**Supplementary Materials and Methods**

*Study Selection*

PubMed searches using key search terms or phrases such as “whole genome sequencing AND pediatric AND undiagnosed” or “Next generation sequencing AND rare disease AND pediatric” were conducted between January 2017 and November 2018. A total of 2,146 titles and abstracts were identified and subsequently screened for inclusion. Of these, 2,117 did not meet inclusion criteria (e.g., major focus on oncology applications, study population > 18 years, article in a foreign language, no outcome or treatment measures reported) and were thus excluded. An additional seven publications identified from a manual search in the reference list of the retrieved articles were included, resulting in a total of 36 included publications.



**Summary of 36 Studies Meeting Inclusion Criteria**

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| Citation | Publication Type | Test(s) | Population |
| Bick et al. 20171 | Primary research | GS | Children with suspected Mendelian disorder |
| Bowling et al. 20172 | Primary research | GS, ES | Children with ID and/or DD |
| Clark et al. 20183 | Meta-analysis | GS, ES | Children with suspected genetic diseases |
| Coulter et al. 20114 | Primary research | CMA | Pediatric patients with DD/ID, ASD and congenital anomalies |
| Farnaes et al. 20185 | Primary research | R-GS | Children (inpatient) less than 1 yr old |
| Gilissen et al. 20146 | Primary research | GS | Children with severe ID |
| Hayeems et al. 20177 | Primary research (economic) | GS, CMA | Children with DD over one year old |
| Howell et al. 20138 | Primary research | CMA | Children with neurological conditions of unknown etiology |
| Howell et al. 20189 | Primary research (economic) | ES | Infants with severe epilepsies of infancy |
| Joshi et al. 201610 | Primary research (economic) | ES | Children with early onset epileptic encephalopathy |
| Kuperberg et al. 201611 | Primary research | ES | Pediatric patients suspected of having a monogenic disorder but remained undiagnosed after extensive testing |
| Lee et al. 201412 | Primary research | ES | Patients with undiagnosed, suspected genetic conditions |
| Lee et al. 201813 | Primary research | CMA | Children with DD or ID |
| Lionel et al. 201714 | Primary research | GS, standard testing | Children with a clinical phenotype suggestive of an underlying genetic disorder |
| Meienberg et al. 201615 | Primary research | GS, ES | Five unrelated females |
| Miller et al. 201516 | Primary research | R-GS | Critically ill infants with suspected genetic disorder |
| Petrikin et al. 201517 | Review | R-GS | Critically ill neonates |
| Petrikin et al. 201818 | Primary research | R-GS | NICU or PICU infants with illness of unknown etiology |
| Retterer et al. 201519 | Primary research | ES | Children and adults with various clinical presentations |
| Saunders et al. 201220 | Primary research | R-GS | Infants presenting without a molecular diagnosis, suspected genetic etiology |
| Soden et al. 201421 | Primary research | GS, ES | Children with NDD |
| Splinter et al. 201822 | Primary research | Any | Children and adults with undiagnosed conditions |
| Stark et al. 201623 | Primary research | ES | Infants with multiple congenital abnormalities and dysmorphic features; suspected monogenic disease |
| Stavropoulos et al. 201624 | Primary research | GS | Children less than 18 yrs old with than two structural malformations; DD of unknown etiology |
| Tammimies et al. 201525 | Primary resarch | CMA, ES | Children with ASD |
| Tan et al. 201726 | Primary research | ES | Children older than 2 yrs with a suspected monogenic disorder |
| Tarailo-Graovac et al. 201627 | Primary research | ES | Children with ID and neurometabolic disorder of unknown etiology |
| Taylor et al. 201528 | Primary research | GS | Broad spectrum of patients with Mendelian and immunological disorders |
| Theunissen et al. 201829 | Primary research | ES | Children in whom mitochondrial genetic cause is suspected |
| Thevenon et al. 201630 | Primary research | ES | Undiagnosed patients with severe ID and epileptic encephalopathy |
| Tsiplova et al. 201731 | Primary research (economic) | GS | Patients with ASD |
| van Diemen et al. 201732 | Primary research | R-GS | Critically ill newborns |
| Vissers et al. 201733 | Primary research | ES, standard genetic testing | Children with neurological symptoms of suspected genetic origin |
| Willig et al. 201534 | Primary research | GS | Infants with suspected genetic disorders, level 4 NICU and PICU |
| Wright et al. 201535 | Primary research | ES | Children with ID, DD, ASD, hearing impairment, CHD, seizures |
| Wright et al. 201836 | Review | GS, ES, TGP | Children with rare diseases with underlying genetic condition |

GS: genome sequencing; ES: exome sequencing; TGP: targeted gene panel; ID: intellectual disability; DD: developmental delay; ASD: Autism Spectrum Disorder; CHD: congenital heart defect; NDD: neurodevelopmental disorder.

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