

SUPPLEMENTARY FIGURE LEGENDS

Figure e-1. Literature search strategy.

Figure e-2. Funnel plots for the meta-analysis. A. CMA. B. EP. C. WES.

Legend: CMA: Chromosomal microarray. EP: Epilepsy panel. WES: Whole-exome sequencing.

Figure e-3. Metaanalysis for WES correcting for potential publication bias. A. Forest plot. B. Funnel plot.

Legend: WES: Whole-exome sequencing.

Figure e-4. Comparison of testing strategies: “no genetic testing” (orange diamond), CMA ± EP ± WES (pink triangle), CMA ± WES ± EP (gray square), EP ± CMA ± WES (green star), EP ± WES ± CMA (purple inverted triangle), WES ± CMA ± EP (blue triangle), and WES ± EP ± CMA (brown square). A. Base case analysis. WES ± EP ± CMA is the most cost-effective option but closely followed by other options slightly above the efficiency frontier. B. Probabilistic sensitivity analysis (second order Monte Carlo simulations). Strategies markedly overlap in cost-effectiveness. C. Acceptability curve. For a willingness to pay of less than approximately \$15,400/diagnosis, in most simulations there is not enough money for any genetic test. For a willingness to pay above approximately

\$15,400/diagnosis, in most simulations, WES ± EP ± CMA is the most cost-effective strategy followed by EP ± WES ± CMA, and WES ± CMA ± EP.

Legend: CMA: Chromosomal microarray. ICER: Incremental cost-effectiveness ratio. EP: Epilepsy panel. WES: Whole-exome sequencing.

Figure e-5. Comparison of testing strategies: “no genetic testing” (orange diamond), CMA ± EP ± WES (pink triangle), CMA ± WES ± EP (gray square), EP ± CMA ± WES (green star), EP ± WES ± CMA (purple inverted triangle), WES ± CMA ± EP (blue triangle), and WES ± EP ± CMA (brown square). A. Base case analysis. EP ± CMA ± WES is the most cost-effective option but closely followed by other options slightly above the efficiency frontier. **B. Probabilistic sensitivity analysis (second order Monte Carlo simulations).** Strategies markedly overlap in cost-effectiveness. **C. Acceptability curve.** For a willingness to pay of less than approximately \$19,500/diagnosis, in most simulations there is not enough money for any genetic test. For a willingness to pay between approximately \$19,500/diagnosis and \$21,000/diagnosis, in most simulations EP ± WES ± CMA is the most cost-effective strategy EP ± CMA ± WES above approximately \$21,000/diagnosis.

Legend: CMA: Chromosomal microarray. ICER: Incremental cost-effectiveness ratio. EP: Epilepsy panel. WES: Whole-exome sequencing.