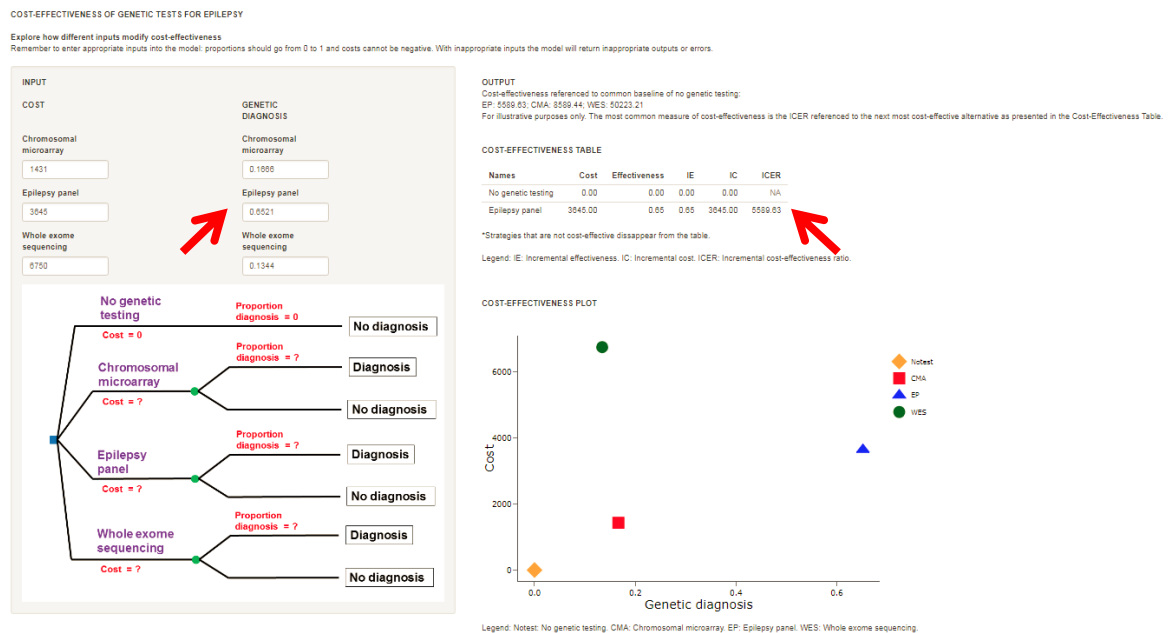


## FILE e-2

## SUBPOPULATIONS

**Epileptic encephalopathies.** In early epileptic encephalopathies, the diagnostic yield of CMA and EP may be higher while the diagnostic yield of WES may be lower <sup>1, 2</sup>. In a study of 29 newborns with epileptic encephalopathy who underwent genetic testing, CMA was diagnostic in 2 of 12 (17%) newborns, EP was diagnostic in 15 of 23 (65%), and WES was diagnostic in 2 of 3 (67%) <sup>2</sup>. In a large study of patients with infantile spasms or Lennox-Gastaut syndrome WES was diagnostic in 42 of 356 (12%) of patients <sup>1</sup>. In a study of children with early-onset epileptic encephalopathy who were undiagnosed after investigations for inborn errors of metabolism, MRI, single-gene disorders, and CMA, the diagnostic yield of WES was 11 of 50 (22%) <sup>3</sup>.

Although there is limited data for specific subgroups, assuming a diagnostic yield of 2/12 for CMA, 15/23 for EP, and 55/409 [(2+42+11)/(3+356+50)] for WES, the most cost-effective test would be EP with an ICER of \$5,589/diagnosis:



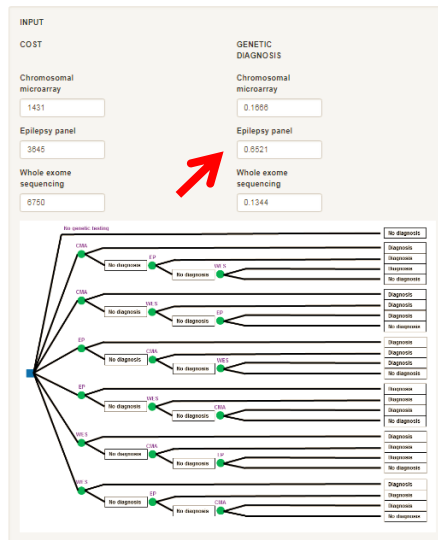
## Diagnostic yield of genetic tests in epilepsy

Therefore, the most cost-effective testing strategy would be EP ± CMA ± WES with an ICER of \$8,143/diagnosis.

### COST-EFFECTIVENESS OF GENETIC TESTS FOR EPILEPSY

Explore how different inputs modify cost-effectiveness

Remember to enter appropriate inputs into the model: proportions should go from 0 to 1 and costs cannot be negative. With inappropriate inputs the model will return inappropriate outputs or errors.



### OUTPUT

Cost-effectiveness referenced to common baseline of no genetic testing

EP ± CMA ± WES: 8143.81; EP ± WES ± CMA: 8578.75; CMA ± EP: 12031.32; WES ± EP ± CMA: 13790.28; WES ± CMA ± EP: 14175.9

For illustrative purposes only. The most common measure of cost-effectiveness is the ICER referenced to the next most cost-effective alternative as presented in the Cost-Effectiveness Table.

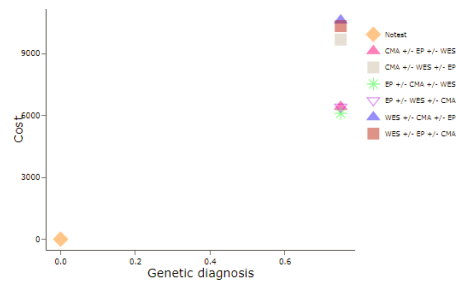
### COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No genetic testing	0.00	0.00	0.00	0.00	NA
EP ± CMA ± WES	8099.94	0.75	0.75	8099.94	8143.81

\*Strategies that are not cost-effective disappear from the table.

Legend: IE: Incremental effectiveness; IC: Incremental cost; ICER: Incremental cost-effectiveness ratio.

### COST-EFFECTIVENESS PLOT



# Diagnostic yield of genetic tests in epilepsy

## COST-EFFECTIVENESS OF GENETIC TESTS FOR EPILEPSY

Explore how different inputs modify cost-effectiveness

Remember to enter appropriate inputs into the model: proportions should go from 0 to 1 and costs cannot be negative. With inappropriate inputs the model will return inappropriate outputs or errors.

**INPUT**

**COST**

Chromosomal microarray  
1431

Epilepsy panel  
3645

Whole exome sequencing  
6750

**GENETIC DIAGNOSIS**

Chromosomal microarray  
0.1666

Epilepsy panel  
0.6522

Whole exome sequencing  
0.1226

## OUTPUT

Cost-effectiveness referenced to common baseline of no genetic testing:

EP +/- CMA +/- WES: 8179.43; CMA +/- EP +/- WES: 8616.67; EP +/- WES +/- CMA: 8622.11; CMA +/- WES +/- EP: 13037.45; WES +/- EP +/- CMA: 13926.63; WES +/- CMA +/- EP: 14310.26  
For illustrative purposes only. The most common measure of cost-effectiveness is the ICER referenced to the next most cost-effective alternative as presented in the Cost-Effectiveness Table.

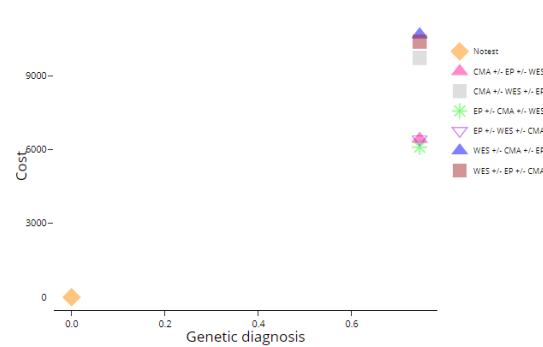
## COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No genetic testing	0.00	0.00	0.00	0.00	NA
EP +/- CMA +/- WES	6099.23	0.75	0.75	6099.23	8179.43

\*Strategies that are not cost-effective disappear from the table.

Legend: IE: Incremental effectiveness. IC: Incremental cost. ICER: Incremental cost-effectiveness ratio.

## COST-EFFECTIVENESS PLOT



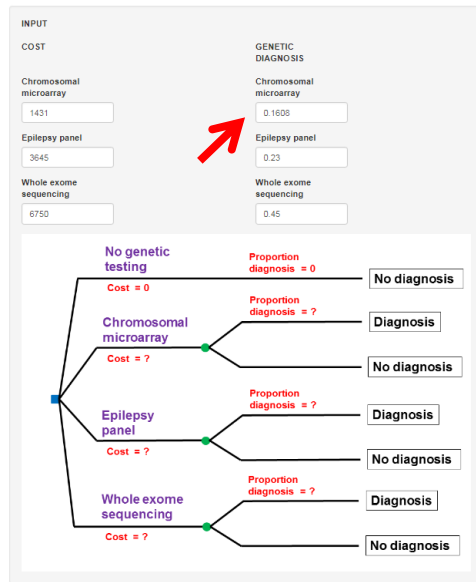
**Adults with childhood onset epilepsy.** The diagnostic yield of CMA in adults with childhood onset epilepsy may be higher. In a study of adults with childhood onset epilepsy and intellectual disability of unknown etiology, CMA was diagnostic in 23/143 (16%) patients<sup>4</sup>. Assuming this higher diagnostic yield for CMA while keeping all other parameters constant (as there is no literature to suggest otherwise), the most cost-effective initial test would be CMA with an ICER of \$8899/diagnosis:

# Diagnostic yield of genetic tests in epilepsy

## COST-EFFECTIVENESS OF GENETIC TESTS FOR EPILEPSY

Explore how different inputs modify cost-effectiveness

Remember to enter appropriate inputs into the model: proportions should go from 0 to 1 and costs cannot be negative. With inappropriate inputs the model will return inappropriate outputs or errors.



## OUTPUT

Cost-effectiveness referenced to common baseline of no genetic testing:

CMA: 8899.25; WES: 15000; EP: 15847.83

For illustrative purposes only. The most common measure of cost-effectiveness is the ICER referenced to the next most cost-effective alternative as presented in the Cost-Effectiveness Table.

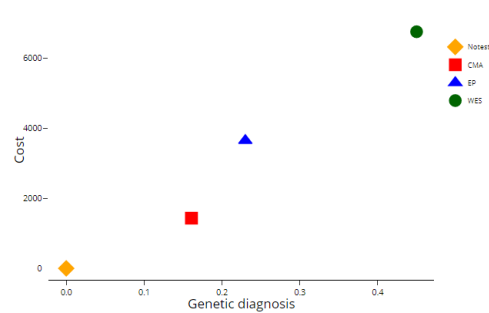
## COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No genetic testing	0.00	0.00	0.00	0.00	N/A
Chromosomal microarray	1431.00	0.16	0.16	1431.00	8899.25
Whole exome sequencing	6750.00	0.45	0.29	5319.00	18392.12

\*Strategies that are not cost-effective disappear from the table.

Legend: IE: Incremental effectiveness; IC: Incremental cost; ICER: Incremental cost-effectiveness ratio.

## COST-EFFECTIVENESS PLOT

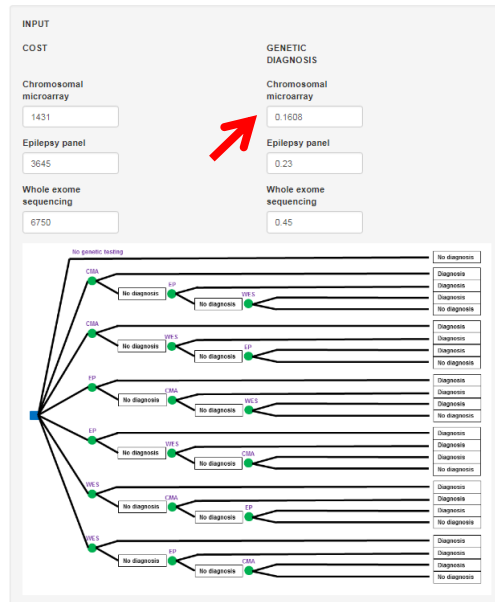


Hence, the most cost-effective testing strategy would be CMA ± WES ± EP with an ICER of \$13,618/diagnosis.

## COST-EFFECTIVENESS OF GENETIC TESTS FOR EPILEPSY

Explore how different inputs modify cost-effectiveness

Remember to enter appropriate inputs into the model: proportions should go from 0 to 1 and costs cannot be negative. With inappropriate inputs the model will return inappropriate outputs or errors.



## OUTPUT

Cost-effectiveness referenced to common baseline of no genetic testing:

CMA +/- WES +/- EP: 13617.75; CMA +/- EP +/- WES: 13731.99; EP +/- CMA +/- WES: 14130.67; WES +/- CMA +/- EP: 14302.6; WES +/- EP +/- CMA: 14521.87; EP +/- WES +/- CMA: 14658

For illustrative purposes only. The most common measure of cost-effectiveness is the ICER referenced to the next most cost-effective alternative as presented in the Cost-Effectiveness Table.

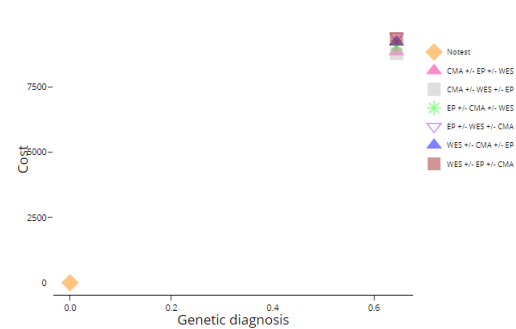
## COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No genetic testing	0.00	0.00	0.00	0.00	N/A
CMA +/- WES +/- EP	8777.99	0.64	0.64	8777.99	13617.75

\*Strategies that are not cost-effective disappear from the table.

Legend: IE: Incremental effectiveness; IC: Incremental cost; ICER: Incremental cost-effectiveness ratio.

## COST-EFFECTIVENESS PLOT



## REFERENCES

1. Euro E-RESC, Epilepsy Phenome/Genome P, Epi KC. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. *American journal of human genetics* 2014;95:360-370.
2. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: Characteristics of a prospective US cohort. *Neurology* 2017;89:893-899.
3. Allen NM, Conroy J, Shahwan A, et al. Unexplained early onset epileptic encephalopathy: Exome screening and phenotype expansion. *Epilepsia* 2016;57:e12-17.
4. Borlot F, Regan BM, Bassett AS, Stavropoulos DJ, Andrade DM. Prevalence of Pathogenic Copy Number Variation in Adults With Pediatric-Onset Epilepsy and Intellectual Disability. *JAMA neurology* 2017.