 – 891*2 = $4790).

The costs reported so far are the costs incurred during a selected diagnostic pathway (e.g., Standard → GS), but not the costs incurred thereafter. During the post genetic testing phase, we assumed—given the limited evidence—that there were no downstream costs. However, we relaxed these assumptions in the scenario analyses using evidence from a follow-up study by Stark et al. (2019). They reported that costs for previously undiagnosed infants were $537.41 AUD per patient. 2018 costs in a US setting were then $410 USD per patient given an exchange rate ($1 AUD = $0.76 USD) at the final date of patient follow-up (October 16) and using the US CPI. Since the median duration of the study was 473 days (1.295 years), this suggests that costs on an annualized basis were $316 USD. For diagnosed patients, they report 1-year costs of $336, $9,447, $146, and $219 among 4 infants who experienced a change in clinical outcome and/or hospital use. A total of 45 infants were diagnosed prior to death, implying an average yearly cost of $225 AUD and annualized costs of $173 USD after again adjusting using the exchange rate and CPI.

Table A8: Cost of standard diagnostic care - infants

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Country</th>
<th>Duration (years)</th>
<th>Mean cumulative costs</th>
<th>SE of cumulative costs</th>
<th>Mean upfront costs</th>
<th>SE of upfront costs</th>
<th>Mean annualized costs</th>
<th>SE of annualized costs</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stark et al. (2017)</td>
<td>All</td>
<td>Australia</td>
<td>1.08</td>
<td>$1,205.37</td>
<td>$241.07</td>
<td>$2,056.48</td>
<td>$441.30</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>All</td>
<td>Australia</td>
<td>1.08</td>
<td>$1,205.37</td>
<td>$241.07</td>
<td>$2,056.48</td>
<td>$441.30</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Costs are in 2020 USD. Three groups were identified during the literature review: “All” - all patients in the study; “Dx’ - patients who were ultimately diagnosed; and “No Dx” - patients who were not diagnosed during the study. Duration is equivalent to the mean duration (in years) of standard diagnostic care reported in Table A6. Annualized costs were estimated by dividing cumulative costs by the duration of time over which they were measured.

Table A9: Cost of standard diagnostic care - children

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Country</th>
<th>Duration (years)</th>
<th>Mean total costs</th>
<th>SE of total costs</th>
<th>Mean costs during initial higher costs period</th>
<th>SE of higher costs period costs</th>
<th>Mean costs during lower costs period (annualized)</th>
<th>SE of lower costs period (annualized)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dragojovic (2019)</td>
<td>All</td>
<td>Canada</td>
<td>6.5</td>
<td>5822.14</td>
<td>4.31</td>
<td>2558.02</td>
<td>325.48</td>
<td>346.89</td>
<td>258.45</td>
<td>498</td>
</tr>
<tr>
<td>Tan (2017)</td>
<td>All</td>
<td>Australia</td>
<td>6.00</td>
<td>8306.40</td>
<td>1055.38</td>
<td>5385.25</td>
<td>684.23</td>
<td>730.29</td>
<td>92.79</td>
<td>44</td>
</tr>
<tr>
<td>Vrijenhoek (2018)</td>
<td>No Dx</td>
<td>Netherlands</td>
<td>2.55</td>
<td>8453.62</td>
<td>495.64</td>
<td>7865.21</td>
<td>461.14</td>
<td>1066.59</td>
<td>62.53</td>
<td>370</td>
</tr>
<tr>
<td>Yeung (2020)</td>
<td>All</td>
<td>Australia</td>
<td>2.86</td>
<td>7068.42</td>
<td>30.71</td>
<td>6327.26</td>
<td>27.49</td>
<td>858.03</td>
<td>3.73</td>
<td>91</td>
</tr>
<tr>
<td>Pooled</td>
<td>All</td>
<td>Australia</td>
<td>2.86</td>
<td>7068.42</td>
<td>30.71</td>
<td>$5328.44</td>
<td>$1,127.45</td>
<td>$825.45</td>
<td>$111.04</td>
<td></td>
</tr>
</tbody>
</table>

Note: Pooled estimate based on random effects meta-analysis. Costs are in 2020 USD. Three groups were identified during the literature review: “All” - all patients in the study; “Dx’ - patients who were ultimately diagnosed; and “No Dx” - patients who were not diagnosed during the study. Duration is equivalent to the mean duration (in years) of standard diagnostic care reported in Table A6. Annualized costs were estimated by dividing cumulative costs by the duration of time over which they were measured.
Table A10: Costs of standard diagnostic care not replaced by GS

<table>
<thead>
<tr>
<th>Panel A. Infants</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel B. Children</td>
<td>$1,783.66</td>
</tr>
</tbody>
</table>

**A7.5 Cost of a stay in the NICU**

When modeling costs for infants based on NICU stays, costs are a function of an infant’s LOS in the NICU and the difference in costs between being treated in a NICU setting and being treated in an outpatient setting. To estimate cost per day in the NICU, we reviewed the peer-reviewed and grey literature. There are numerous studies evaluating NICU costs associated with prematurity, but fewer that are specific to a population with genetic disease or suspected genetic disease. We identified two references that we believe are most relevant for this model: Gonzaludo et al (2019) and the final report from “Project Baby Bear” in California ([https://radygenomics.org/wp-content/uploads/2020/07/PBB-Final-Report_07.14.20.pdf](https://radygenomics.org/wp-content/uploads/2020/07/PBB-Final-Report_07.14.20.pdf)). While the Project Baby Bear report does not specifically report a cost per day in the NICU, the data allow us to generate an estimate. First, the report notes that healthcare savings were $2,488,861 for the 178 patients in the study, and that 94% of the cost savings ($2,339,529) were driven by decreases in LOS, which were estimated at 513 days overall (or 2.88 days per patient). Thus, the cost savings from LOS would equal ~$4,560/day.

Gonzaludo et al utilized the HCUP KID database and evaluated hospitalization costs using a curated list of ICD-9 codes for two different subsets of patients: GD minimum (GDmin) included patients with clinical indicators of genetic disease where the ICD-9 code was the primary diagnosis code; GD maximum (GDmax) included patients where the ICD-9 index code could be primary or secondary in the list of diagnosis codes. GDmin and GDmax define different size populations: GDmin identified 0.4% of neonates while GDmax defined 10% of neonates. We believe that GDmin is a closer representation of the NICU population we are aiming to define in the model in terms of population size. In addition, the mean LOS for GDmin (22.3d) is closer to estimates from published studies evaluating this population in the literature than the mean LOS for GDmax (9.7d). Focusing on GDmin, the study reported that mean LOS was 22.3d (SE 1.3), and that mean total costs per discharge were $81,222 (SE $6,546), leading to a cost/day estimate of $3,642 (in 2012 dollars). Following CPI adjustment, the estimate would be ~$4,145.02. To be conservative, we elected to utilize the Gonzaludo et al-based estimate for the base case parameter estimate. Finally, as discussed below, uncertainty regarding this estimate is addressed in the sensitivity analysis.

For infants, we also included a parameter for cost in the outpatient setting after discharge. This cost
was estimated using data from the Centers for Medicare & Medicaid Services (CMS) (Centers for Medicare & Medicaid Services, 2016) estimating that overall medical costs were $10,348 per year in 2016, and outpatient costs takes 40% of the total healthcare costs.\(^9\) A per day estimate was generated ($10,348*0.4/365.25 = $11.33) and then inflated to 2020 dollars ($12.33 per day). We acknowledge the imprecision of this estimate, as it is not specific to this patient population and may represent an under- or over-estimate. However, we included the parameter to allow for flexibility of testing different assumptions. As shown in Figure A3, varying this parameter has minimal impact on the overall model results.

LOS in the NICU with standard care was based on time until hospital discharge from Petrikin et al. (2018) among all subjects in the "control" arm, or 55.5 days (SE = 10.0).\(^6\) LOS for GS was then computed from the expected reduction in hospital days estimated by Farnaes et al. (2018) of 2.95 days (SE = 1.48).\(^5\) Applying the reduction in hospital days with GS to the estimates of LOS with standard care implied a mean length of stay with GS of 52.6 days (SE = 10.2). One key limitation that is worth noting is that there were no studies that examined the impact of different diagnostic pathways (e.g., Standard → GS) on LOS, so we assumed that only the first genetic test used in a given diagnostic pathway impacts LOS.

### A7.6 Change in clinical management

In the model, change in clinical management is measured as the proportion of patient’s with a diagnosis whose clinical management is altered because of their diagnosis. Table A10 reports the evidence base that we use to estimate this proportion for both infants and children, pooling studies for ES and GS. The proportions for infants were similar across studies, with most studies reporting that between 50% to 70% of infants with a diagnosis had a change in management. Results for children were less consistent with estimates ranging from as low as 26% to as high as 100%, although the pooled estimate for children was similar to the pooled estimate for infants. The sample size was also considerably lower for infants than for children so we included the Soden et al. (2014) study even though the study consisted of patients with neurodevelopmental disorders rather than patients with “any suspected genetic disorder”.\(^50\) We believe that this decision was reasonable because the sample size is very small when it is excluded and the estimates from Soden et al. (2014) were similar to the pooled estimate.\(^50\)
Table A11: Change in clinical management

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>N</th>
<th>%</th>
<th>Measure of clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panel A. Infants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meng et al. (2017)(^{51})</td>
<td>53</td>
<td>102</td>
<td>51.96%</td>
<td>Affected medical management</td>
</tr>
<tr>
<td>Petrikin et al. (2015)(^{52})</td>
<td>13</td>
<td>20</td>
<td>65.00%</td>
<td>Acute clinical usefulness</td>
</tr>
<tr>
<td>Petrikin et al. (2018)(^6)</td>
<td>7</td>
<td>13</td>
<td>53.85%</td>
<td>Change in medical management</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td><strong>53.99%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Panel B. Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bick et al. (2017)(^{53})</td>
<td>6</td>
<td>8</td>
<td>75.00%</td>
<td>Dx affected Tx or medical surveillance</td>
</tr>
<tr>
<td>Soden et al. (2014)(^{50})</td>
<td>22</td>
<td>45</td>
<td>48.89%</td>
<td>Dx changed patient management and/or clinical impression of the pathophysiology</td>
</tr>
<tr>
<td>Tan et al. (2017)(^2)</td>
<td>6</td>
<td>23</td>
<td>26.09%</td>
<td>Clinical management was altered</td>
</tr>
<tr>
<td>Valencia et al. (2015)(^30)</td>
<td>12</td>
<td>12</td>
<td>100.00%</td>
<td>Change in medical management</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td><strong>60.32%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: Pooled estimate based on random effects meta-analysis for binomial data.

A8: Computation and probabilistic sensitivity analysis

Parameter uncertainty was quantified using PSA, which propagates uncertainty in the model input parameters throughout the model by randomly sampling the input parameters from their joint probability distribution (Baio and Dawid, 2015; Claxton et al., 2005).\(^{54,55}\) The simulation therefore proceeds in two steps: first, model parameters are sampled from their joint probability distribution and second, for each randomly sampled parameter set, model outcomes are simulated for individual patients as described in Section A5.

Probability distributions for the model parameters are determined according to the distributional properties of the statistical estimates, which, in turn, depend on the statistical techniques used and the distributions of the underlying data. We used beta distributions for probabilities, normal distributions for sample means, and gamma distributions for right-skewed data (e.g., rates, diagnostic costs). The PSA parameter distributions are summarized in Table A11.

Samples, \(x\), were randomly drawn from normal distributions using the mean and standard deviations of the parameters of interest, \(x \sim N(\mu, \sigma^2)\), where \(\mu\) is the mean and \(\sigma\) is the standard deviation.
Table A12: Parameter distributions for probabilistic sensitivity analysis

<table>
<thead>
<tr>
<th>Parameter(s)</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic yield (logit scale)</td>
<td>Normal</td>
</tr>
<tr>
<td>Log rate for mortality</td>
<td>Normal</td>
</tr>
<tr>
<td>Rate for time to next event (next event = diagnosis, next test, or post-genetic testing phase)</td>
<td>Gamma</td>
</tr>
<tr>
<td>Rate for length of stay in the NICU</td>
<td>Gamma</td>
</tr>
<tr>
<td>Medical costs</td>
<td>Gamma</td>
</tr>
<tr>
<td>Probability of change in clinical management</td>
<td>Beta</td>
</tr>
<tr>
<td>Rate for number of genetic tests</td>
<td>Gamma</td>
</tr>
</tbody>
</table>

Probabilities defined on $[0, 1]$ were drawn from a beta distribution,

$$p(\pi | y) = Beta(y, n - y)$$

(A5)

where $y$ represents the number of successes (e.g., diagnoses) in $n$ trials (e.g., with sample size $n$). This beta distribution is an approximation of the posterior distribution of a binomial distribution with uninformative beta priors.

Samples were drawn from gamma distributions by first estimating the shape parameter, $\kappa > 0$, and the scale parameter, $\theta > 0$, using the sample mean and sample standard deviation of the parameter of interest. In particular, given a sample mean, $x$, and a sample standard deviation, $s^2$, we have,

$$\theta = \frac{s^2}{x}$$

$$\kappa = \frac{x}{\theta}.$$  

(A6)

Random samples, $x$, were then drawn from the gamma distribution as $x \sim Gamma(\kappa, \theta)$.

Model parameters were estimated and randomly drawn using the programming language R and patients were simulated for each random draw of the parameters using C++.
A9: Supplemental figures

The tornado diagrams below demonstrate the impact of each variable to the incremental costs of testing strategies GS and Standard→GS to Standard.

A9.1 Infant model using diagnostic workup costs

For the model of acutely-ill infants focusing on diagnostic costs, the incremental cost is most sensitive to mortality rate and least sensitive to post-genetic testing costs in infants for both GS and Standard → GS strategies. For the GS strategy, reducing mortality rate to zero leads to an increase in costs (base-case: $2,156 USD, zero mortality: $2,685) in the Standard strategy but had little impact to the GS strategy (base-case: $9,189, zero mortality: $9,189), since GS only generates costs in the beginning of the simulation, driving the change. The Standard → GS strategy was more sensitive to mortality rate, resulting in a bigger change from base case when reducing the mortality rate to zero (base-case: $7,540, zero-mortality: $10,671). Increasing time-horizon to 9 years did not affect the incremental costs for either strategies and the difference is likely a result of the Monte Carlo sampling effect. This is because all diagnosis costs happened before the end of the 5-year time-horizon and no post-diagnosis costs were included in this particular analysis for either base-case or the time-horizon scenario analysis. The diagnosis yield increases up to the third year and remains consistent around ± 41%, which is in consistent with diagnostic yield in base-case. The mean duration of diagnostic trajectory is 172.20 days with the credible interval of 88.74 – 283.80 days in base-case.

A9.2 Infants model using NICU LOS costs

When NICU costs is the focus of the analysis, the GS only strategy (base-case: $209,472, zero-mortality: $285,650) and Standard → GS (base-case: $226,444, zero mortality: $297,357) was more sensitive to reducing the mortality rate than Standard (base-case: $227,973, zero mortality: $288,954). Inpatient costs affected the incremental costs between GS and Standard more in both directions than incremental costs between Standard->GS and Standard.

A9.3 Children

For children, standard costs for children was more sensitive to the time-horizon (base-case: $7,355, 1 year time-horizon: $4,586, 15 year time-horizon: $7,826), since post-diagnosis costs were not included in the analysis, so GS costs did not increase with time. Additionally, proportion of diagnosed was reduced to ±16% for Standard and ±19% for Standard→GS when time-horizon was reduced to 1 year, and the GS diagnosis probability remained the same as base-case.
Figure A2: One-way sensitivity analysis of incremental costs relative to standard care for infants (diagnostic cost model)

Notes: The following scenarios were run: (1) adjusting the cost of standard care by ±30%, (2) adjusting the duration of the diagnostic trajectory by ±30, (3) using a mortality rate of ≈ 0 as the lower bound and adjusting the mortality rate by ±30% to create an upper bound, (4) adding post genetic testing costs in an upper bound scenario (no lower bound was run since the default model did not include post genetic testing costs), and (5) using time horizons of 1 and 8 years for the lower and upper bounds, respectively.
Figure A3: One-way sensitivity analysis of incremental costs relative to standard care for infants (NICU LOS cost model)

Notes: The following scenarios were run: (1) using a mortality rate of ≈ 0 as the lower bound and adjusting the mortality rate by +30% to create an upper bound, (2) adjusting inpatient costs by ±30%, (3) adjusting outpatient costs by ±30%, and (4) using time horizons of 1 and 8 years for the lower and upper bounds, respectively.
Figure A4: One-way sensitivity analysis of incremental costs relative to standard care for children

Notes: The following scenarios were run: (1) adjusting the cost of standard care by ±30%, (2) adjusting the duration of the diagnostic trajectory by ±30%, (3) using a mortality rate of ≈ 0 as the lower bound and adjusting the mortality rate by ±30% to create an upper bound, (4) adding post genetic testing costs in an upper bound scenario (no lower bound was run since the default model did not include post genetic testing costs), and (5) using time horizons of 1 and 15 years for the lower and upper bounds, respectively.
References


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