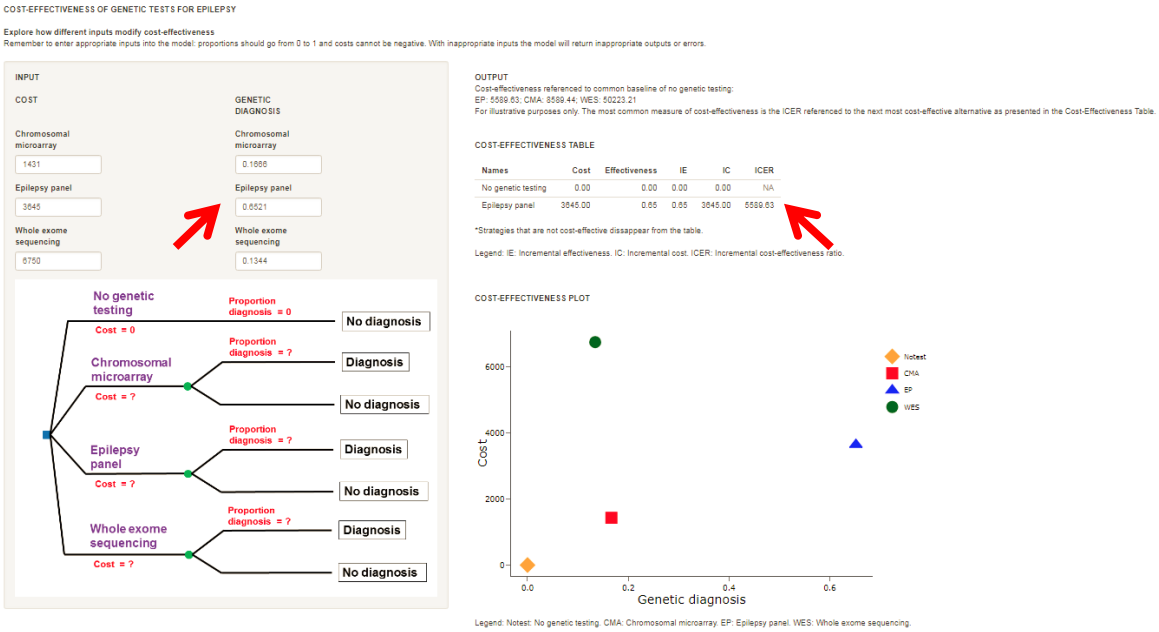
FILE e-2

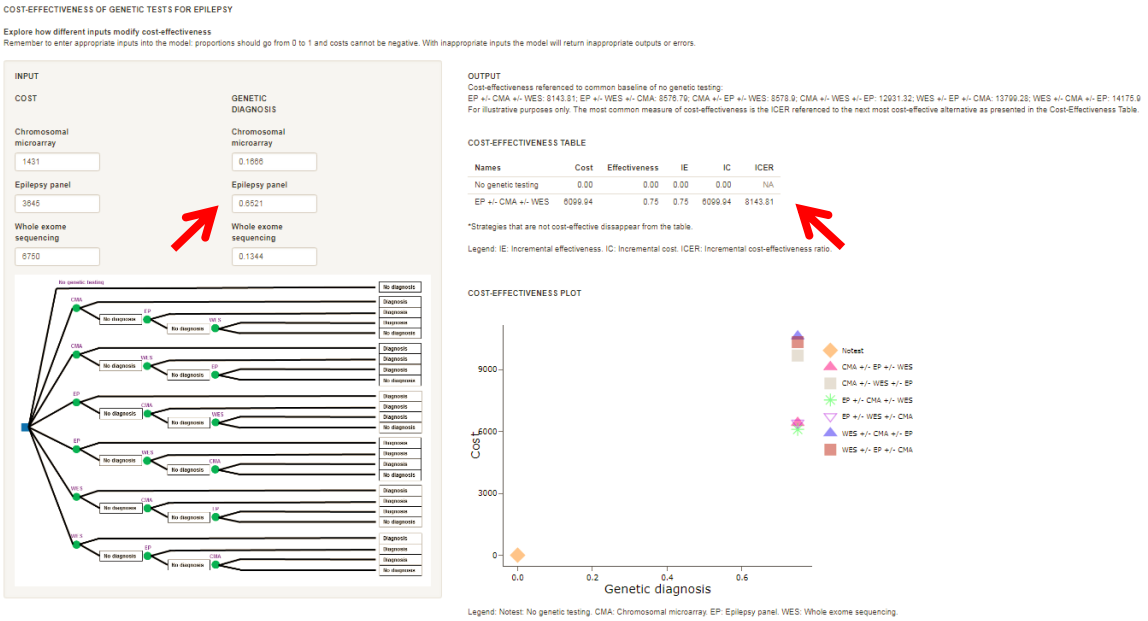
SUBPOPULATIONS

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 [1, 2]. 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%) [2]. In a large study of patients with infantile spasms or Lennox-Gastaut syndrome WES was diagnostic in 42 of 356 (12%) of patients [1]. 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%) [3].

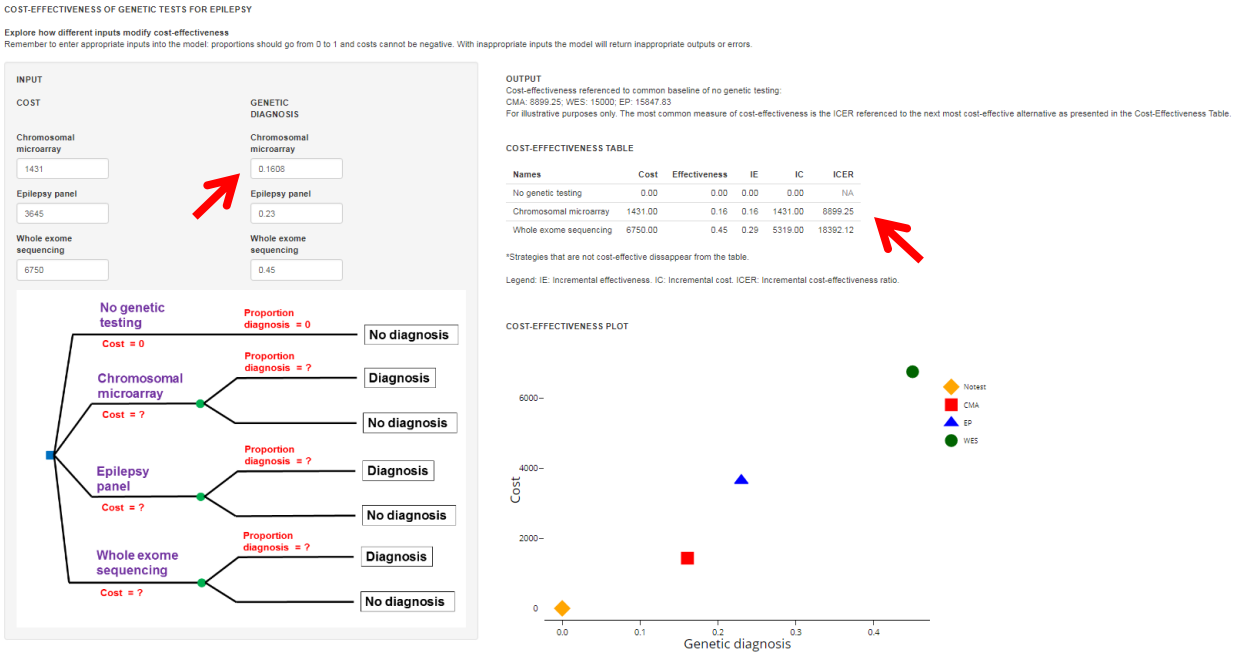
Although there is limited data for specific subgroups, assuming a diagnostic yield of 2/12 for CMA, 15/23 for EP, and 55/409 [(2+42+11)/(3+356+50)] for WES, the most cost-effective test would be EP with an ICER of $5, 589/diagnosis:



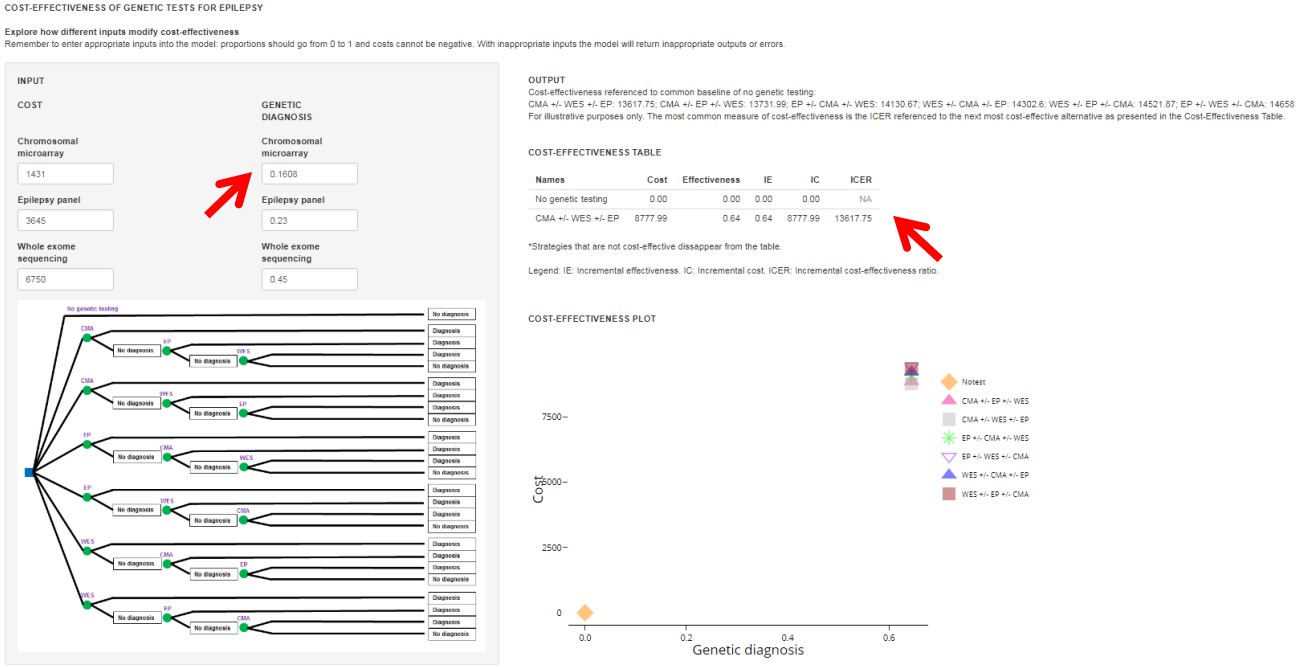
Therefore, the most cost-effective testing strategy would be EP ± CMA ± WES with an ICER of $8,143/diagnosis.



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 [4]. 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:



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



REFERENCES

1. Euro EPINOMICS-RES CONSORTIUM, Epilepsy Phenome/Genome Project, Epi 4K Consortium. 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.