Cost-effectiveness of earlier whole-genome sequencing in rare genetic childhood epilepsy

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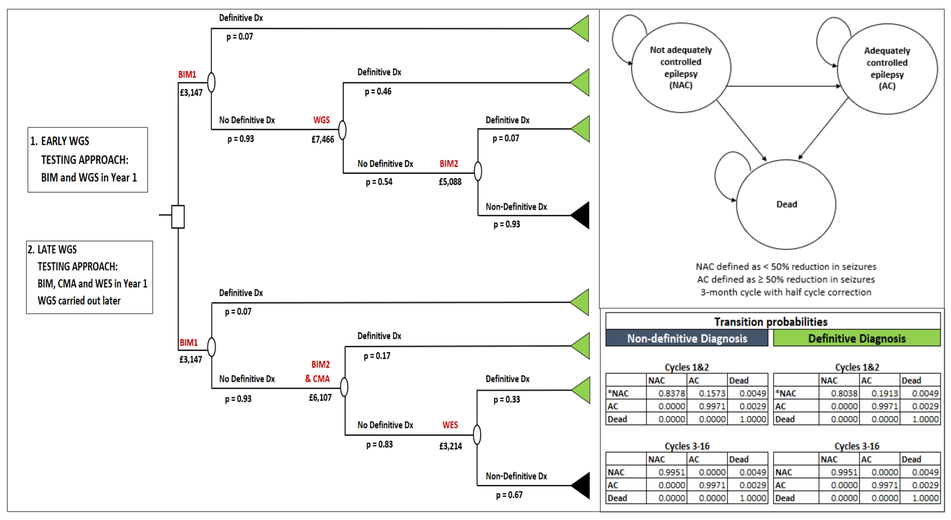
Introduction

> Diagnosis of rare genetic childhood epilepsy is a major challenge. Diagnostic delay is estimated at 3-6 years and over 50% of patients remain without a definitive molecular diagnosis.
> Whole-genome sequencing (WGS) has improved the chances of molecular diagnosis, and it has a higher yield than whole-exome sequencing (WES), gene panels and chromosomal microarray (CMA). While the high cost limits adoption, WGS may be more cost-effective if applied early to reduce the length of diagnostic pathway and associated healthcare costs.
> The aim of the study was to assess the cost-effectiveness of early diagnostic WGS in children aged under five years with suspected rare genetic epilepsy from the perspective of the UK National Health Service (NHS).

Methods

Model structure

> A cost-effectiveness model with 5-year time horizon was constructed using an eight-month decision tree (Year 1) followed by a four-year Markov model (Years 2-5) (Figure 1).
> Two diagnostic approaches were compared in a hypothetical cohort of patients with new onset of daily/weekly seizures and potential developmental delay:
  1. WGS replaced all other genetic and genomic tests in Year 1 ("early WGS")
  2. CMA+WES were carried out in Year 1 and patients without a definitive diagnosis received WGS in Year 5 ("late WGS")
> Decision tree modelled the proportion of patients with or without definitive diagnosis following the diagnostic testing in Year 1.
> From Year 2 to 5, both patients with or without definitive diagnosis entered into the Markov part of the model in "not adequately controlled" (NAC) epilepsy state. Following anti-epileptic drug (AED) treatment, they either remained in NAC or transitioned to "adequately controlled" (AC) epilepsy state or Dead at different transition probabilities. Patients in AC state either remained in the same state or transitioned to Dead.



Abbreviations:

Definitive Dx = confirmed diagnosis of the underlying cause of epilepsy

Non-definitive Dx = no definitive diagnosis of the underlying cause of epilepsy

BIM1 and BIM2 = initial and advanced biochemistry, histopathology and imaging

CMA = chromosomal microarray

WES = whole-exome sequencing

WGS = whole-genome sequencing

Figure 1. Decision tree followed by a Markov model structure

> The Markov model simulated the impact of a definitive diagnosis in Years 2-5 on seizure control, and subsequently on healthcare resource utilisation (HCRU), costs, and life-years gained (LYG).
> All patients without a definitive diagnosis continued to undergo BIM as part of routine monitoring.
> Transition probabilities were obtained for seizure control that was not specific to any drug or epilepsy disorder.[1] Optimal treatment effect from AED was achieved within first two cycles (6 months), including 3.4[2] percentage point increased probability of patients achieving AC after a definitive diagnosis. Thereafter, the treatment effect was constant and the same for all patients.
> Misdiagnosis from tests, adverse events from AEDs, and treatment switching were not included in the study.
> Diagnostic yields of WGS, WES, CMA and biochemistry, histopathology and imaging (BIM) were not accessible from NHS sources, and were obtained from a study by Ontario Health.[3]
> Mortality rates were based on national lifetables[4] and literature[5].
> HCRU for AC was obtained for childhood epilepsy with at least daily or weekly seizures.[6] Multipliers were applied to obtain HCRU for NAC.[7] HCRU consisted of average annual accident & emergency visits, outpatient visits, inpatient stay, and AEDs.
> Unit costs of HCRU and diagnostic tests were obtained from NHS sources.
> All study costs were in 2019-2020 prices. Costs and LYG were discounted annually at 3.5%.

Key assumptions

> None of the patients died (i.e. there was no mortality) in Year 1.
> Gene panel testing has been phased out and replaced with genomic testing.
> CMA was carried out prior to WES to identify chromosomal abnormalities.
> Delay with WGS was caused by limited test provision.

Analysis outputs

> Year 1 model measured the short-term cost-effectiveness of WGS in achieving a definitive diagnosis prior to commencing treatment with AEDs. Five-year model assessed the longer term impact of earlier testing with WGS on healthcare costs and LYG.
> An incremental cost effectiveness ratio (ICER) was calculated for additional cost per additional molecular diagnosis in Year 1 and per additional LYG over Years 1-5.
> Deterministic sensitivity analysis (DSA) was used to assess the impact of individual parameter uncertainty on the results.
> Probabilistic sensitivity analysis (PSA) was carried out to explore the combined impact of input parameters on cost-effectiveness outcomes using Monte Carlo simulation with 1000 runs.
> Cost-effectiveness plane (CEAP) and acceptability curve (CEAC) were produced from PSA.

Results

Year 1 model results for costs and definitive diagnoses

> Deterministic ICER for early WGS (vs WES+CMA) in Year 1 was £26,938 per definitive diagnosis (Table 1) and probabilistic results were similar suggesting no significant uncertainty (Table 2).
> CEAP fell mostly into the north-east quadrant, and CEAC showed that early WGS had 39% probability of being cost-effective when using a threshold of £20,000 (Figure 2).
> Early WGS simplified the diagnostic pathway, reduced the number of tests taken and incurred fewer genetic counselling appointments.
> Based on DSA the main cost driver was WGS, which at £2,539 per single test was more than twice as expensive as WES at £1,020.
> Reducing the cost of WGS test to £2,039 would bring the incremental cost to zero.

Table 1. Incremental costs and definitive diagnoses from the 1-year model: deterministic

Genomic approach	Costs	Def. Dx	Incr. cost	Incr. Def.Dx	ICER
LATE WGS	£11,554	0.485	-	-	-
EARLY WGS	£12,895	0.535	£1,341	0.050	£26,938

Table 2. Incremental costs and definitive diagnoses from the 1-year model: probabilistic

Genomic approach	Costs	Def. Dx	Incr. cost	Incr. Def.Dx	ICER
LATE WGS	£11,519 (£10,252 to £12,852)	0.486 (0.451 to 0.519)	-	-	-
EARLY WGS	£12,882 (£11,107 to £14,769)	0.535 (0.447 to 0.631)	£1,362	0.049	£27,581

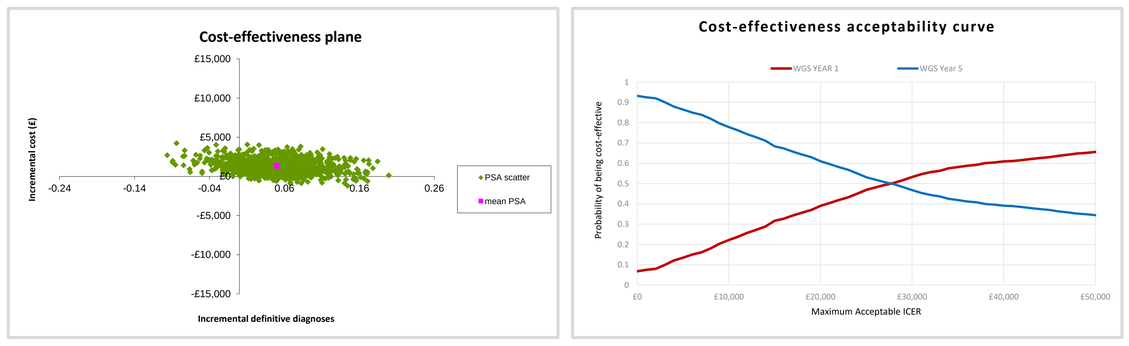


Figure 2. CEAP and CEAC for the incremental costs and definitive diagnoses in Year 1

Five-year model results for costs and LYG

> Early WGS (vs CMA+WES in Year 1 and WGS end of Year 5) was the more cost-effective approach resulting in £5,740 cost savings and a very small positive incremental LYG (Tables 3).
> Probabilistic results were similar suggesting no significant uncertainty (Table 4).
> CEAP fell mostly into the south-east quadrant, and the probability of early WGS being cost-effective was 100% therefore creating two horizontal CEACs at 0 and 1 for the two diagnostic approaches (Figure 3).
> WGS was again the parameter that had most impact on the incremental cost.

Table 3. Incremental costs and LYG from the 5-year model: deterministic

Genomic approach	Costs	LYG	Incr. cost	Incr. LYG	ICER
LATE WGS	£55,342	4.262	-	-	-
EARLY WGS	£49,603	4.262	-£5,740	< 0.001	-£44,536,394

Table 4. Incremental costs and LYG from the 5-year model: probabilistic

Genomic approach	Costs	LYG	Incr. cost	Incr. LYG	ICER
LATE WGS	£56,486 (£45,026 to £71,607)	4.263 (4.234 to 4.290)	-	-	-
EARLY WGS	£50,617 (£39,860 to £64,817)	4.263 (4.234 to 4.290)	-£5,869	< 0.001	-£44,880,845

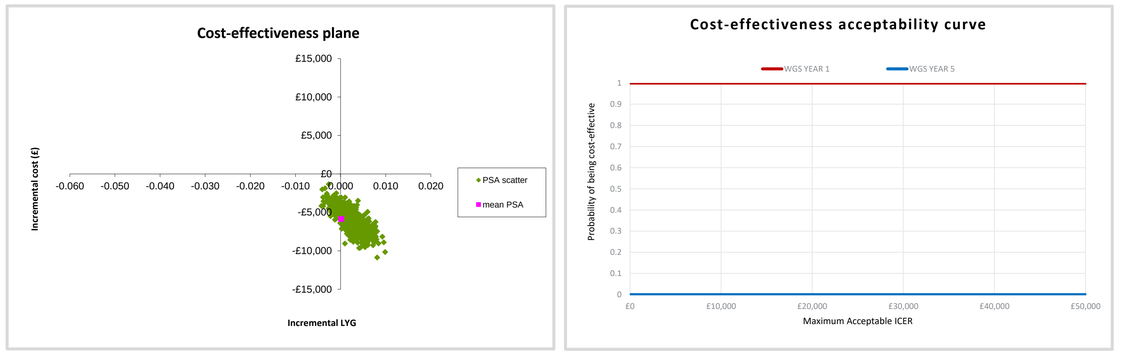


Figure 3. CEAP and CEAC for the incremental costs and LYG over 5 years

Conclusions

> The higher cost of WGS impedes its adoption, but 5-year cost-effectiveness results suggested value for money when WGS is performed as the first genetic/genomic test.
> The factor that made early WGS more cost-effective was its higher yield to obtain a definitive diagnosis, which in turn reduced the longer term costs as the patients with a definitive diagnosis avoided further investigations and achieved better seizure control and lower healthcare usage.
> The short-term findings were consistent with previous research in that WGS was more expensive but achieved a higher proportion of definitive diagnoses compared to the other diagnostic tests. For longer term outcomes, no comparable studies were identified.
> A key limitation was a lack of data concerning the yield of genetic/genomic testing in the NHS.

References
1. Raspin C, et al. An economic evaluation of vagus nerve stimulation as an adjunctive treatment to anti-seizure medications for the treatment of drug-resistant epilepsy in England. J Med Econ. 2021;24(1):1037-51; **2.** Balestrini S, et al. Real-life survey of pitfalls and successes of precision medicine in genetic epilepsies. Journal of Neurology, Neurosurgery & Psychiatry. 2021:jnnp-2020-325932; **3.** Ontario Health. Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: A Health Technology Assessment. Ont Health Technol Assess Ser. 2020;20(11):1-178; **4.** Office for National Statistics (ONS). National life tables: England and Wales. Release date: 24 September 2020. 2020; **5.** Appleton RE. Mortality in paediatric epilepsy. Archives of Disease in Childhood. 2003;88(12):1091; **6.** Myland M, et al. Seizure frequency, healthcare resource utilisation and mortality in childhood epilepsy: a retrospective cohort study using the THIN database. Arch Dis Child. 2019;104(11):1070-6; **7.** Manjunath R, et al. Burden of uncontrolled epilepsy in patients requiring an emergency room visit or hospitalization. Neurology. 2012;79(18):1908-16.