Author/s:
Downie, L;Amor, DJ;Halliday, J;Lewis, S;Martyn, M;Goranitis, I

Title:
Exome Sequencing for Isolated Congenital Hearing Loss: A Cost-Effectiveness Analysis

Date:
2021-07-01

Citation:
Downie, L., Amor, D. J., Halliday, J., Lewis, S., Martyn, M. & Goranitis, I. (2021). Exome Sequencing for Isolated Congenital Hearing Loss: A Cost-Effectiveness Analysis. Laryngoscope, 131 (7), pp.E2371-E2377. https://doi.org/10.1002/lary.29356.

Persistent Link:
https://hdl.handle.net/11343/276796

Goranitis Ilias (Orcid ID: 0000-0001-7946-8324)

Exome sequencing for isolated congenital hearing loss: a cost-effectiveness analysis

Sequencing for hearing loss is cost-effective

Lilian Downie[1234], MBBS, David J. Amor[1234], PhD, Jane Halliday[24], PhD, Sharon Lewis[24], PhD, Melissa Martyn[245], PhD, Ilias Goranitis[267], PhD (Corresponding author).

P: +61 3 8341 6200, F: +61 3 8341 6390

E: ilias.goranitis@unimelb.edu.au

A: MCRI Flemington Rd Parkville Victoria Australia 3052

[1] Victorian Clinical Genetics Services, Melbourne Australia.

[2] Murdoch Children's Research Institute, Melbourne Australia.

[3] Royal Children's Hospital, Melbourne Australia.

[4] Department of Paediatrics, University of Melbourne, Melbourne Australia.

[5] Melbourne Genomics Health Alliance, Melbourne Australia.

[6] Centre for Health Policy, University of Melbourne, Melbourne Australia.

[7] Australian Genomics Health Alliance, Australia

The study was funded by the State Government of Victoria (Department of Health and Human Services) and the 10 member organisations of the Melbourne Genomics Health Alliance. The authors have no conflicts of interest to declare.

Abstract

Objective

To assess the relative cost-effectiveness of exome sequencing for isolated congenital deafness compared with standard care.

Methods

A decision tree was used to model the costs and outcomes associated with exome sequencing and standard care for infants presenting with isolated congenital deafness. Incremental cost-effectiveness and cost-benefit analyses were undertaken from the perspective of the Australian healthcare system using an 18-year time horizon.

Results

Exome sequencing resulted in an incremental cost of AU$1000 per child and an additional 30 diagnoses per 100 children tested. The incremental cost-effectiveness ratio was AU$3333 per additional diagnosis. The mean societal willingness to pay for exome sequencing was estimated at AU$4600 per child tested relative to standard care, resulting in a positive net benefit of AU$3600. Deterministic and probabilistic sensitivity analyses confirmed the cost-effectiveness of exome sequencing.

Conclusions

Our findings demonstrate the cost-effectiveness of exome sequencing in congenital hearing loss, through increased diagnostic rate and consequent improved process of care by reducing or ceasing diagnostic investigation or facilitating targeted further investigation. We

recommend equitable funding for exome sequencing in infants presenting with isolated congenital hearing loss.

Keywords: hearing loss, deafness, genetics, genomics, economic evaluation, cost-effectiveness

Level of evidence: N/A

Introduction

Exome sequencing (ES) has become the gold standard for investigation of genetic disease.[1] Despite this, ES is not a routine part of the health care system, partly due to its high cost. There is strong evidence that ES produces the highest diagnostic yield in patients with genetic disorders,[1] and it is now emerging that these results can also have high clinical utility and significant economic consequences to the health system.[2] The size of these consequences depends on the disease group and patient population tested, making generalization about the cost-effectiveness of ES impracticable.[3] Health-economic evidence is increasingly sought to inform funding decisions, yet robust evidence that is applicable to specific clinical situations is rarely available.[3] Challenges to producing this evidence include a lack of long-term impact data, difficulty in obtaining quality adjusted life years (QALYs) for infant populations, and a lack of empirical evidence on the personal utility derived from ES, for example avoiding the diagnostic odyssey and relieving parental guilt.[4] In addition, the cost and performance of ES technologies are moving targets making analyses difficult to apply to future funding decisions.[5]

The majority of congenital hearing loss (HL) has a genetic etiology.[6] Despite a recommendation that ES becomes standard of care for this indication,[7] this has largely not been implemented. This is due to resource limitations and the scarcity of data demonstrating cost-effectiveness and clinical utility. Additionally, access to treatment options, such as hearing aids and cochlear implantation, is not dependent on a specific genetic diagnosis.

In a recent study investigating the genetic causes of congenital HL, we identified a high clinical utility in the diagnosed cohort.[8] Care was able to be streamlined and many diagnostic investigations avoided. In this follow-up analysis we examine the cost-

effectiveness of ES for children presenting with isolated HL relative to standard care. The costs and outcomes of the two strategies are described and evaluated incrementally. The objective was to provide evidence to inform decision-making about funding for ES for patients presenting with isolated congenital HL.

Materials and methods

The study utilized data from a population-derived cohort of infants who received ES early in the trajectory of care (prior to 1 year of age), as part of the Melbourne Genomics Health Alliance Congenital Deafness flagship,[9] and other published secondary evidence. For the primary clinical study, published in detail,[8-10] and briefly described here, 106 infants were recruited and offered ES with targeted analysis of deafness genes (available from https://panelapp.agha.umccr.org/panels/209/ and listed in Table 1) and multiplex ligation-dependent probe amplification (MLPA) for *OTOA/STRC*. This cohort included infants with bilateral congenital sensorineural HL with ≥40dB of loss in the best ear, including syndromic and non-syndromic presentations ascertained over a two-year period. This cost-effectiveness analysis is focused on infants presenting with isolated deafness, no other findings on clinical examination at initial assessment, and not fulfilling eligibility criteria for ES by local genetics services which are: multisystem disease (defined as more than one primary pathology associated with the undiagnosed condition) or complex progressive neurological condition. The rationale was to exclude infants presenting with complex syndromes, in which the evidence for providing funded sequencing is already established.[2] The study received Human Research Ethics Committee Approval (Melbourne Health Human Research Ethics Committee (13/MH/326).

A decision tree (Figure 1) was designed to model the diagnostic pathway with and without ES for this cohort. The decision tree is based on results of the primary study[8] and recommended investigations for children with congenital HL.[11] The primary study findings were that 22/106 participants had *GJB2/6* pathogenic variants, 16/106 had another non syndromic genetic cause and 21/106 had a syndrome diagnosis. Eight of those syndromic diagnoses presented as isolated HL and were included in this analysis. For the infants with non-syndromic genetic causes identified, further investigations were avoided. For those with a syndromic diagnosis, tailored care was provided. We have previously recommended that sequencing of *GJB2/6* be offered prior to ES,[6] and have designed our model based on this approach. Standard care is that all children diagnosed with congenital HL are offered an appointment with a pediatrician and investigation with *GJB2/6* sequencing. Recommendations for further investigation in childhood are summarized in Table 2, and include: MRI, family audiograms, ophthalmology assessment, electrocardiogram, renal ultrasound and vestibular testing. These are based on whether the infant has an etiological diagnosis made and if not, the severity of HL and other examination findings. The pathway deviates when infants have a confirmed genetic etiology for their HL. This can lead either to cessation of diagnostic investigation or management tailored toward the specific diagnosis. With a diagnosis of a non syndromic genetic aetiology, no further investigation is recommended. With no diagnosis the following further investigation is recommended: in those with severe or profound loss an ECG is performed to exclude the rare association with long-QT syndrome and MRI is required in the first year of life, and therefore done with general anaesthetic, to assess suitability for cochlear implantation. In infants who have a family history of renal disease, or external ear anomalies, a renal ultrasound is recommended. Vestibular testing is considered in those with progressive sensorineural HL and delayed

motor milestones, however due to this not being widely available and difficult to perform in young children it has not been included in the modelling.

Costs

A health-care system costing perspective was adopted and unit costs were sought from the Australian Medicare Benefits Schedule,[12] Victorian Clinical Genetics Service genomics price list (vcgs.org.au) and the Royal Children's Hospital costing centre. All costs are presented in 2020 Australian dollars (currently 0.72 USD). Unit costs and sources are shown in Table 3. Where necessary, costs were inflated to 2020 Australian Dollars. The cost of ES with analysis of 141 deafness genes (available from https://panelapp.agha.umccr.org/panels/209/) and MLPA is AU$1995 and a genetic counselling episode costs AU$184. Additional costs associated with tailored care (AU$5081) arise for those who receive a syndromic diagnosis through ES. This figure is the mean of the costs projected over 18 years for the 8 primary study participants in this category and discounted at 5% annual rate: five had biallelic variants in *SCL26A4* (Pendred syndrome) which resulted in one off MRI under general anesthetic (AU$1000) and regular pediatric follow up (yearly at AU$272/year); two had a diagnosis of Usher syndrome which resulted in a yearly ophthalmology evaluation (including field test, retinal imaging and specialist examination) (yearly at AU$350/year); and one had a diagnosis of hypoparathyroidism, sensorineural deafness and renal dysplasia due to a pathogenic variant in *GATA3*, which incurs projected costs of AU$843/year (renal and endocrine specialist appointment, biochemistry and renal ultrasound). All those with a syndromic diagnosis had a follow up genetic counselling session (AU$184), for those without a diagnosis or with a non-syndromic genetic diagnosis a follow up genetic counselling session was not included in the costing These costs are based on recommended care for these outcomes and not on the actual costs incurred by these participants.

Outcomes

The diagnostic yield of *GJB2/6* sequencing (22%),was drawn from a systematic review[13] and mirrored that of our smaller study.[6] The additional diagnostic yield of ES (39%) following a negative GJBS/6, was informed by our primary clinical study[8] and published evidence on matched cohorts[13-22] identified through a literature review (Table 3). Evidence was synthesized using Bayesian methods to enhance the generalizability of our findings. The monetary value of the benefit of ES, also referred to as personal utility, was derived from a recently published discrete choice experiment (DCE).[23] The study elicited societal preferences and values for different components of personality utility from genomic sequencing. Personal utility was captured by disease severity (mild, moderate or severe), diagnostic yield, treatment or prevention options availability, improvement in the process of care (not likely, somewhat likely or very likely), and cost of the test. We used the study estimates to generate a willingness-to-pay (WTP) for exome testing in the context of a child presenting with isolated HL based on the compensating variation formula.[24] The WTP estimated assumed a moderate severity, diagnostic yield of 30%, no treatment or prevention options availability, and very likely improvement in the process of care.

Cost-effectiveness analysis

An incremental cost-effectiveness analysis was undertaken to assess the costs and outcomes of ES relative to standard of care from the perspective of the health care system. An annual discount rate of 5% was applied for costs, as per recommended guidelines in Australia.[25] Alternative discounting rates were explored in a sensitivity analysis. A time horizon of 18 years was applied to encapsulate the entirety of paediatric care (0-18 years). The following deterministic sensitivity analyses were performed: variation of the cost of ES from AU$1000 to AU$3000 and variation in the cost of tailored care from AU$2500 to

AU$7500. A tornado diagram was used to illustrate how variations in these key variables impact on the incremental cost-effectiveness ratio (ICER). A probabilistic sensitivity analysis was additionally conducted to quantify decision uncertainty at various thresholds of WTP per additional confirmed genetic diagnosis. A Monte Carlo simulation was performed with 10,000 repeated random draws from probability distributions. Gamma distributions were used for costs, and beta distributions were applied to the remaining parameters (Table 3). Decision uncertainty was presented using cost-effectiveness acceptability curves,[26] which plot the probability of each intervention being cost-effective at varying levels of WTP per additional genetic diagnosis. Analyses were undertaken in TreeAge Pro 2018.

Results

The standard care pathway (see Figure 1) incurs a total cost of AU$3200 per child with a diagnostic yield of 22%. The ES pathway incurs a total cost of AU$4200 per child and results in a diagnostic yield of 52%. Thus, ES results in an incremental cost of AU$1000 per child and in an additional 30 diagnoses per 100 children tested. The ICER is AU$3333 per additional diagnosis (Table 4).

Figure 2 shows how the ICER changes with variations in key model parameters. Indicatively, ranging the cost of ES from $1000 to $3000 results in an ICER between $750 and $5880 per additional diagnosis. An increased diagnostic yield from 39% to 50% for ES would reduce the ICER to $2070 per additional diagnosis. Varying the probability of having tailored management, the corresponding cost, or discount rate had marginal effect on study findings.

The mean societal WTP for ES per child tested and relative to standard care for this cohort was estimated at AU$4600 (95% CI: $4350, $4850). This monetary valuation of the

ES benefits is significantly higher than the estimated incremental mean cost difference of AU$1000 between the ES and standard care pathways, which results in a positive net benefit of AU$3600. Given that ES results in an additional 30 diagnoses per 100 children tested, the mean WTP for ES per additional diagnosis would be AU$15,333 (95% CI: $14,500, $16,170). As shown in the cost-effectiveness acceptability curves of Figure 3, there is 100% probability that ES is cost-effective at this threshold of WTP per additional diagnosis.

Discussion

This study evaluated the cost-effectiveness of ES in infants presenting with isolated congenital HL, from the perspective of the healthcare system. ES results in an additional cost of $1000 per child tested and an additional 30 diagnoses being confirmed out of 100 children tested. The estimated ICER was $3333 per additional diagnosis, which represents good value for public healthcare spending, as the expected societal WTP for genomic sequencing in isolated congenital HL was $4600.

This is the first study evaluating the cost-effectiveness of ES for this indication from a health care system perspective. Previous literature has evaluated alternative technology or funding perspectives. Alternative technology has included evaluation of targeted mutation sequencing or targeted microarray, without genomic sequencing as a comparator, and concluded that these approaches are cost-effective for increasing the diagnostic yield.[27,28] An alternative funding perspective, from the health insurer, demonstrated cost-effectiveness for ES in deafness despite using a lower diagnostic yield of 20%. [29] We have included the entirety of pediatric care and the downstream costs of those who are found to have a syndromic diagnosis, which is a significant cost that is commonly overlooked. Whilst these would vary significantly due to the rarity of those conditions and the variation in

recommended care for each, this inclusion has provided a comprehensive analysis for funders whilst still demonstrating cost-effectiveness.

The major benefit for funding ES is the increase in diagnostic yield, which has important flow on effects to children and families. The impact of the diagnostic odyssey on both parents and children is a significant burden, which needs to be incorporated into evaluating healthcare interventions.[30,31] Previous research has demonstrated psychological benefits for adult individuals who receive a genetic diagnosis and therefore an explanation for deafness.[32] This was demonstrated with increases in perceived personal control and reduction in anxiety for the diagnosed versus the undiagnosed group. This work demonstrated that obtaining a genetic diagnosis increases self-knowledge and psychological well-being with downstream benefits to individuals and society.

Furthermore, early molecular diagnosis will provide an opportunity to access advancements in treatment. Despite access to hearing aids and cochlear implantation not being dependent on a molecular diagnosis, it can help predict outcomes,[33] and is likely to inform management as treatments evolve. Precision therapies, driven by molecular diagnoses, are emerging for isolated HL[34,35] and deafness-associated syndromes such as Usher syndrome.[36] Streamlining treatment options to those who are most likely to benefit will have large economic impacts.[37] This makes ES for HL a worthy investment for the healthcare dollar.

Further, the ability to access reproductive options is limited to those with a molecular diagnosis. Whilst attitudes toward reproductive options around isolated deafness vary among cultures,[38] research indicates that families value this information in the prenatal setting, even if they would not use it to terminate a pregnancy.[39] In addition, reproductive options are more frequently sought for related severe conditions such as Usher syndrome.[40] Having access to

early ES would allow these families to consider prenatal testing and/or in vitro fertilization pre-implantation genetic diagnosis for either isolated or syndromic deafness.

The strengths of this study are the inclusion of both clinical and personal utility which are in line with published recommendations for evaluating genomic technologies.[41] The study has incorporated personal utility derived from a recently published DCE and a long time horizon as well as ensuring savings and expenditure are considered. Importantly, adjusting these variables to account for uncertainty did not significantly affect the cost-effectiveness estimates. If, as demonstrated in the tornado plot (Figure 2), the cost of ES falls or the diagnostic yield increases as more HL genes are discovered, these results will have underestimated the cost-effectiveness of ES for this indication. These factors create a highly realistic model for healthcare funders to consider and comply with the framework recommended for health economic evaluation.[42] This study has the benefit of being informed by a primary study in combination with evidence from a comprehensive literature review. Including a wider range of diagnostic evidence has increased the reliability and generalizability of our results.

Exome sequencing is used in this analysis because this is the locally available technology, however, both targeted sequencing panels and genome sequencing are relevant alternative technologies that may be utilized in this setting. By incorporating deterministic sensitivity analysis (varying input in the model and analyzing the outcome) we have made this data generalizable to any next generation sequencing technology. We believe the analysis demonstrates the cost-effectiveness of comprehensive genetic testing by any of these modalities for this indication.

We recognize the limitations of this work, firstly that the gold standard of health economic evaluation is a cost-utility analysis. This method incorporates Quality-Adjusted

Life-Years (QALYs) which unfortunately are not possible to obtain for an infant cohort like ours. In addition, QALYs tend to omit non-health and process outcomes related to the personal utility of genomic sequencing. In our primary study cohort there were no 'non genetic' aetiological diagnoses made through the standard care pathway and therefore this has not been factored into this analysis. It is possible that children would get a diagnosis through the recommended investigation pathway and this may subsequently reduce screening costs or increase costs associated with care. Lastly, the WTP estimate was based on a DCE that adopted a generic design to enable welfare estimates across genetic contexts. A DCE specifically designed for HL could have provided a more accurate picture of the value of ES in this context. Nevertheless, the large difference in the costs and benefits of ES relative to standard care estimated in this study provide a further reassurance around the cost-effectiveness of ES.

Conclusion

In summary, the benefits associated with funding ES for apparently isolated congenital HL are that it streamlines care for those who are found to have a syndromic diagnosis and eliminates unnecessary interventions for those with a non-syndromic diagnosis, creating efficiency and value for health care providers and hospitals. Currently ES is available with limited access through clinical services, for those who fulfill criteria as part of research or through insurance. For many, the test is only available if self-funded and this is often not an option for families. This inequity of access is best addressed by a streamlined funding approach. This study has provided a comprehensive analysis of the costs and outcomes associated with offering ES to infants presenting with isolated congenital deafness and demonstrated cost-effectiveness. We recommend that ES be funded for HL.

References

1. Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D, 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 genomic medicine.* 2018;3:16.
2. Stark Z, Schofield D, Martyn M, Rynehart L, Shrestha R, Alam K, et al. Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2018.
3. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2018;20(10):1122-1130.
4. Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. *Pharmacogenomics.* 2013;14(15):1833-1847.
5. Dragojlovic N, Elliott AM, Adam S, van Karnebeek C, Lehman A, Mwenifumbo JC, et al. The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: a benchmarking study. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2018;20(9):1013-1021.
6. Downie L, Halliday J, Burt R, Lunke S, Lynch E, Martyn M, et al. Exome sequencing in infants with congenital hearing impairment: a population-based cohort study. *European journal of human genetics : EJHG.* 2020;28(5):587-596.
7. Shearer AE, Smith RJ. Massively Parallel Sequencing for Genetic Diagnosis of Hearing Loss: The New Standard of Care. *Otolaryngology--head and neck surgery :*

official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2015;153(2):175-182.

8. Downie L, Halliday J, Burt R, Lunke S, Lynch E, Martyn M, et al. Exome sequencing in infants with congenital hearing impairment: a population-based cohort study. *European journal of human genetics : EJHG.* 2019.
9. Downie L, Halliday JL, Burt RA, Lunke S, Lynch E, Martyn M, et al. A protocol for whole-exome sequencing in newborns with congenital deafness: a prospective population-based cohort. *BMJ Paediatr Open.* 2017;1(1):e000119.
10. Downie L, Halliday J, Lewis S, Lunke S, Lynch E, Martyn M, et al. Exome sequencing in newborns with congenital deafness as a model for genomic newborn screening: the Baby Beyond Hearing project. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2020.
11. Sung V, Downie L, Paxton G, Liddle K, Birman C, W. C, et al. Childhood Hearing Australasian Medical Professionals (CHAMP) network: consensus guidelines on investigation and clinical management of childhood hearing loss. *Journal of Paediatric and Child Health (in press).* 2019.
12. Australia M. Pharmaecutical Benefits Schedule item reports. Published 2018. AccessedAccessed May 2020.
13. Kenneson A, Van Naarden Braun K, Boyle C. GJB2 (connexin 26) variants and nonsyndromic sensorineural hearing loss: a HuGE review. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2002;4(4):258-274.
14. Sloan-Heggen CM, Bierer AO, Shearer AE, Kolbe DL, Nishimura CJ, Frees KL, et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. *Hum Genet.* 2016;135(4):441-450.

15. Mehta D, Noon SE, Schwartz E, Wilkens A, Bedoukian EC, Scarano I, et al. Outcomes of evaluation and testing of 660 individuals with hearing loss in a pediatric genetics of hearing loss clinic. *American Journal of Medical Genetics Part A.* 2016;170(10):2523-2530.

16. Bademci G, Foster J, Mahdieh N, Bonyadi M, Duman D, Cengiz FB, et al. Comprehensive analysis via exome sequencing uncovers genetic etiology in autosomal recessive nonsyndromic deafness in a large multiethnic cohort. *Genetics in Medicine.* 2016;18(4):364-371.

17. Zazo Seco C, Wesdorp M, Feenstra I, Pfundt R, Hehir-Kwa JY, Lelieveld SH, et al. The diagnostic yield of whole-exome sequencing targeting a gene panel for hearing impairment in The Netherlands. *European Journal of Human Genetics.* 2017;25(3):308-314.

18. Likar T, Hasanhodzic M, Teran N, Maver A, Peterlin B, Writzl K. Diagnostic outcomes of exome sequencing in patients with syndromic or non-syndromic hearing loss. *PLoS ONE [Electronic Resource]*. 2018;13(1):e0188578.

19. Sheppard S, Biswas S, Li MH, Jayaraman V, Slack I, Romasko EJ, et al. Utility and limitations of exome sequencing as a genetic diagnostic tool for children with hearing loss. *Genetics in Medicine.* 2018:1-14.

20. Cabanillas R, Dineiro M, Cifuentes GA, Castillo D, Pruneda PC, Alvarez R, et al. Comprehensive genomic diagnosis of non-syndromic and syndromic hereditary hearing loss in Spanish patients. *BMC Medical Genomics.* 2018;11 (1) (no pagination)(58).

21. Sakuma N, Moteki H, Takahashi M, Nishio SY, Arai Y, Yamashita Y, et al. An effective screening strategy for deafness in combination with a next-generation

sequencing platform: A consecutive analysis. *Journal of human genetics.* 2016;61(3):253-261.

22. Atik T, Onay H, Aykut A, Bademci G, Kirazli T, Tekin M, et al. Comprehensive Analysis of Deafness Genes in Families with Autosomal Recessive Nonsyndromic Hearing Loss. *PLoS ONE [Electronic Resource]*. 2015;10(11):e0142154.
23. Goranitis I, Best S, Christodoulou J, Stark Z, Boughtwood T. The personal utility and uptake of genomic sequencing in pediatric and adult conditions: eliciting societal preferences with three discrete choice experiments. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2020.
24. Small KA, Rosen HS. Applied Welfare Economics with Discrete Choice Models. *Econometrica.* 1981;49(1):105-130.
25. (PBAC). PBAC. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Commitee. In: Australian Government DoHaA, ed. Canberra: Australia2008.
26. Briggs A SM, Claxton K. *Decision modelling for health economic evaluation.* Oxford, UK: Oxford University Press; 2006.
27. Gardner P, Oitmaa E, Messner A, Hoefsloot L, Metspalu A, Schrijver I. Simultaneous multigene mutation detection in patients with sensorineural hearing loss through a novel diagnostic microarray: a new approach for newborn screening follow-up. *Pediatrics.* 2006;118(3):985-994.
28. Choi BY, Park G, Gim J, Kim AR, Kim BJ, Kim HS, et al. Diagnostic application of targeted resequencing for familial nonsyndromic hearing loss. *PLoS One.* 2013;8(8):e68692.
29. Sabatini LM, Mathews C, Ptak D, Doshi S, Tynan K, Hegde MR, et al. Genomic Sequencing Procedure Microcosting Analysis and Health Economic Cost-Impact

Analysis: A Report of the Association for Molecular Pathology. *J Mol Diagn.* 2016;18(3):319-328.

30. Carmichael N, Tsipis J, Windmueller G, Mandel L, Estrella E. "Is it going to hurt?": the impact of the diagnostic odyssey on children and their families. *J Genet Couns.* 2015;24(2):325-335.

31. Wu Y, Al-Janabi H, Mallett A, Quinlan C, Scheffer IE, Howell KB, et al. Parental health spillover effects of paediatric rare genetic conditions. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2020.

32. Palmer CG, Boudreault P, Baldwin EE, Fox M, Deignan JL, Kobayashi Y, et al. Deaf genetic testing and psychological well-being in deaf adults. *J Genet Couns.* 2013;22(4):492-507.

33. Shearer AE, Eppsteiner RW, Frees K, Tejani V, Sloan-Heggen CM, Brown C, et al. Genetic variants in the peripheral auditory system significantly affect adult cochlear implant performance. *Hearing research.* 2017;348:138-142.

34. Novartis. Hearing Restoration Clinical Trial *US Clinical Trials Register.* 2014;NCT02132130.

35. Therapeutics F. First in Human Safety Study of FX-322 in Adults undergoing Cochlear Implantation *US Clinical Trials Register.* 2016;NCT03300687.

36. DiCarlo JE, Mahajan VB, Tsang SH. Gene therapy and genome surgery in the retina. *The Journal of clinical investigation.* 2018;128(6):2177-2188.

37. Graydon K, Waterworth C, Miller H, Gunasekera H. Global burden of hearing impairment and ear disease. *J Laryngol Otol.* 2019;133(1):18-25.

38. Nahar R, Puri RD, Saxena R, Verma IC. Do parental perceptions and motivations towards genetic testing and prenatal diagnosis for deafness vary in different cultures? *Am J Med Genet A.* 2013;161a(1):76-81.

39. Bowman-Smart H, Savulescu J, Mand C, Gyngell C, Pertile MD, Lewis S, et al. 'Is it better not to know certain things?': views of women who have undergone non-invasive prenatal testing on its possible future applications. *Journal of medical ethics.* 2019;45(4):231-238.

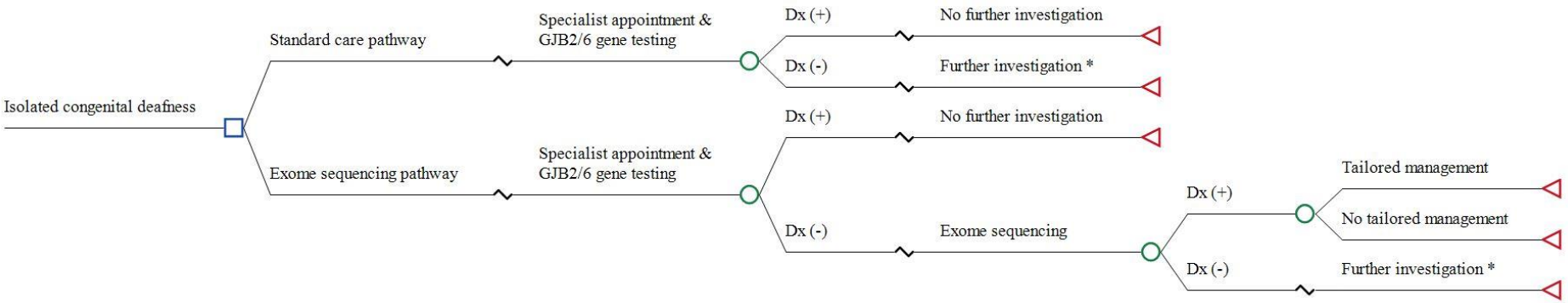
40. Pradhan M, Hayes I, Vincent A. An audit of genetic testing in diagnosis of inherited retinal disorders: a prerequisite for gene-specific intervention. *Clin Exp Ophthalmol.* 2009;37(7):703-711.

41. directors Abo. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2015;17(6):505-507.

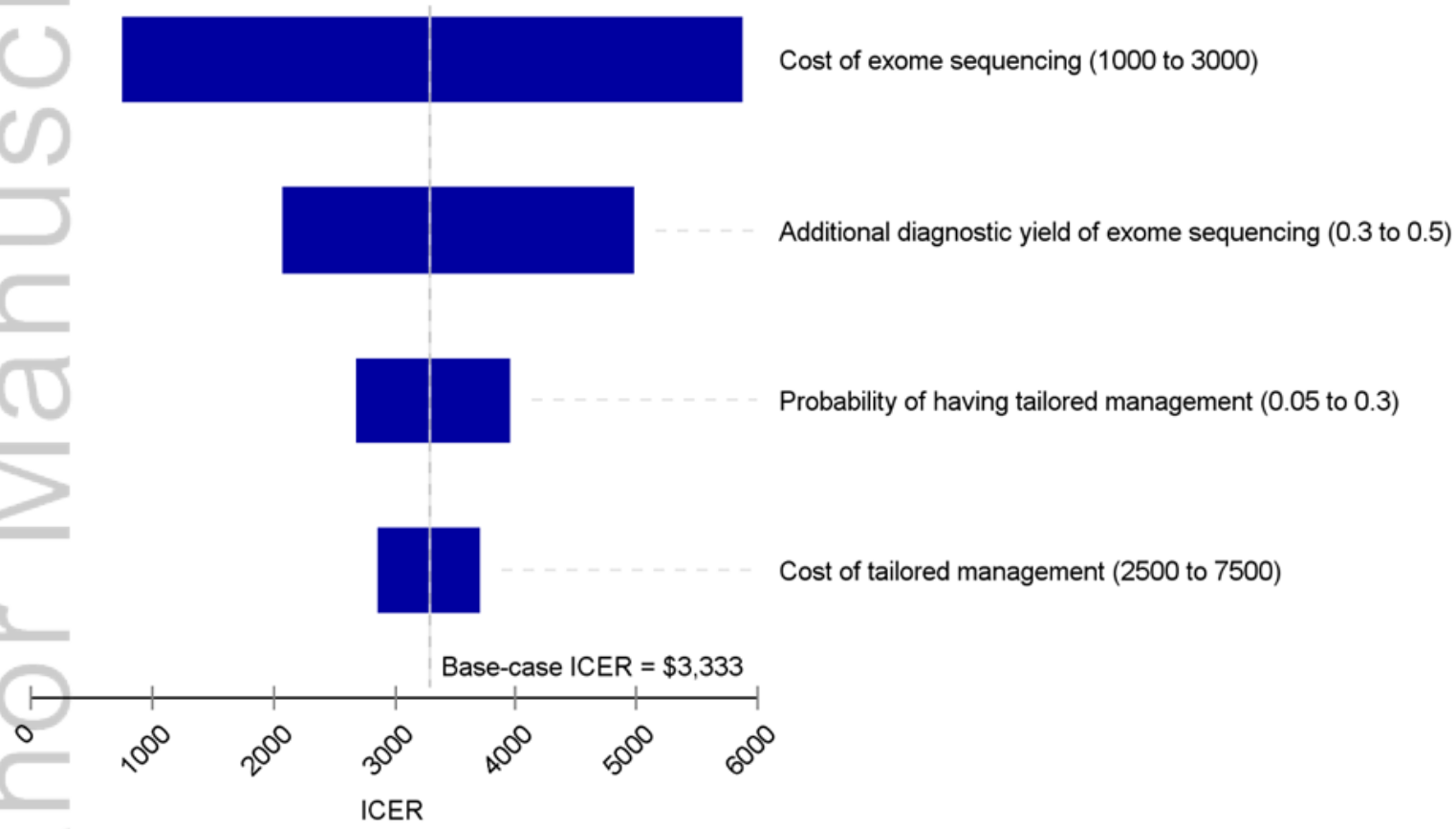
42. Belsley JC, L. Chediak, L. Currie, G. Goranitis, I. Marshall, D. . Global Data Access for Solving Rare Disease. A Health Economics Value Framework. *World economic forum* 2020.

Figures and tables

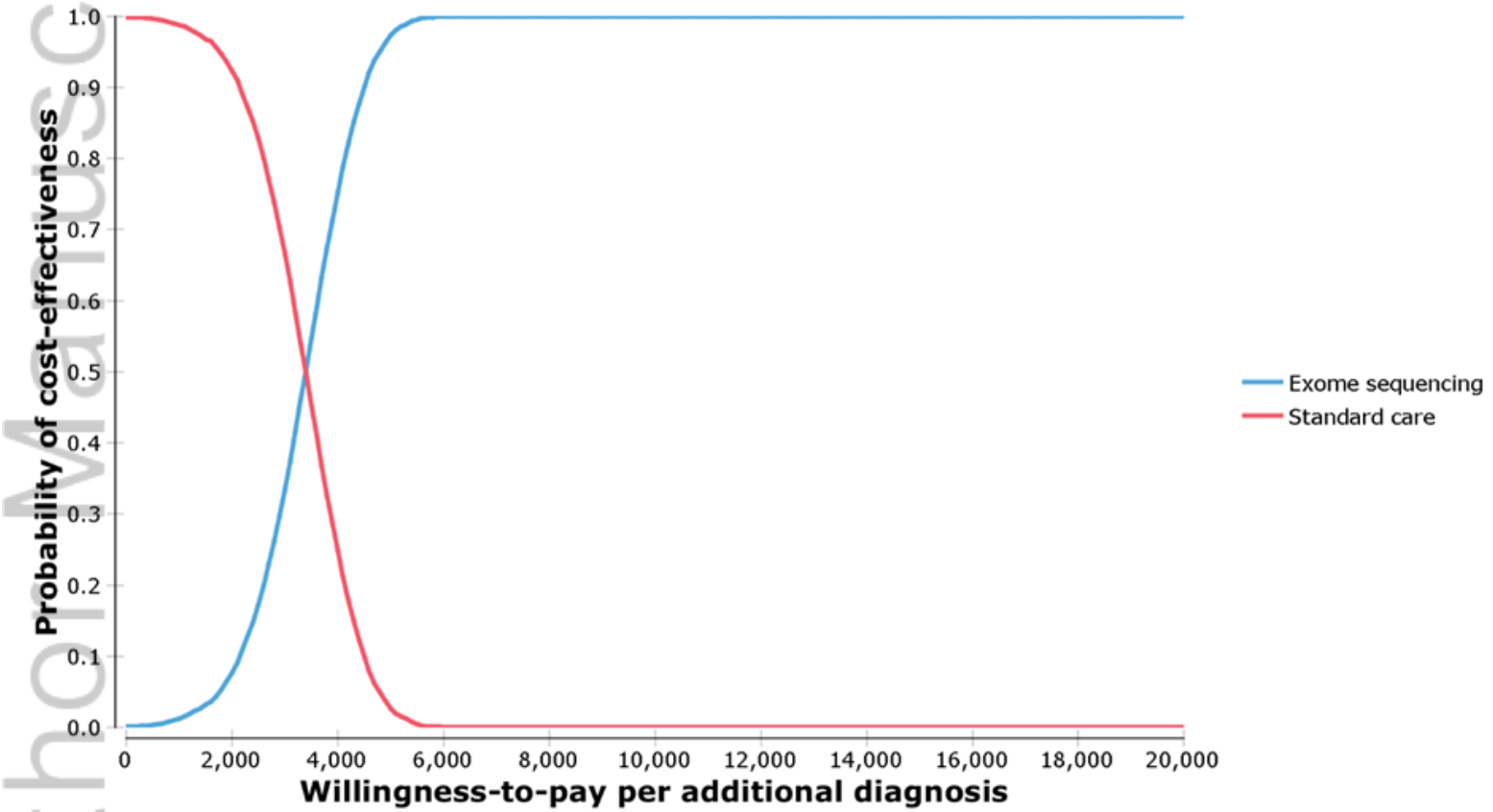
Figure 1. Decision tree



**Further investigation is outlined in Table 1 and may include; MRI brain, family audiograms, ophthalmology assessment, ECG, renal ultrasound and vestibular testing.*[11]



LARY_29356_FIgure 2 Tornado plot.png



LARY_29356_FIgure 3 Cost-effectiveness acceptability curves.png

Table 1. Deafness genes analyzed

ABHD12, ACTB, ACTG1, ADCY1, ADGRV1, AIFM1, ALMS1, ATP2B2, ATP6V1B1, BCS1L, BDP1, BSND, CABP2, CACNA1D, CATSPER2, CCDC50, CDH23, CEACAM16, CHD7, CIB2, CISD2, CLDN14, CLIC5, CLPP, CLRN1, COCH, COL11A1, COL11A2, COL2A1, COL4A5, COL4A6, COL9A1, COL9A2, COL9A3, CRYM, DFNA5, DFNB31, DFNB59, DIABLO, DIAPH1, DIAPH3, DNMT1, DSPP, EDN3, EDNRB, ELMOD3, EPS8, ESPN, ESRRB, EYA1, EYA4, FGF3, FOXI1, GATA3, GIPC3, GJB1, GJB2, GJB3, GJB4, GJB6, GPSM2, GRHL2, GRXCR1, GRXCR2, HARS, HARS2, HGF, HOMER2, HOXA2, HSD17B4, ILDR1, KARS, KCNE1, KCNJ10, KCNQ1, KCNQ4, LARS2, LHFPL5, LHX3, LOXHD1, LRTOMT, MARVELD2, MASP1, MIR96, MITF, MSRB3, MT-RNR1, MT-TS1, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, NR2F1, OPA1, OSBPL2, OTOA, OTOF, OTOG, OTOGL, P2RX2, PAX2, PAX3, PCDH15, PDZD7, PMP22, PNPT1, POU3F4, POU4F3, PRPS1, PTPRQ, RDX, SALL1, SALL4, SERPINB6, SIX1, SIX5, SLC17A8, SLC26A4, SLC4A11, SLITRK6, SMPX, SNAI2, SOX10, SOX2, STRC, SYNE4, TBC1D24, TECTA, TIMM8A, TJP2, TMC1, TMIE, TMPRSS3, TNC, TPRN, TRIOBP, TSPEAR, USH1C, USH1G, USH2A, WFS1

Table 2. Diagnostic pathway of further investigation

Further investigation	Mild/Moderate (57%)	Severe/Profound (43%)
MRI brain	✓	
MRI brain with general anesthetic		✓
Family audiograms	✓	✓
Ophthalmology assessment	✓	✓
ECG with cardiologist interpretation		✓
Renal ultrasound	*If indicated*	
Vestibular testing	*If indicated*	

✓ *denotes that the item is included in the costing*

MRI magnetic resonance imaging, ECG electrocardiogram

Table 2. Diagnostic pathway of further investigation

Further investigation	Mild/Moderate (57%)	Severe/Profound (43%)
MRI brain	✓	
MRI brain with general anesthetic		✓
Family audiograms	✓	✓
Ophthalmology assessment	✓	✓
ECG with cardiologist interpretation		✓
Renal ultrasound	*If indicated*	
Vestibular testing	*If indicated*	

✓ *denotes that the item is included in the costing*

MRI magnetic resonance imaging, ECG electrocardiogram

Table 3. Costs and outcomes

Model parameters	Mean value	Distribution	Source
Resource use items	**Unit costs (AU$)**		
GJB2/6	350		VCGS
Exome sequencing (deafness genes + MLPA)	1995		VCGS
Paediatrician appointment	272	Parameters were held fixed	[11]
Genetic counselling consult - first	184		VCGS
Genetic counselling consult - repeat	147		VCGS
Cost of diagnostic investigations†	3300	Gamma (15.5, 217)	
MRI brain (no anaesthetic)/with sedation	403/448		[11]
MRI brain (anaesthetic)	1000		RCH
Ophthalmology appointment	283		RCH
Electrocardiogram	71		[11]
Family audiogram	62		[11]
Renal ultrasound	55		[11]
Cost of tailored management‡	5081	Gamma (15.5, 324)	
Outcomes	**Probabilities**		
GJB2/6 sequencing diagnostic yield	0.22	Beta (461, 1640)	[12]
Exome sequencing additional diagnostic yield	0.39	Beta (455, 724)	[6, 12-21]
Chance of having a syndromic diagnosis and therefore incurring additional investigation	0.17	Beta (8, 39)	[6]

MLPA: Multiplex ligand-dependent probe amplification, MRI: magnetic resonance imaging, VCGS: Victorian Clinical Genetics Service, RCH: Royal Children's Hospital

† *Weighted mean value estimated as shown in table S1 using combinations of resource use items listed below in italics*

‡*Discounted estimate at 5% annual rate as per national guidelines*[24]

Table 3. Costs and outcomes

Model parameters	Mean value	Distribution	Source
Resource use items	**Unit costs (AU$)**		
GJB2/6	350		VCGS
Exome sequencing (deafness genes + MLPA)	1995		VCGS
Paediatrician appointment	272	Parameters were held fixed	[11]
Genetic counselling consult - first	184		VCGS
Genetic counselling consult - repeat	147		VCGS
Cost of diagnostic investigations†	3300	Gamma (15.5, 217)	
MRI brain (no anaesthetic)/with sedation	403/448		[11]
MRI brain (anaesthetic)	1000		RCH
Ophthalmology appointment	283		RCH
Electrocardiogram	71		[11]
Family audiogram	62		[11]
Renal ultrasound	55		[11]
Cost of tailored management‡	5081	Gamma (15.5, 324)	
Outcomes	**Probabilities**		
GJB2/6 sequencing diagnostic yield	0.22	Beta (461, 1640)	[12]
Exome sequencing additional diagnostic yield	0.39	Beta (455, 724)	[6, 12-21]
Chance of having a syndromic diagnosis and therefore incurring additional investigation	0.17	Beta (8, 39)	[6]

MLPA: Multiplex ligand-dependent probe amplification, MRI: magnetic resonance imaging, VCGS: Victorian Clinical Genetics Service, RCH: Royal Children's Hospital

† *Weighted mean value estimated as shown in table S1 using combinations of resource use items listed below in italics*

‡*Discounted estimate at 5% annual rate as per national guidelines*[24]

Table 4. Cost-effectiveness results

	Cost (AU$)	Diagnostic yield	Incremental WTP per child	ICER per additional diagnosis
Standard care pathway	$3200	22%	–	–
Exome sequencing pathway	$4200	52%	$4600	$3333

WTP: willingness-to-pay; ICER: incremental cost-effectiveness ratio

Table 4. Cost-effectiveness results

	Cost (AU$)	Diagnostic yield	Incremental WTP per child	ICER per additional diagnosis
Standard care pathway	$3200	22%	–	–
Exome sequencing pathway	$4200	52%	$4600	$3333

WTP: willingness-to-pay; ICER: incremental cost-effectiveness ratio