Supplementary material

Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability

A systematic review and meta-analysis

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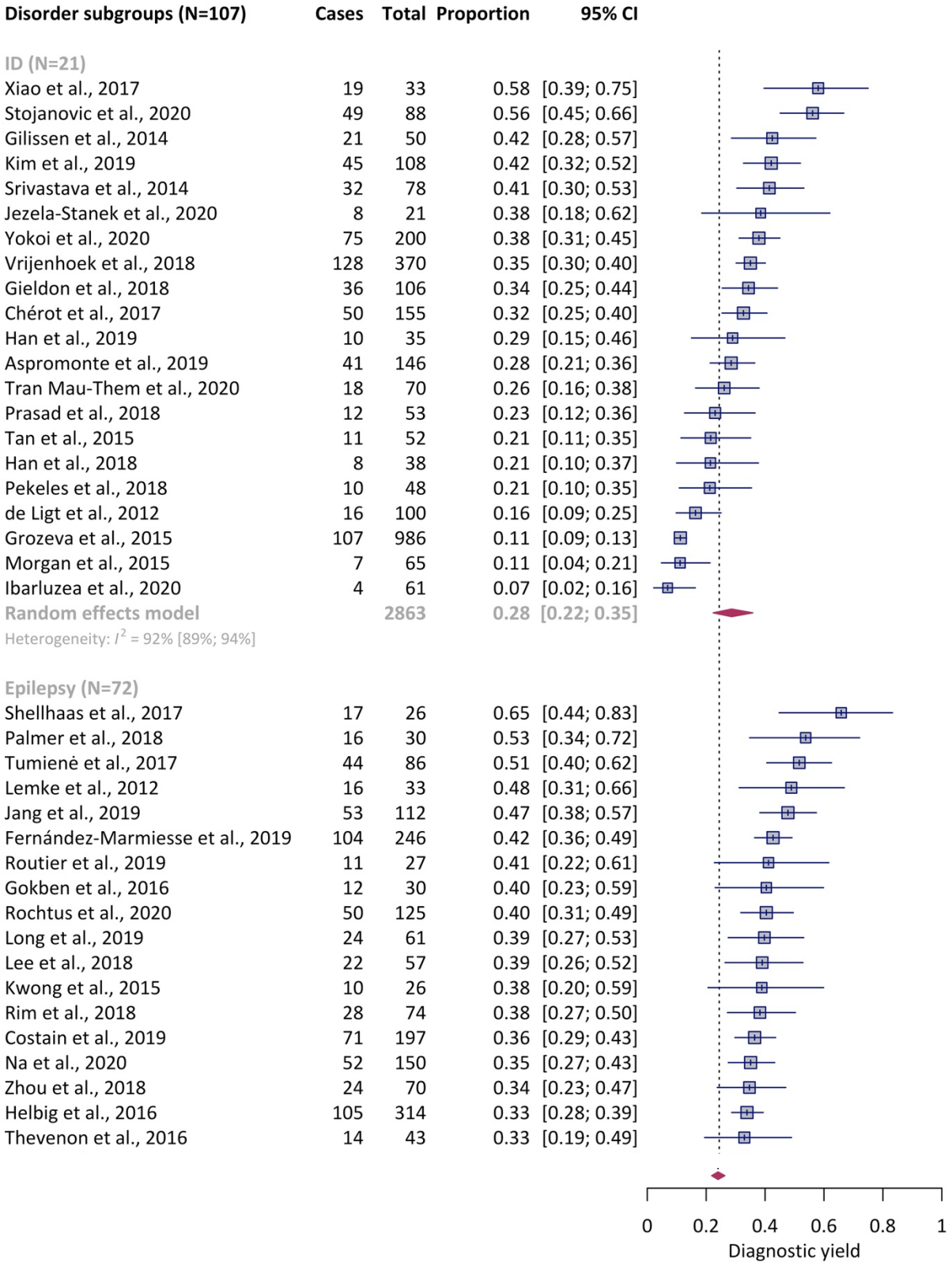
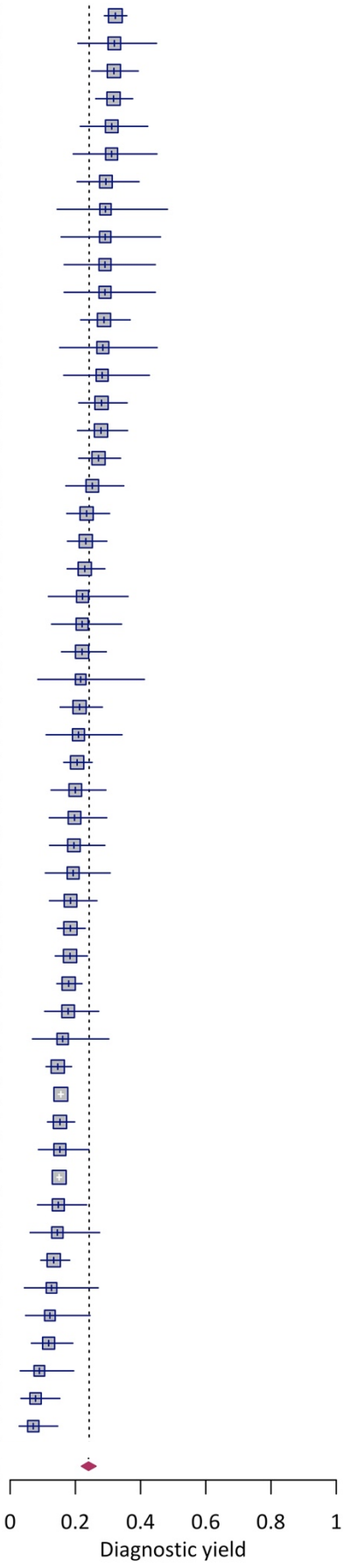
1. Cohorts stratified into subgroups

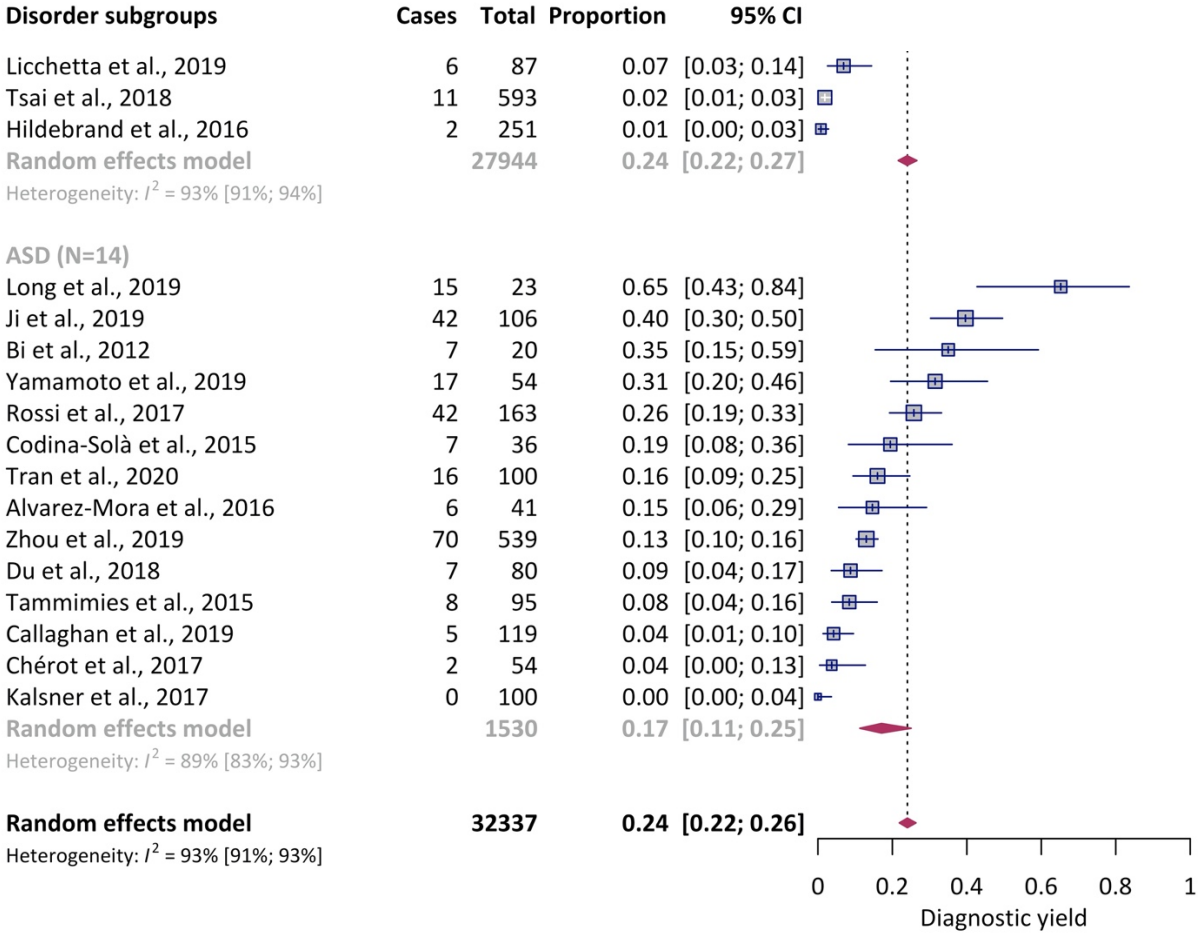
1.1. By disorder

1.1.1. Figure S1. Meta-analysis of the diagnostic yield by disorder



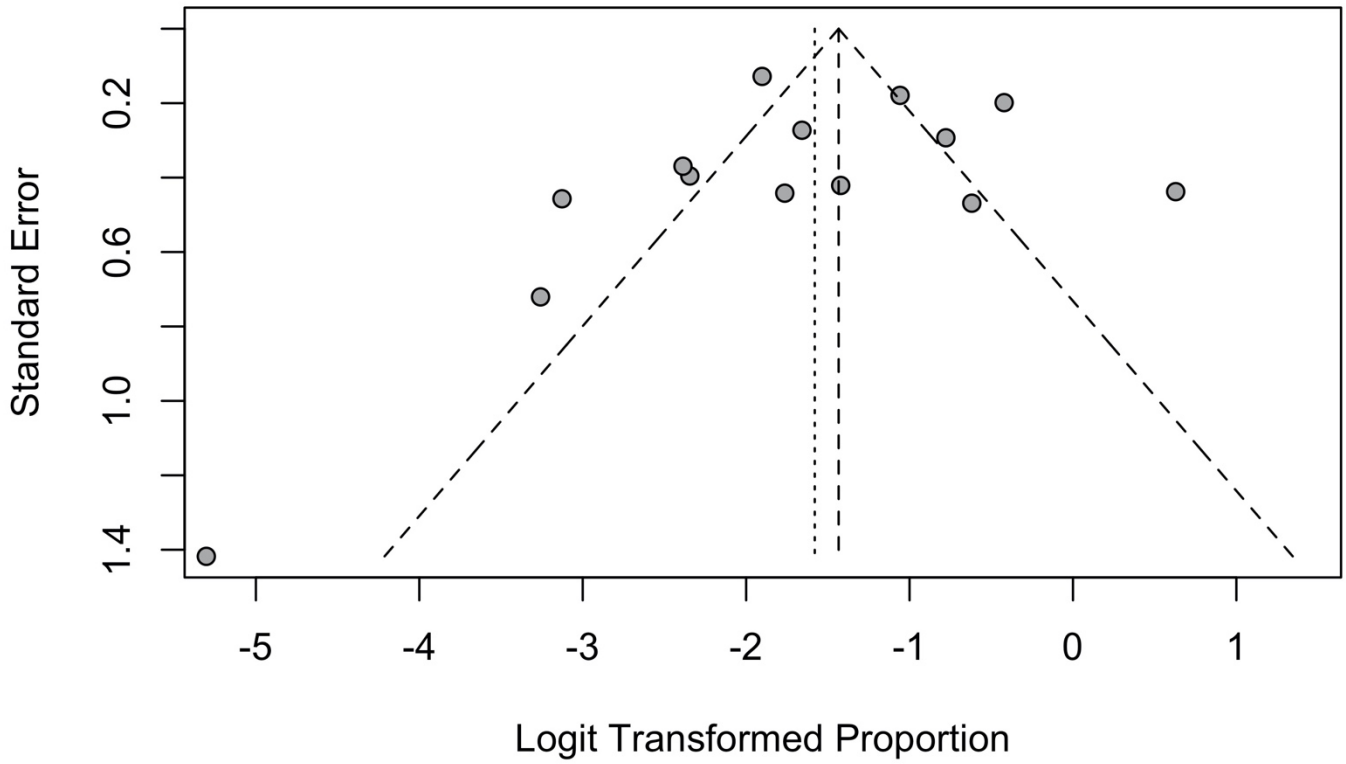
Disorder subgroups	Cases	Total	Proportion	95% CI
Yang et al., 2018	235	733	0.32	[0.29; 0.36]
Papuc et al., 2018	20	63	0.32	[0.21; 0.45]
Zhang et al., 2017	55	174	0.32	[0.25; 0.39]
Peng et al., 2019	86	273	0.32	[0.26; 0.37]
Muona et al., 2014	26	84	0.31	[0.21; 0.42]
Aspromonte et al., 2019	17	55	0.31	[0.19; 0.45]
Benson et al., 2020	28	96	0.29	[0.20; 0.39]
Fung et al., 2018	9	31	0.29	[0.14; 0.48]
Wirrell et al., 2015	11	38	0.29	[0.15; 0.46]
Yamamoto et al., 2019	13	45	0.29	[0.16; 0.44]
Krey et al., 2019	13	45	0.29	[0.16; 0.44]
Berg et al., 2017	42	147	0.29	[0.21; 0.37]
Halvardson et al., 2016	11	39	0.28	[0.15; 0.45]
Tonduti et al., 2018	14	50	0.28	[0.16; 0.42]
Staněk et al., 2018	42	151	0.28	[0.21; 0.36]
Miao et al., 2018	39	141	0.28	[0.20; 0.36]
Hamdan et al., 2017	53	197	0.27	[0.21; 0.34]
Snoeijen-Schouwenaars et al., 2018	25	100	0.25	[0.17; 0.35]
Liu et al., 2018	40	172	0.23	[0.17; 0.30]
Johannesen et al., 2020	46	200	0.23	[0.17; 0.29]
Møller et al., 2016	49	216	0.23	[0.17; 0.29]
Allen et al., 2015	11	50	0.22	[0.12; 0.36]
Borlot et al., 2019	14	64	0.22	[0.13; 0.34]
Balciuniene et al., 2019	33	151	0.22	[0.16; 0.29]
Wang et al., 2014	6	28	0.21	[0.08; 0.41]
Berkovic et al., 2019	35	166	0.21	[0.15; 0.28]
Kodera et al., 2013	11	53	0.21	[0.11; 0.34]
Parrini et al., 2016	71	349	0.20	[0.16; 0.25]
Oates et al., 2018	19	96	0.20	[0.12; 0.29]
Ortega-Moreno et al., 2017	17	87	0.20	[0.12; 0.29]
Sanders et al., 2019	18	93	0.19	[0.12; 0.29]
Arafat et al., 2017	13	68	0.19	[0.11; 0.30]
Wang et al., 2019	22	120	0.18	[0.12; 0.26]
Butler et al., 2017	62	339	0.18	[0.14; 0.23]
Zhang et al., 2015	46	253	0.18	[0.14; 0.23]
Trump et al., 2016	71	400	0.18	[0.14; 0.22]
Hoelz et al., 2019	16	91	0.18	[0.10; 0.27]
Michaud et al., 2014	7	44	0.16	[0.07; 0.30]
Symonds et al., 2019	48	333	0.14	[0.11; 0.19]
Lindy et al., 2018	1315	8565	0.15	[0.15; 0.16]
Hesse et al., 2018	46	305	0.15	[0.11; 0.20]
Mercimek-Mahmutoglu et al., 2015	14	93	0.15	[0.08; 0.24]
Truty et al., 2019	1451	9769	0.15	[0.14; 0.16]
Wu et al., 2020	14	96	0.15	[0.08; 0.23]
Segal et al., 2016	7	49	0.14	[0.06; 0.27]
Kang et al., 2019	32	243	0.13	[0.09; 0.18]
Perucca et al., 2017	5	40	0.12	[0.04; 0.27]
Tsang et al., 2019	6	50	0.12	[0.05; 0.24]
Krenn et al., 2020	13	112	0.12	[0.06; 0.19]
Angione et al., 2019	5	57	0.09	[0.03; 0.19]
Muir et al., 2019	7	92	0.08	[0.03; 0.15]
Licchetta et al., 2019	6	87	0.07	[0.03; 0.14]





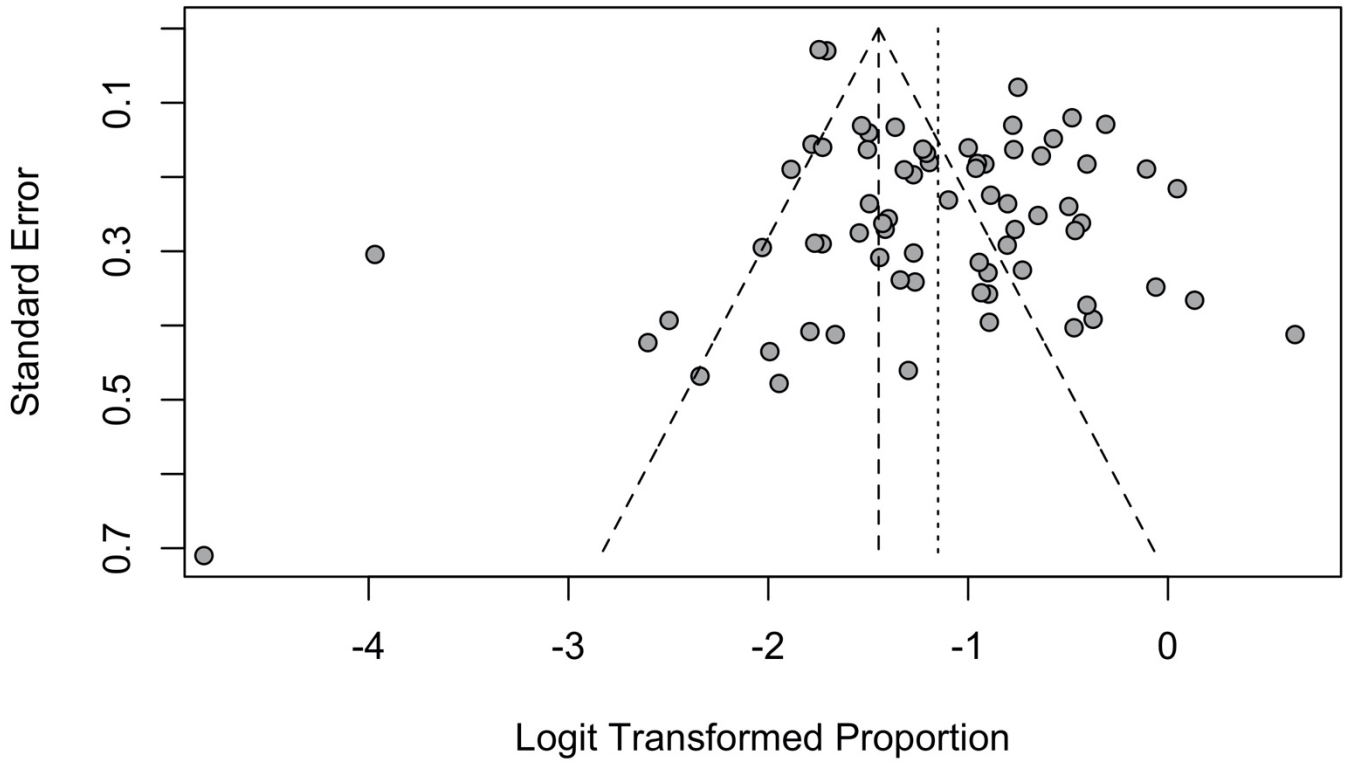
Abbreviations: CI = confidence interval, I^2 = estimated proportion of the variance in study estimates that is due to heterogeneity, Proportion = fraction of individuals with a positive genetic test, i.e. pathogenic or likely pathogenic variant.

1.1.2. Figure S2. Funnel plot of all ASD studies



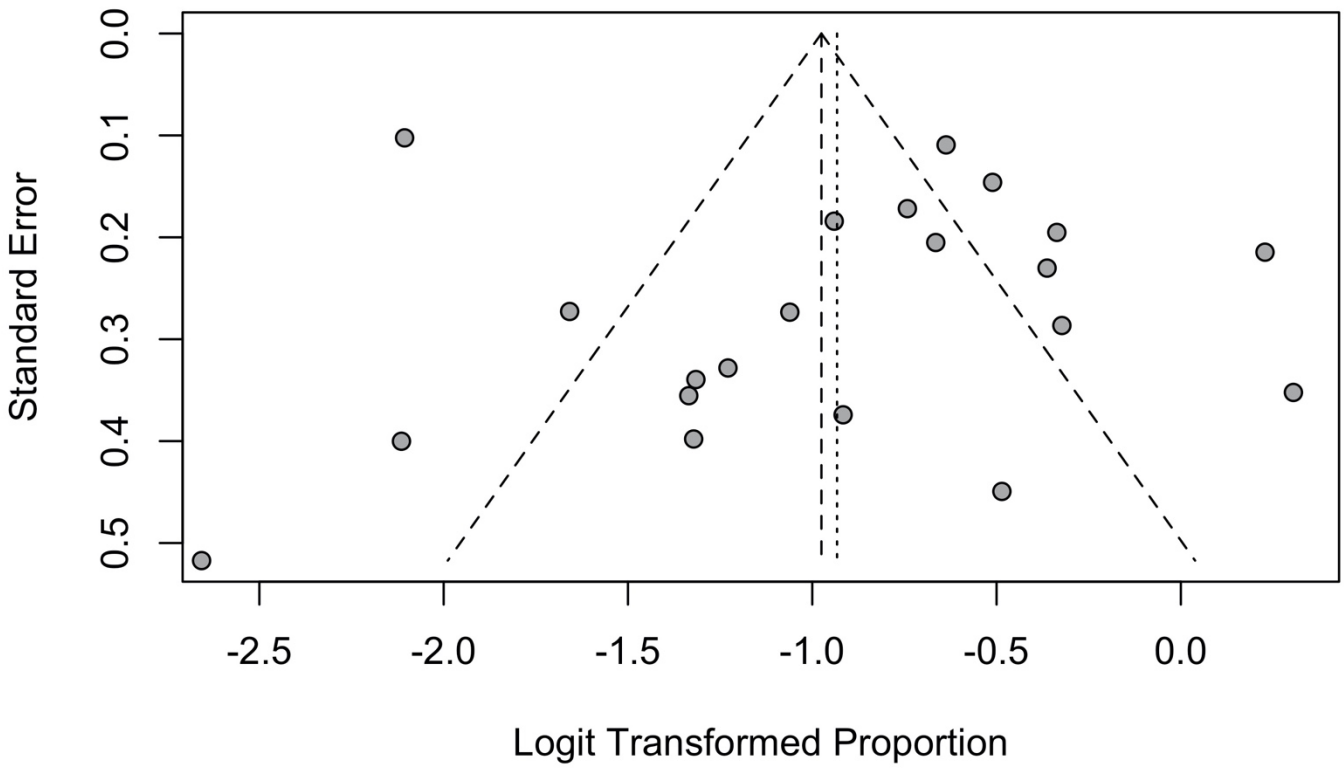
Grey dots = Original studies.

1.1.3. Figure S3. Funnel plot of all epilepsy studies



Grey dots = Original studies.

1.1.4. Figure S4. Funnel plot of all ID studies



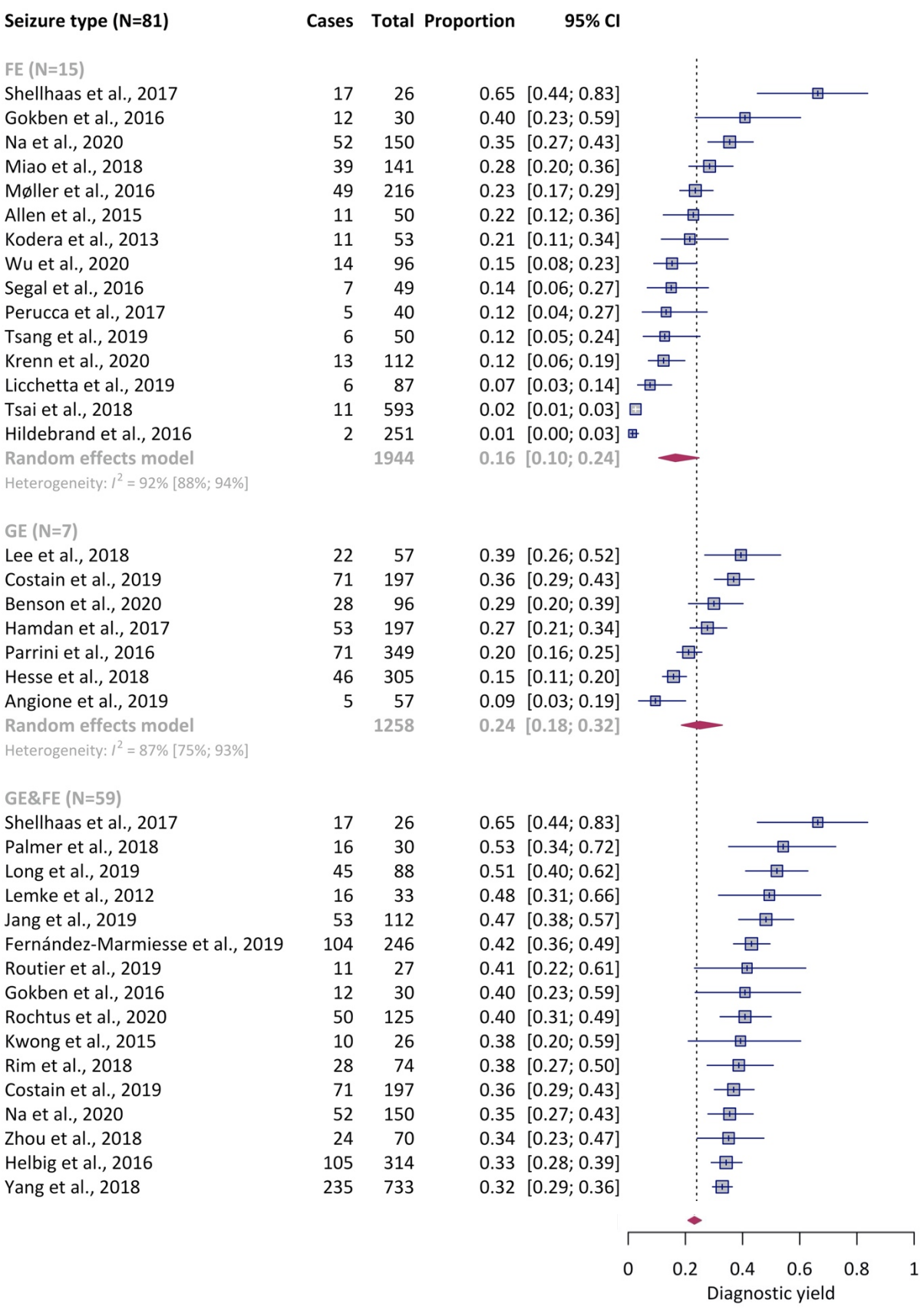
Grey dots = Original studies.

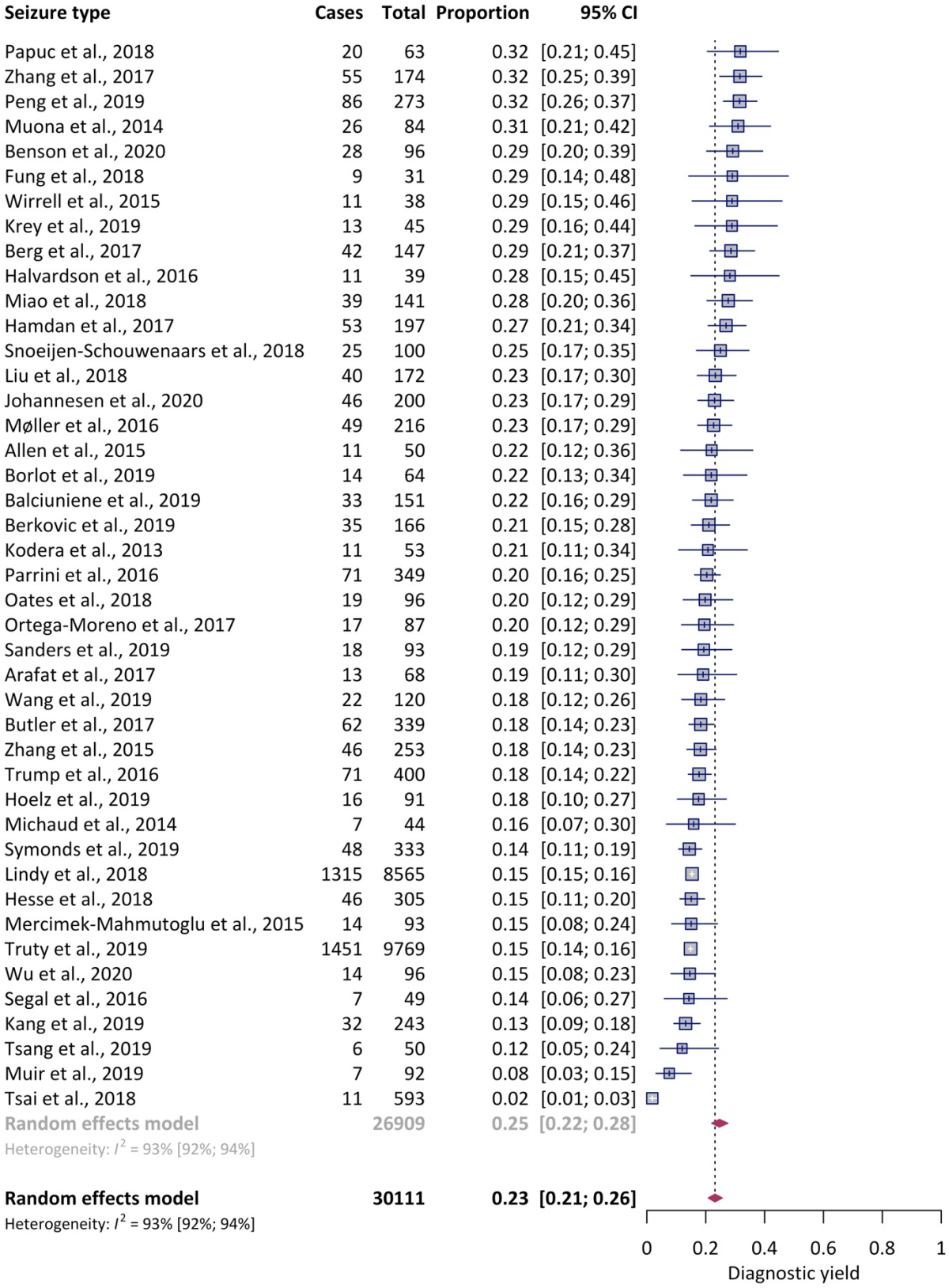
1.1.5. Figure S5. Error bar plot of the diagnostic yield by disorder

Abbreviations: ASD = autism spectrum disorder, ID = intellectual disability.

1.2. Meta analyses by disorder subtype

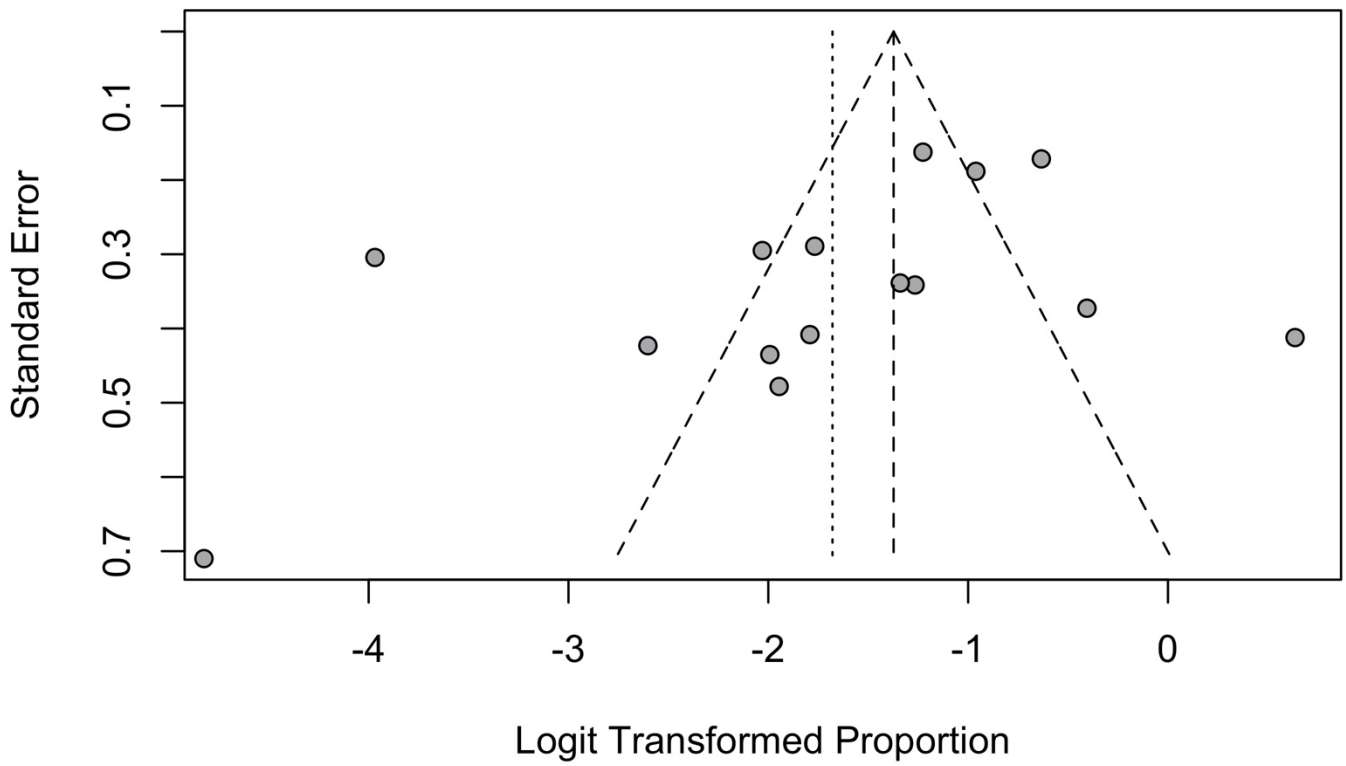
1.2.1. Figure S6. Meta-analysis of the diagnostic yield by seizure type





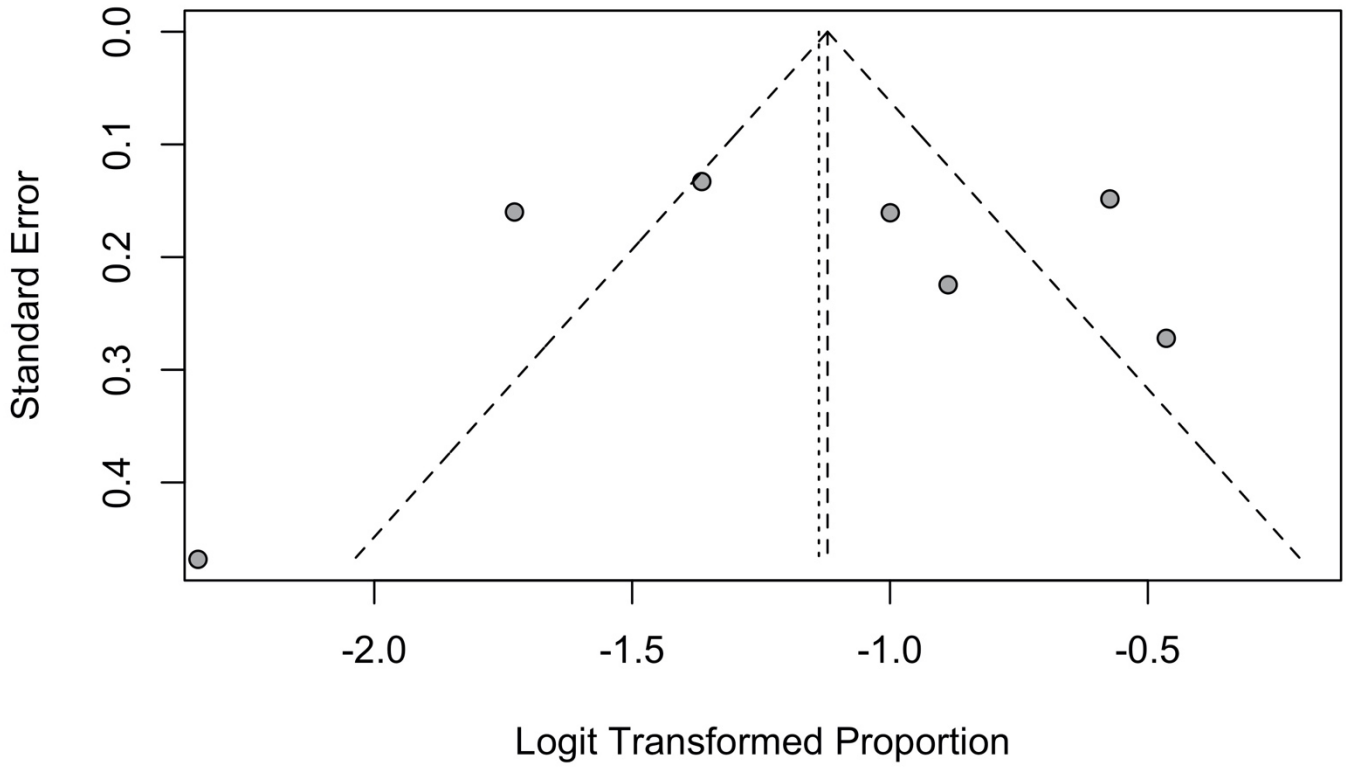
Abbreviations: CI = confidence interval, I^2 = estimated proportion of the variance in study estimates that is due to heterogeneity, Proportion = fraction of individuals with a positive genetic test, i.e. pathogenic or likely pathogenic variant.

1.2.2. Figure S7. Funnel plot of all FE studies



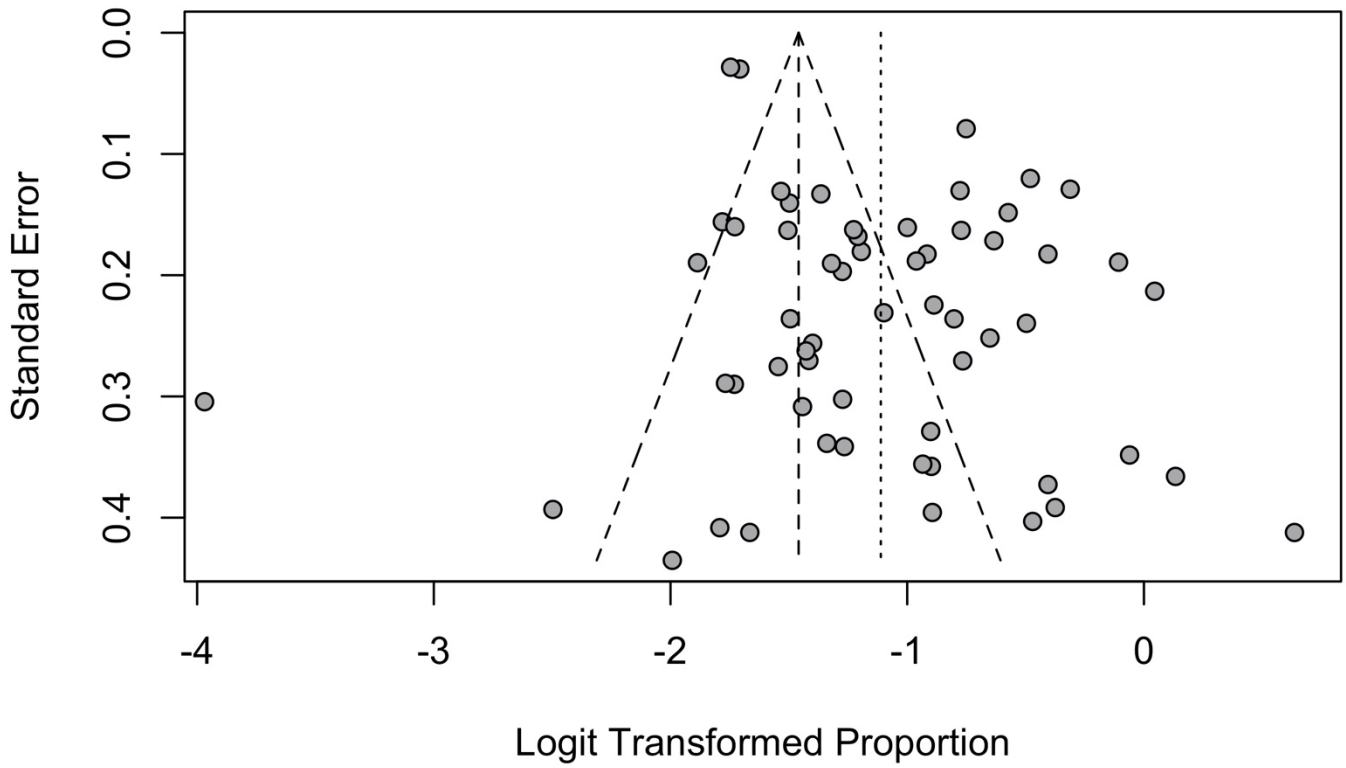
Grey dots = Original studies.

1.2.3. Figure S8. Funnel plot of all GE studies



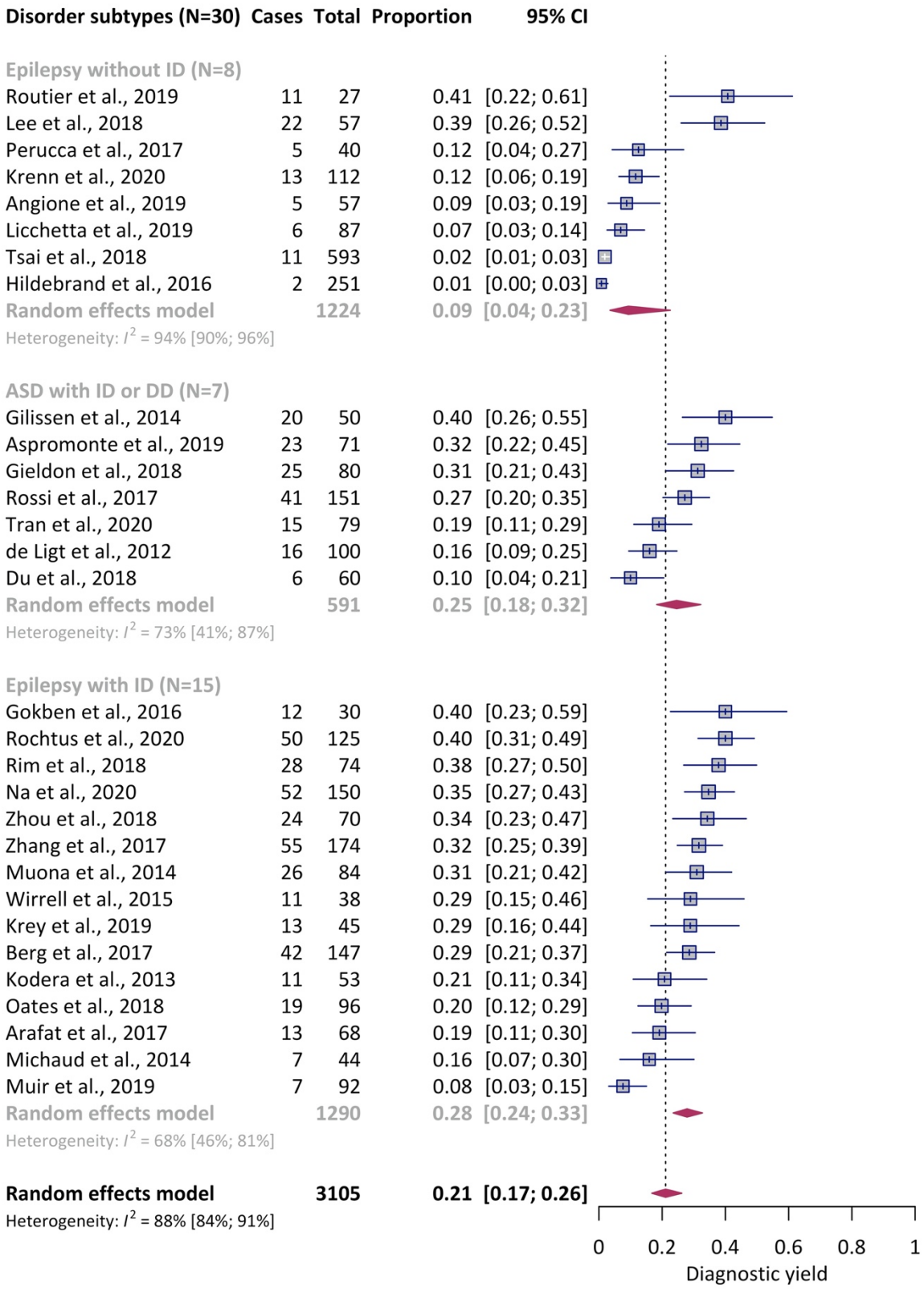
Grey dots = Original studies.

1.2.4. Figure S9. Funnel plot of all GE&FE studies



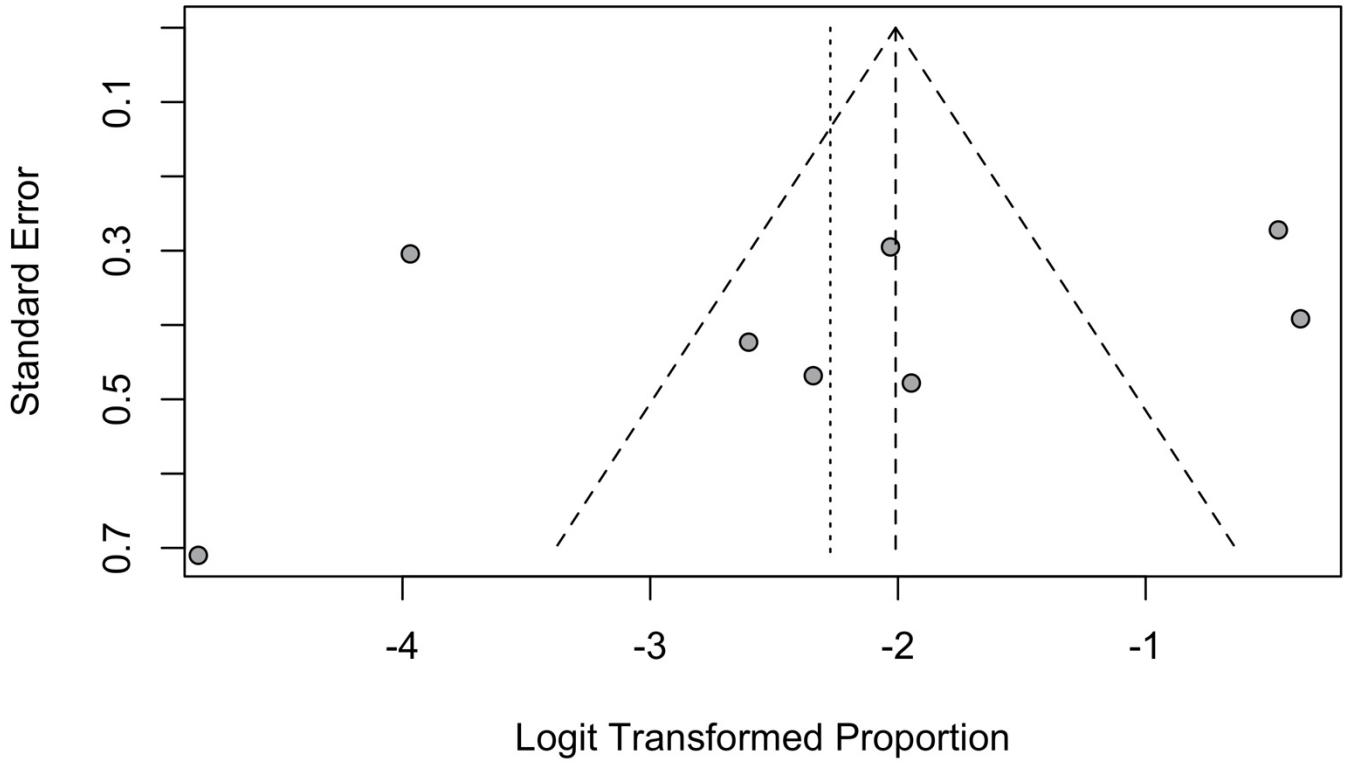
Grey dots = Original studies.

1.2.5. Figure S10. Meta-analysis of the diagnostic yield by disorder subtype



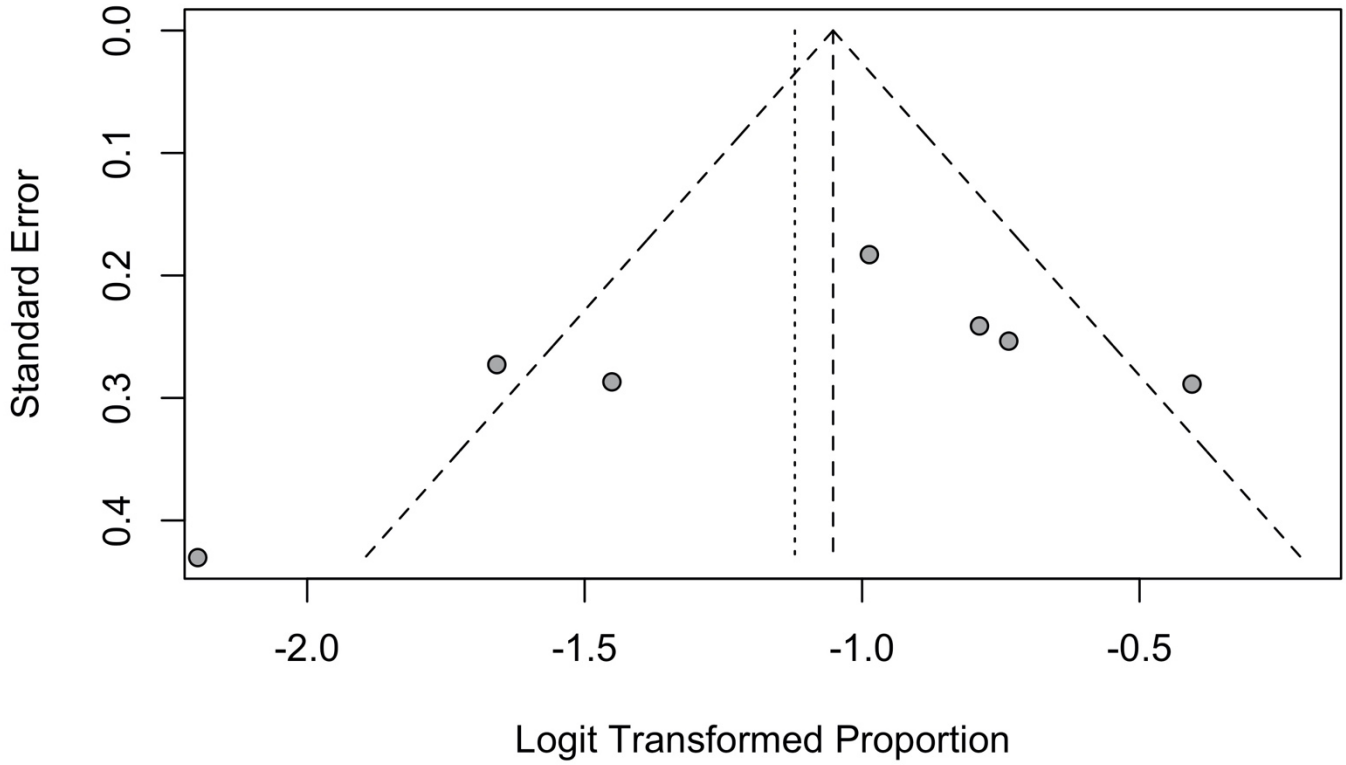
Abbreviations: ID = intellectual disability, CI = confidence interval, I^2 = estimated proportion of the variance in study estimates that is due to heterogeneity, Proportion = fraction of individuals with a positive genetic test, i.e. pathogenic or likely pathogenic variant.

1.2.6. Figure S11. Funnel plot of all epilepsy without ID studies



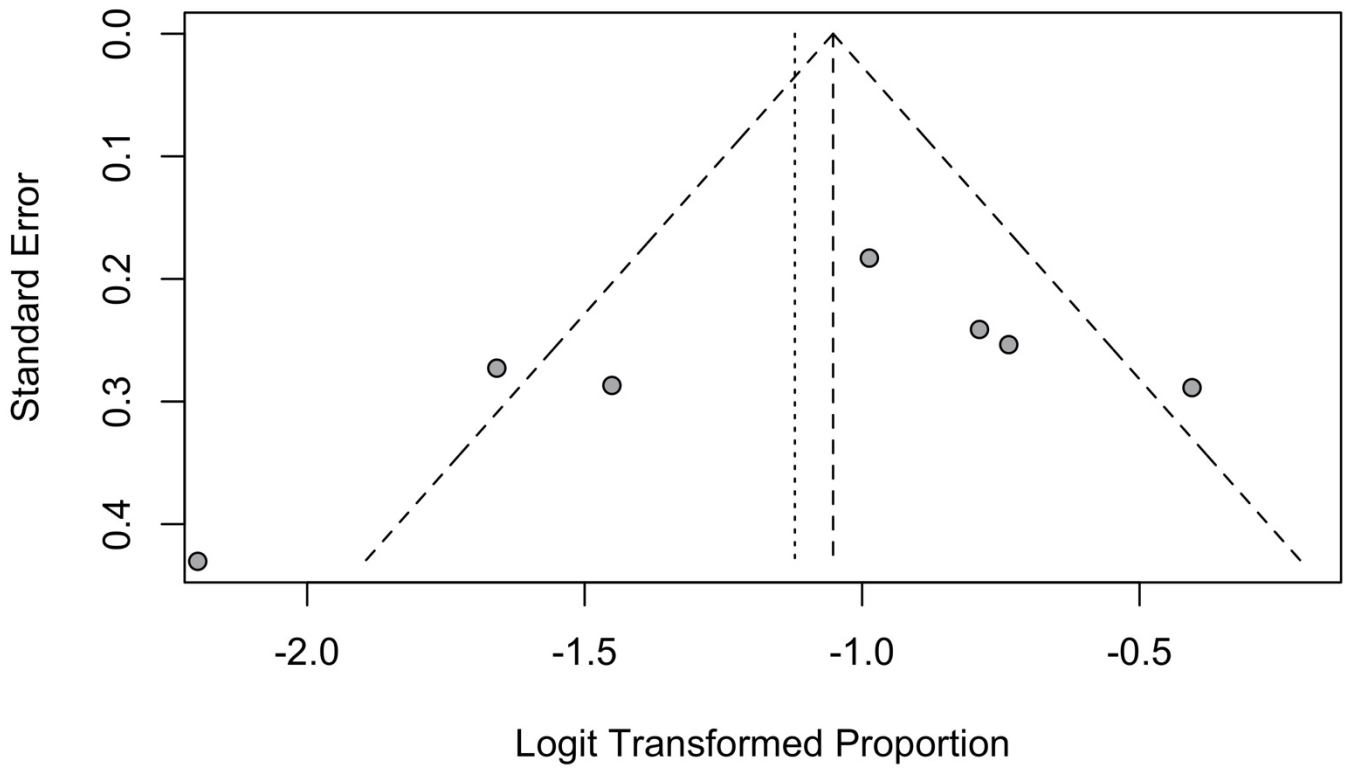
Grey dots = Original studies.

1.2.7. Figure S12. Funnel plot of all ASD with ID or DD studies



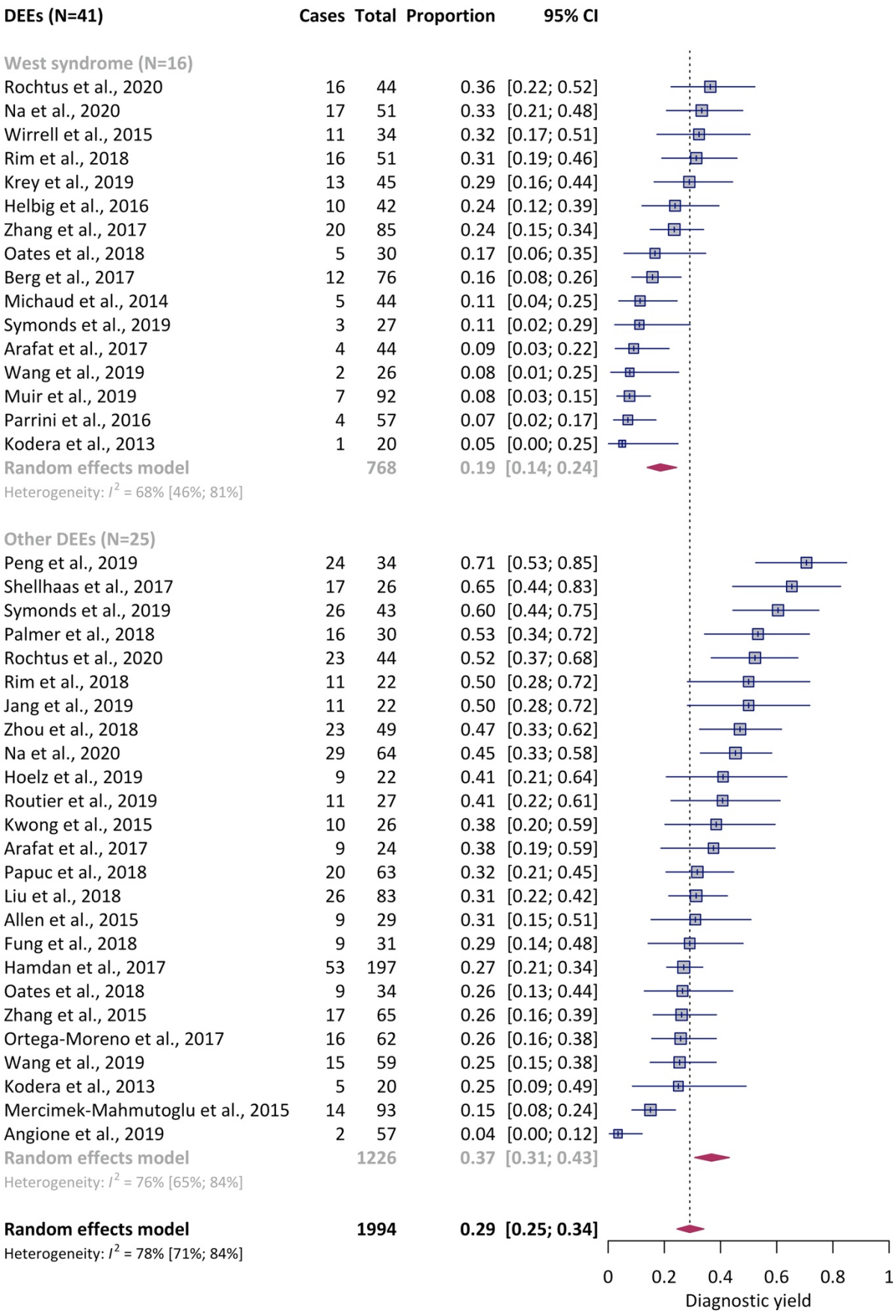
Grey dots = Original studies.

1.2.8. Figure S13. Funnel plot of all epilepsy with ID studies



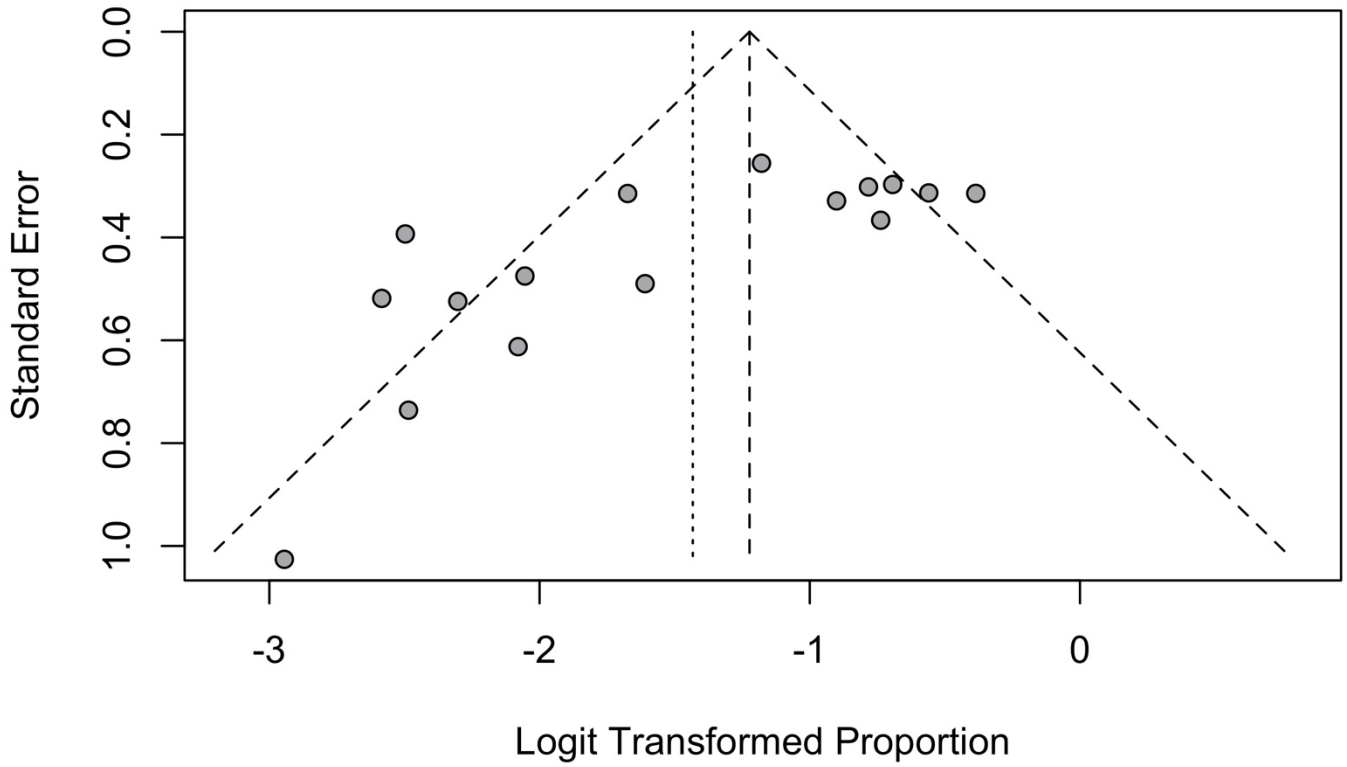
Grey dots = Original studies.

1.2.9. S14. Meta-analysis of the diagnostic yield by DEE



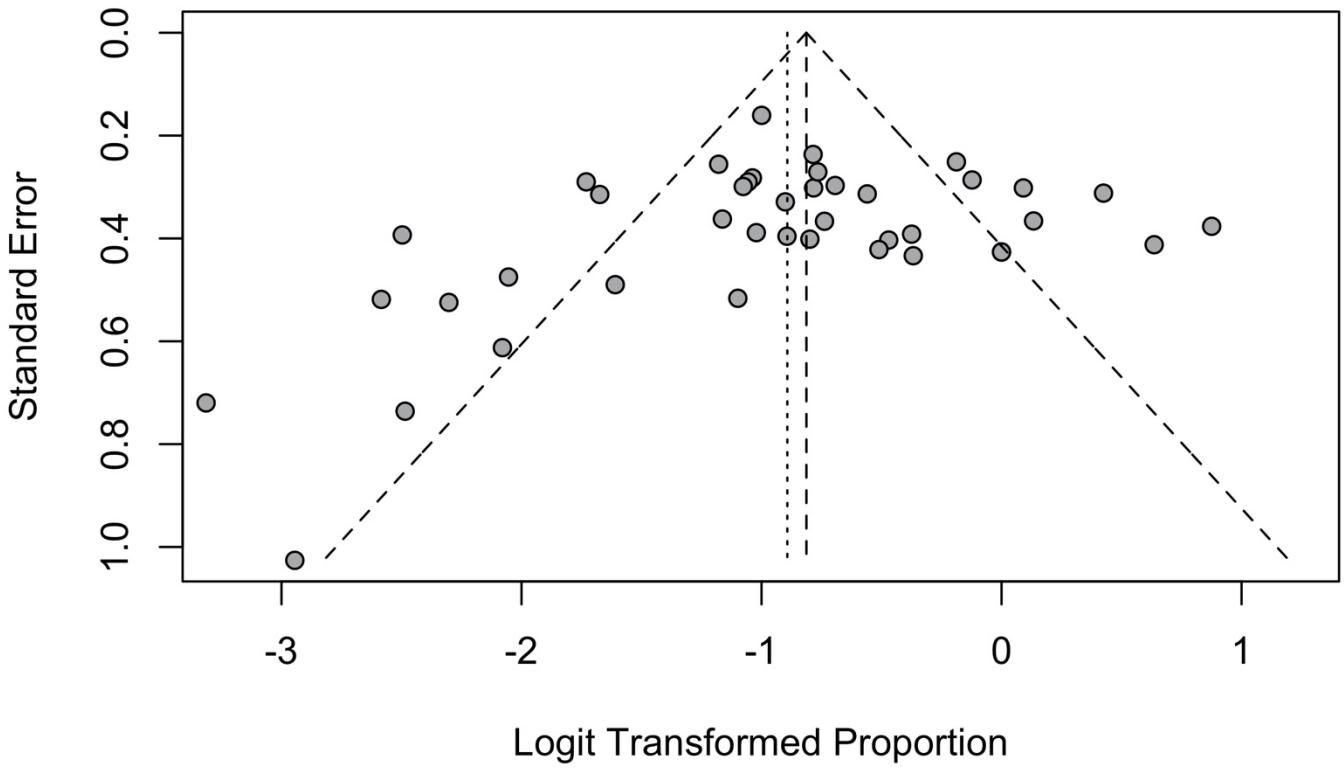
Abbreviations: DEEs = developmental epileptic encephalopathies, CI = confidence interval, I^2 = estimated proportion of the variance in study estimates that is due to heterogeneity, Proportion = fraction of individuals with a positive genetic test, i.e. pathogenic or likely pathogenic variant.

1.2.10. Figure S15. Funnel plot of all WS studies



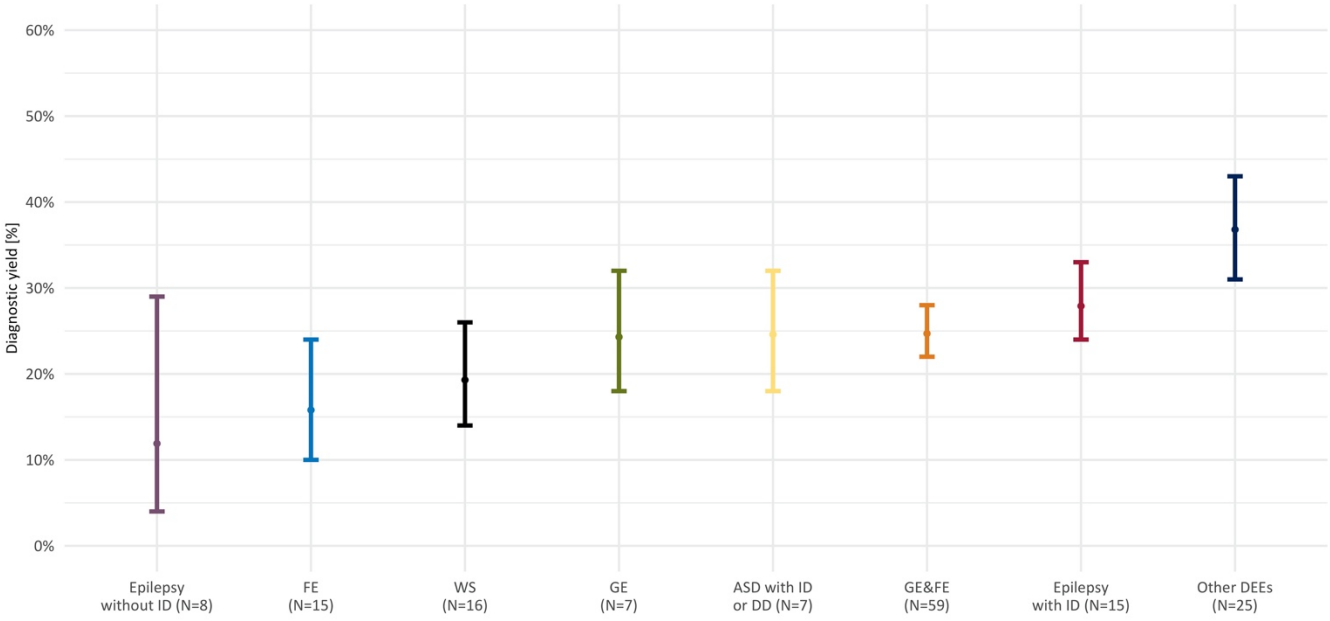
Grey dots = Original studies.

1.2.11. Figure S16. Funnel plot of all other DEE studies



Grey dots = Original studies.

1.2.12. Figure S17. Error bar plot by subtype

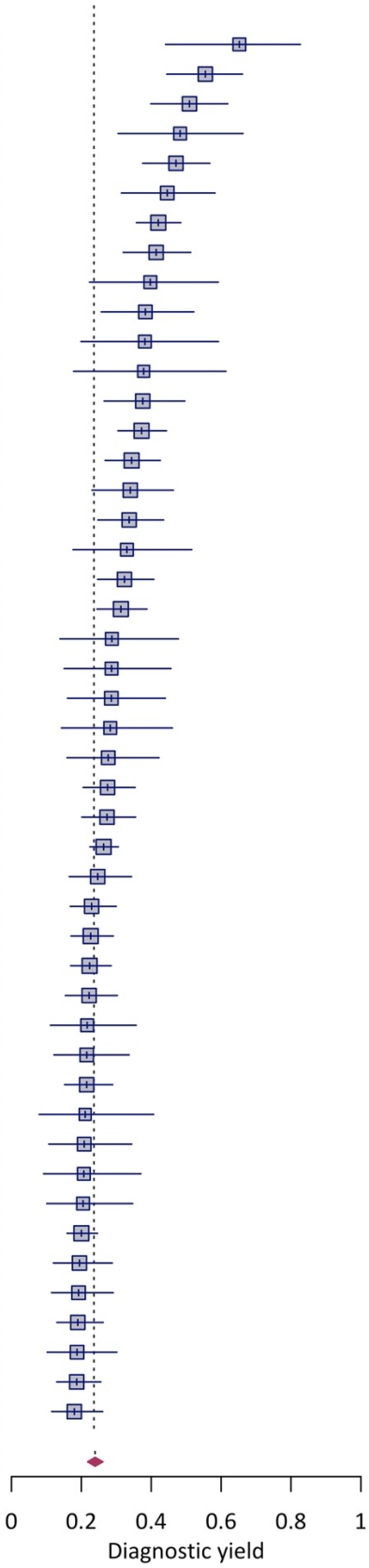


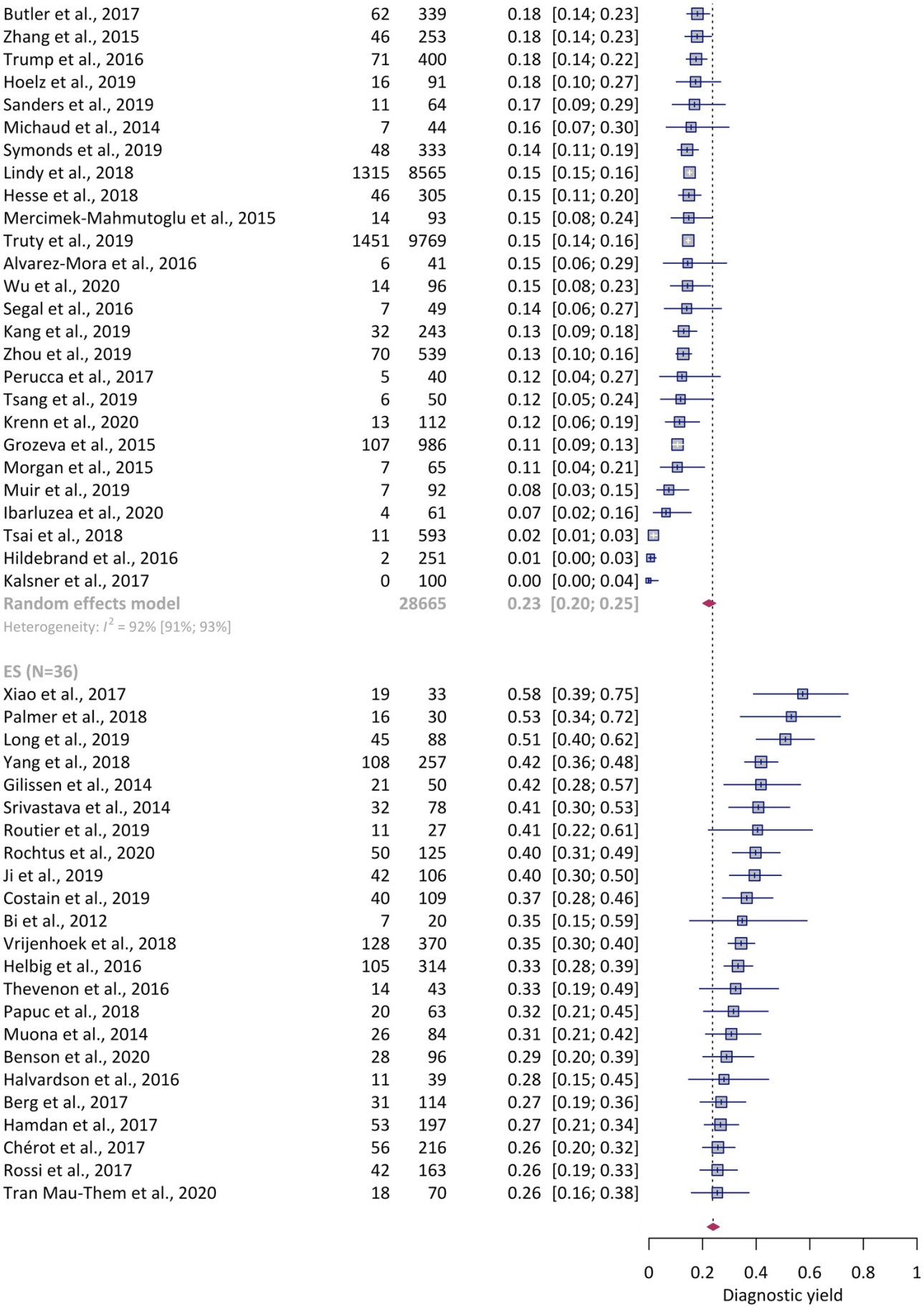
Abbreviations: GE&FE = combined generalized and focal epilepsy, FE = focal epilepsy, GE = generalized epilepsy, WS = West syndrome, ASD with ID or DD = autism spectrum disorder with intellectual disability or developmental delay, DEEs = developmental epileptic encephalopathies.

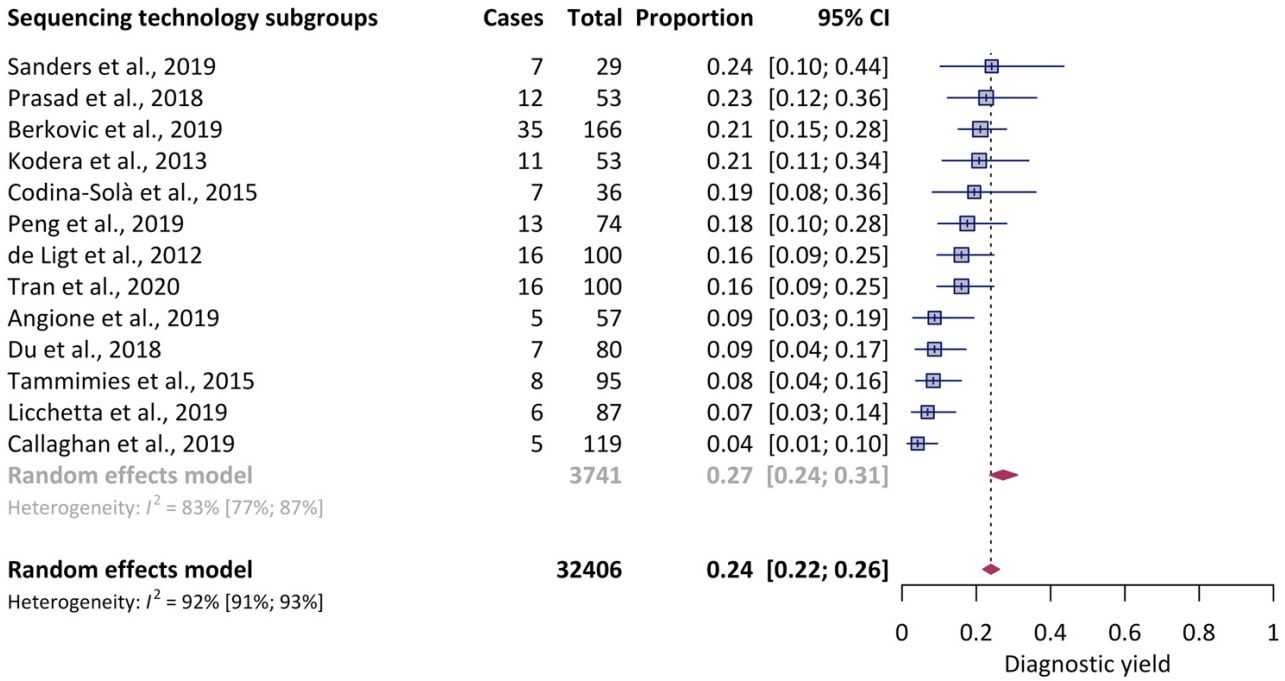
1.3. Meta analyses by sequencing technology

1.3.1. Figure S18. Meta-analysis of the diagnostic yield of sequencing technologies

Sequencing technology subgroups (N=109)	Cases	Total	Proportion	95% CI
Panel (N=73)				
Shellhaas et al., 2017	17	26	0.65	[0.44; 0.83]
Stojanovic et al., 2020	49	88	0.56	[0.45; 0.66]
Tumienė et al., 2017	44	86	0.51	[0.40; 0.62]
Lemke et al., 2012	16	33	0.48	[0.31; 0.66]
Jang et al., 2019	53	112	0.47	[0.38; 0.57]
Peng et al., 2019	26	58	0.45	[0.32; 0.58]
Fernández-Marmiesse et al., 2019	104	246	0.42	[0.36; 0.49]
Kim et al., 2019	45	108	0.42	[0.32; 0.52]
Gokben et al., 2016	12	30	0.40	[0.23; 0.59]
Lee et al., 2018	22	57	0.39	[0.26; 0.52]
Kwong et al., 2015	10	26	0.38	[0.20; 0.59]
Jezela-Stanek et al., 2020	8	21	0.38	[0.18; 0.62]
Rim et al., 2018	28	74	0.38	[0.27; 0.50]
Yokoi et al., 2020	75	200	0.38	[0.31; 0.45]
Na et al., 2020	52	150	0.35	[0.27; 0.43]
Zhou et al., 2018	24	70	0.34	[0.23; 0.47]
Gieldon et al., 2018	36	106	0.34	[0.25; 0.44]
Berg et al., 2017	11	33	0.33	[0.18; 0.52]
Peng et al., 2019	46	141	0.33	[0.25; 0.41]
Zhang et al., 2017	55	174	0.32	[0.25; 0.39]
Fung et al., 2018	9	31	0.29	[0.14; 0.48]
Wirrell et al., 2015	11	38	0.29	[0.15; 0.46]
Krey et al., 2019	13	45	0.29	[0.16; 0.44]
Han et al., 2019	10	35	0.29	[0.15; 0.46]
Tonduti et al., 2018	14	50	0.28	[0.16; 0.42]
Staněk et al., 2018	42	151	0.28	[0.21; 0.36]
Miao et al., 2018	39	141	0.28	[0.20; 0.36]
Yang et al., 2018	127	476	0.27	[0.23; 0.31]
Snoeijen-Schouwenaars et al., 2018	25	100	0.25	[0.17; 0.35]
Liu et al., 2018	40	172	0.23	[0.17; 0.30]
Johannesen et al., 2020	46	200	0.23	[0.17; 0.29]
Møller et al., 2016	49	216	0.23	[0.17; 0.29]
Yamamoto et al., 2019	30	133	0.23	[0.16; 0.31]
Allen et al., 2015	11	50	0.22	[0.12; 0.36]
Borlot et al., 2019	14	64	0.22	[0.13; 0.34]
Balciuniene et al., 2019	33	151	0.22	[0.16; 0.29]
Wang et al., 2014	6	28	0.21	[0.08; 0.41]
Tan et al., 2015	11	52	0.21	[0.11; 0.35]
Han et al., 2018	8	38	0.21	[0.10; 0.37]
Pekeles et al., 2018	10	48	0.21	[0.10; 0.35]
Parrini et al., 2016	71	349	0.20	[0.16; 0.25]
Oates et al., 2018	19	96	0.20	[0.12; 0.29]
Ortega-Moreno et al., 2017	17	87	0.20	[0.12; 0.29]
Aspromonte et al., 2019	29	150	0.19	[0.13; 0.27]
Arafat et al., 2017	13	68	0.19	[0.11; 0.30]
Costain et al., 2019	31	163	0.19	[0.13; 0.26]
Wang et al., 2019	22	120	0.18	[0.12; 0.26]

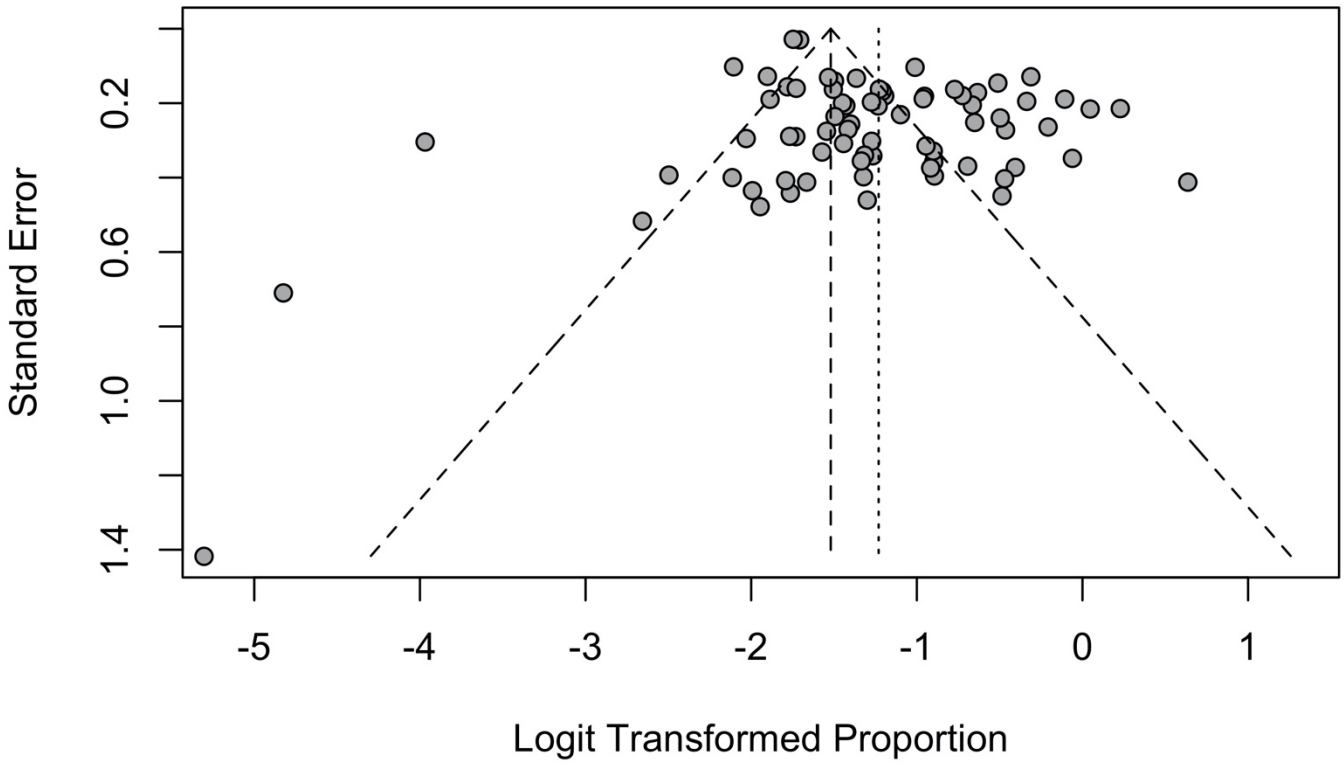



Sequencing technology subgroups Cases Total Proportion 95% CI
Butler et al., 2017 62 339 0.18 [0.14; 0.23]
Zhang et al., 2015 46 253 0.18 [0.14; 0.23]
Trump et al., 2016 71 400 0.18 [0.14; 0.22]
Hoelz et al., 2019 16 91 0.18 [0.10; 0.27]
Sanders et al., 2019 11 64 0.17 [0.09; 0.29]
Michaud et al., 2014 7 44 0.16 [0.07; 0.30]
Symonds et al., 2019 48 333 0.14 [0.11; 0.19]
Lindy et al., 2018 1315 8565 0.15 [0.15; 0.16]
Hesse et al., 2018 46 305 0.15 [0.11; 0.20]
Mercimek-Mahmutoglu et al., 2015 14 93 0.15 [0.08; 0.24]
Truty et al., 2019 1451 9769 0.15 [0.14; 0.16]
Alvarez-Mora et al., 2016 6 41 0.15 [0.06; 0.29]
Wu et al., 2020 14 96 0.15 [0.08; 0.23]
Segal et al., 2016 7 49 0.14 [0.06; 0.27]
Kang et al., 2019 32 243 0.13 [0.09; 0.18]
Zhou et al., 2019 70 539 0.13 [0.10; 0.16]
Perucca et al., 2017 5 40 0.12 [0.04; 0.27]
Tsang et al., 2019 6 50 0.12 [0.05; 0.24]
Krenn et al., 2020 13 112 0.12 [0.06; 0.19]
Grozeva et al., 2015 107 986 0.11 [0.09; 0.13]
Morgan et al., 2015 7 65 0.11 [0.04; 0.21]
Muir et al., 2019 7 92 0.08 [0.03; 0.15]
Ibarluzea et al., 2020 4 61 0.07 [0.02; 0.16]
Tsai et al., 2018 11 593 0.02 [0.01; 0.03]
Hildebrand et al., 2016 2 251 0.01 [0.00; 0.03]
Kalsner et al., 2017 0 100 0.00 [0.00; 0.04]
Random effects model 28665 0.23 [0.20; 0.25]
Heterogeneity: I^2 = 92% [91%; 93%]
ES (N=36)
Xiao et al., 2017 19 33 0.58 [0.39; 0.75]
Palmer et al., 2018 16 30 0.53 [0.34; 0.72]
Long et al., 2019 45 88 0.51 [0.40; 0.62]
Yang et al., 2018 108 257 0.42 [0.36; 0.48]
Gilissen et al., 2014 21 50 0.42 [0.28; 0.57]
Srivastava et al., 2014 32 78 0.41 [0.30; 0.53]
Routier et al., 2019 11 27 0.41 [0.22; 0.61]
Rochtus et al., 2020 50 125 0.40 [0.31; 0.49]
Ji et al., 2019 42 106 0.40 [0.30; 0.50]
Costain et al., 2019 40 109 0.37 [0.28; 0.46]
Bi et al., 2012 7 20 0.35 [0.15; 0.59]
Vrijenhoek et al., 2018 128 370 0.35 [0.30; 0.40]
Helbig et al., 2016 105 314 0.33 [0.28; 0.39]
Thevenon et al., 2016 14 43 0.33 [0.19; 0.49]
Papuc et al., 2018 20 63 0.32 [0.21; 0.45]
Muona et al., 2014 26 84 0.31 [0.21; 0.42]
Benson et al., 2020 28 96 0.29 [0.20; 0.39]
Halvardson et al., 2016 11 39 0.28 [0.15; 0.45]
Berg et al., 2017 31 114 0.27 [0.19; 0.36]
Hamdan et al., 2017 53 197 0.27 [0.21; 0.34]
Chérot et al., 2017 56 216 0.26 [0.20; 0.32]
Rossi et al., 2017 42 163 0.26 [0.19; 0.33]
Tran Mau-Them et al., 2020 18 70 0.26 [0.16; 0.38]
0
0.2
0.4
0.6
0.8
1
Diagnostic yield



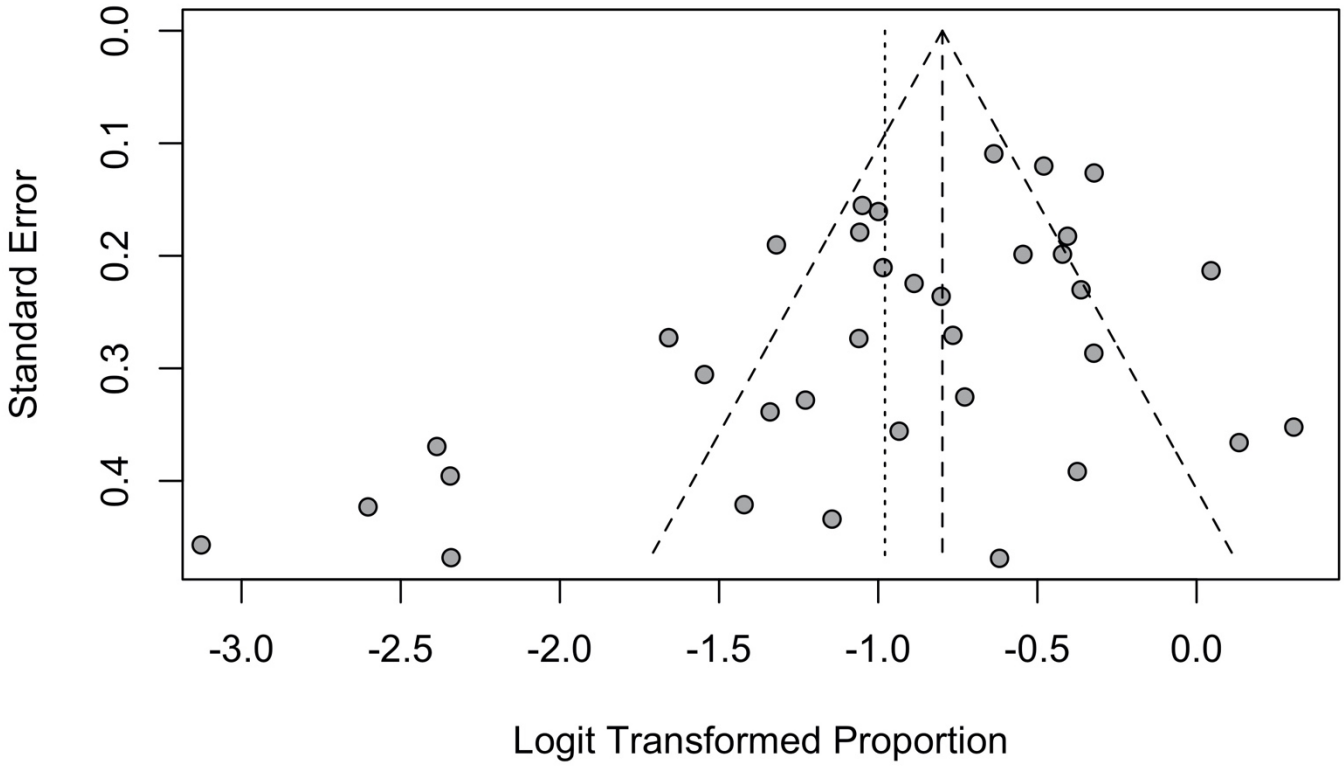
Abbreviations: CI = confidence interval, I^2 = estimated proportion of the variance in study estimates that is due to heterogeneity, Proportion = fraction of individuals with a positive genetic test, i.e. pathogenic or likely pathogenic variant.

1.3.2. Figure S19. Funnel plot of all Panel studies



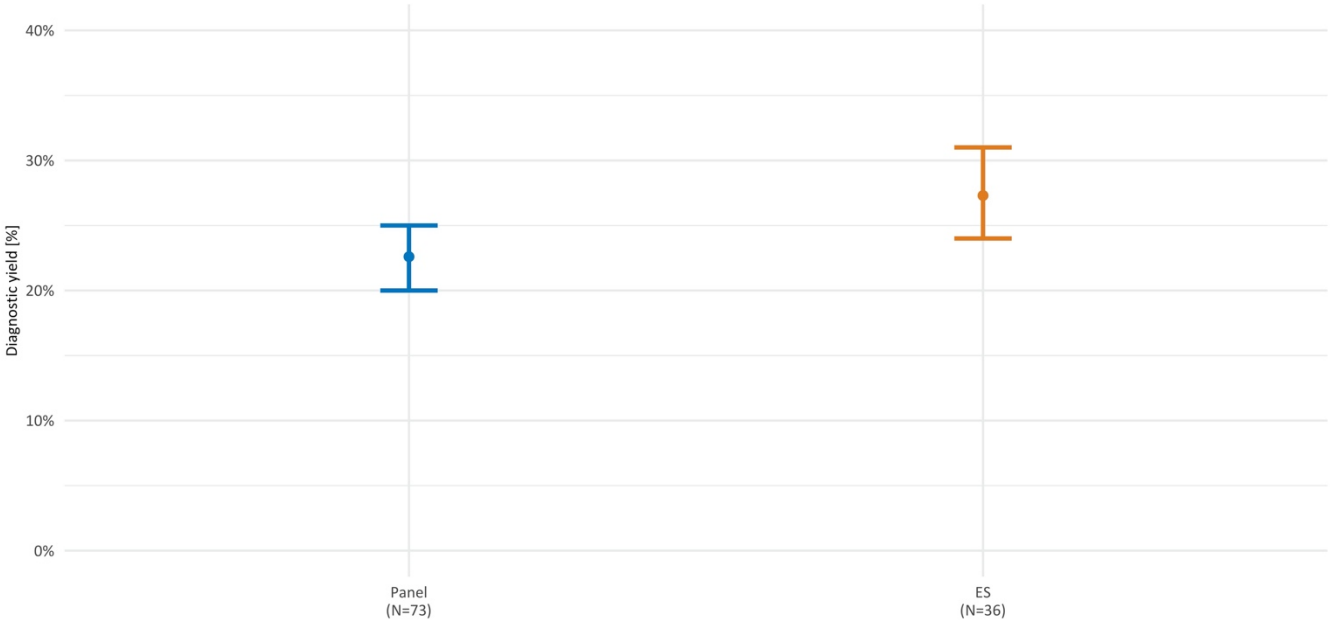
Grey dots = Original studies.

1.3.3. Figure S20. Funnel plot of all ES studies



Grey dots = Original studies.

1.3.4. Figure S21. Error bar plot of the diagnostic yield by sequencing technology

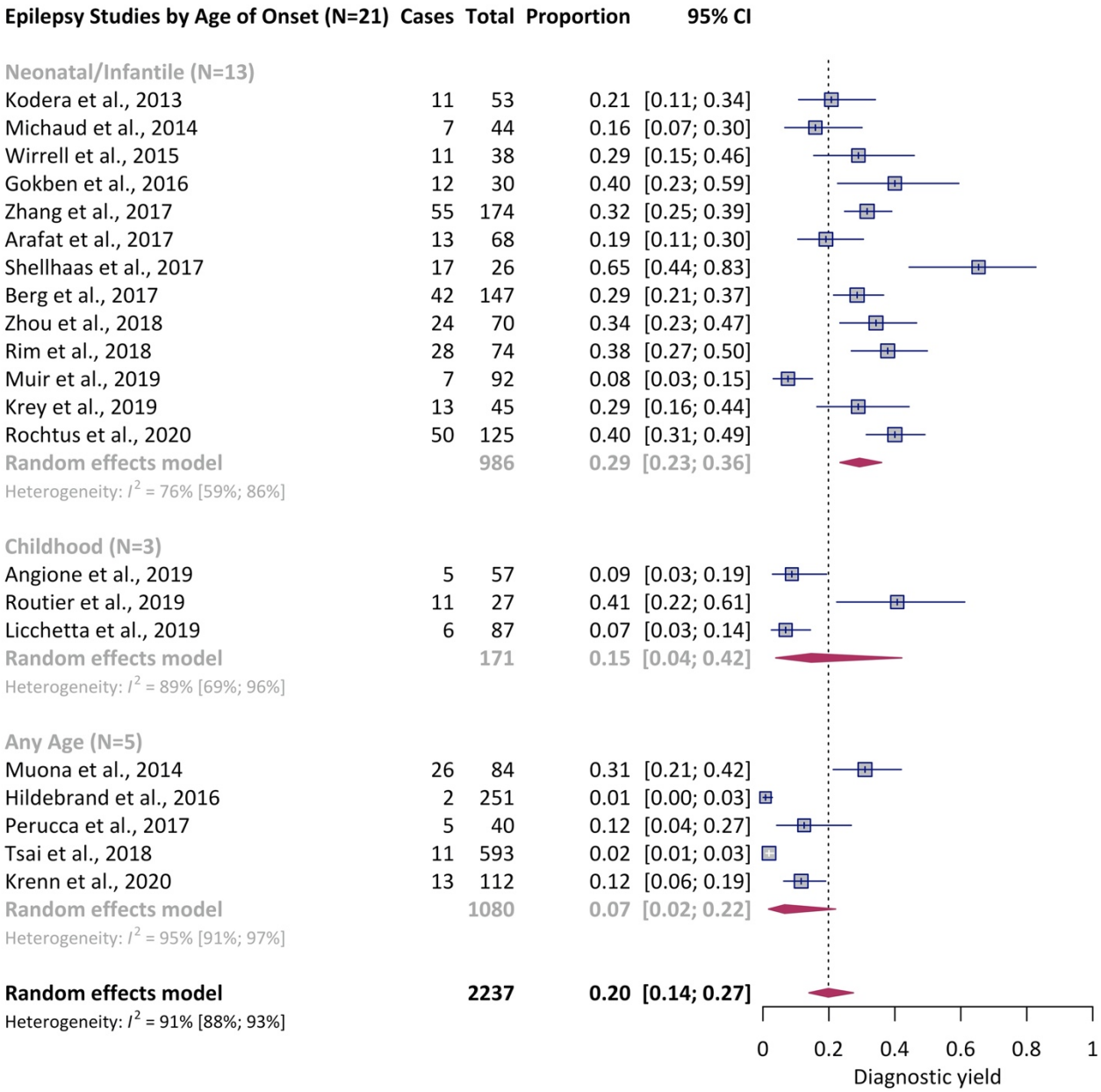


The diagnostic yield across Panel and ES.

Abbreviations: Panel = targeted gene panel sequencing, ES = exome sequencing.

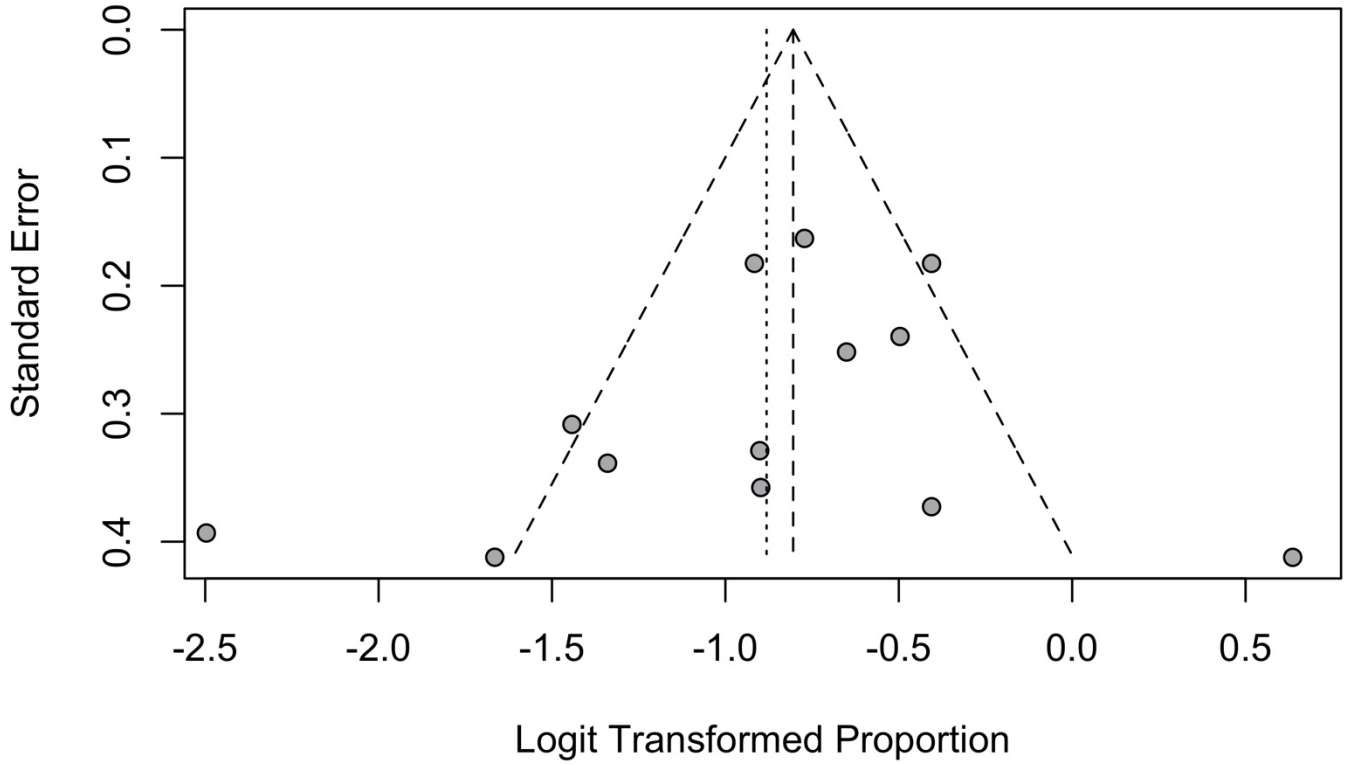
1.4. Meta analyses by age of onset

1.4.1. Figure S22. Meta-analysis of the diagnostic yield of all epilepsy studies by age of onset



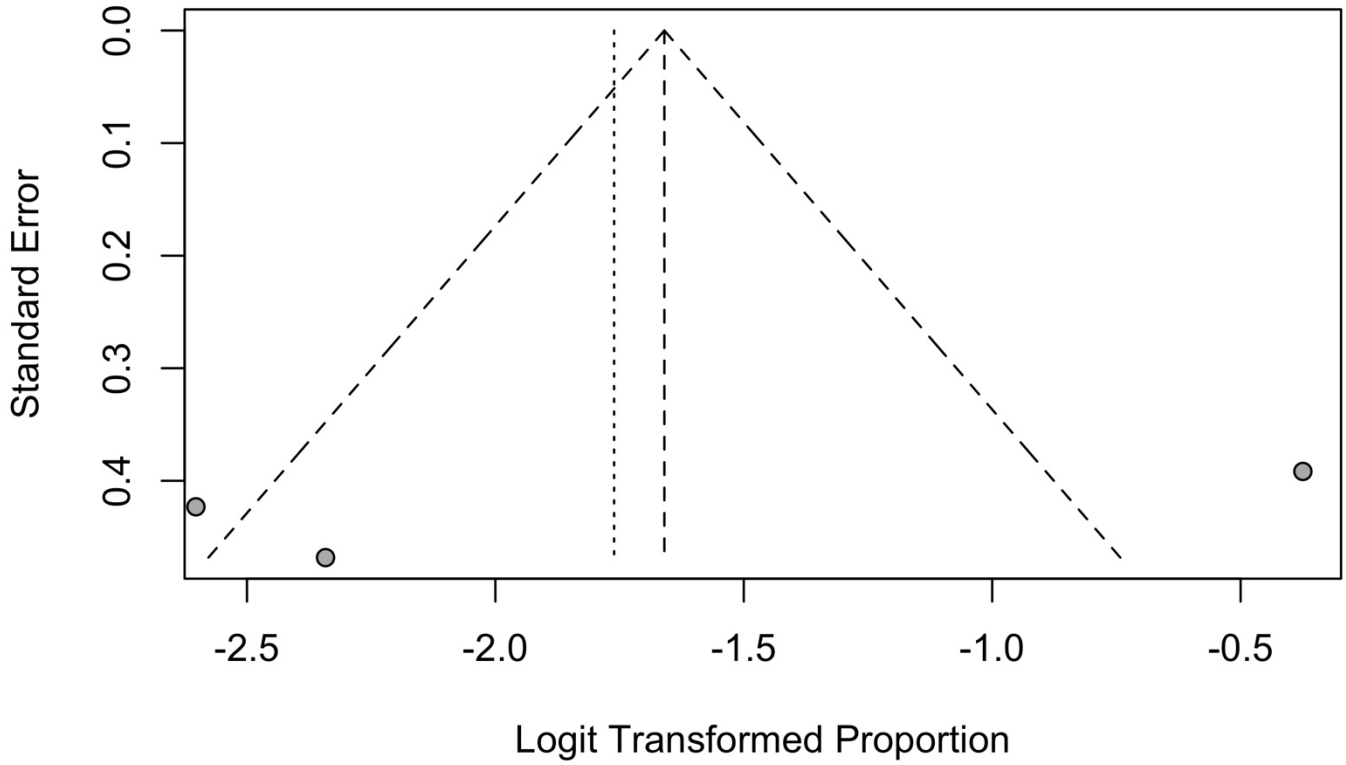
Abbreviations: CI = confidence interval, I^2 = estimated proportion of the variance in study estimates that is due to heterogeneity, Proportion = fraction of individuals with a positive genetic test, i.e. pathogenic or likely pathogenic variant.

1.4.2. Figure S23. Funnel plot of all Neonatal/Infantile studies



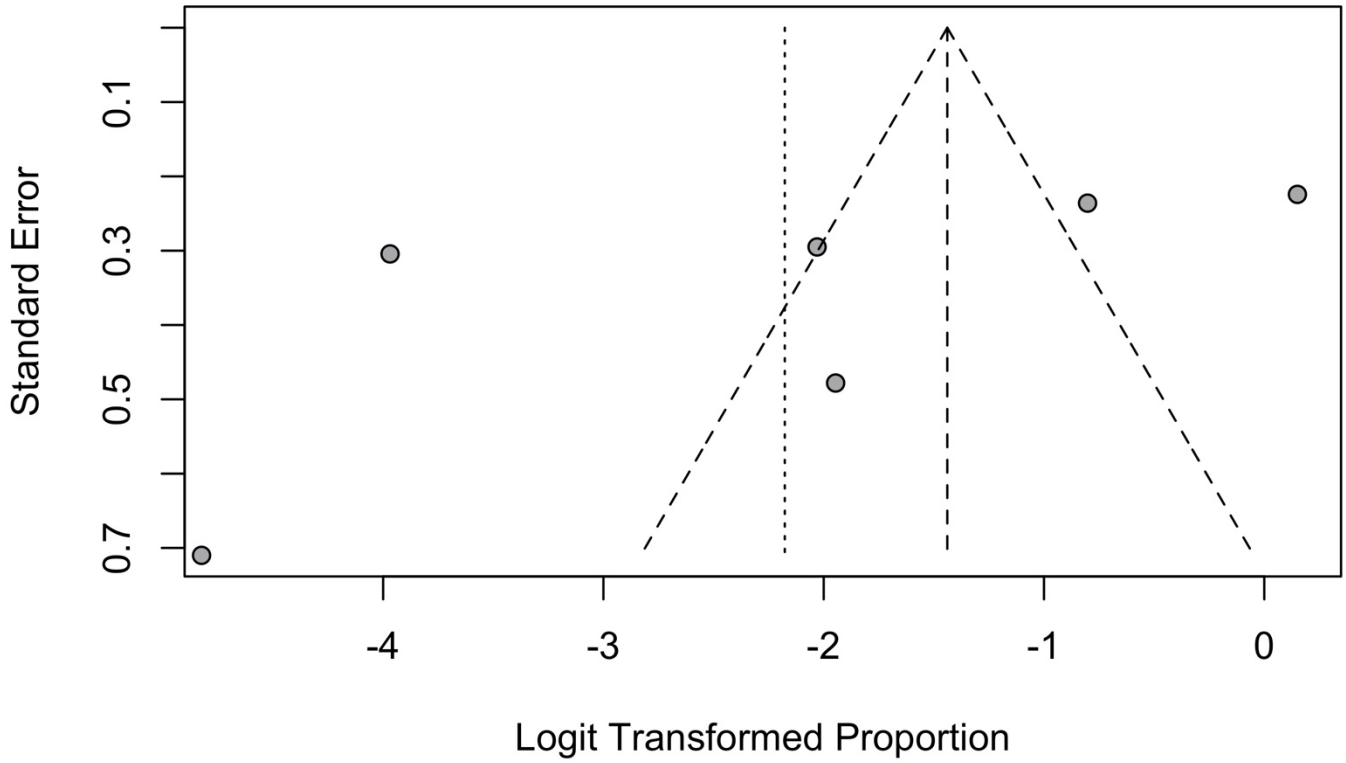
Grey dots = Original studies.

1.4.3. Figure S24. Funnel plot of all Childhood studies



Grey dots = Original studies.

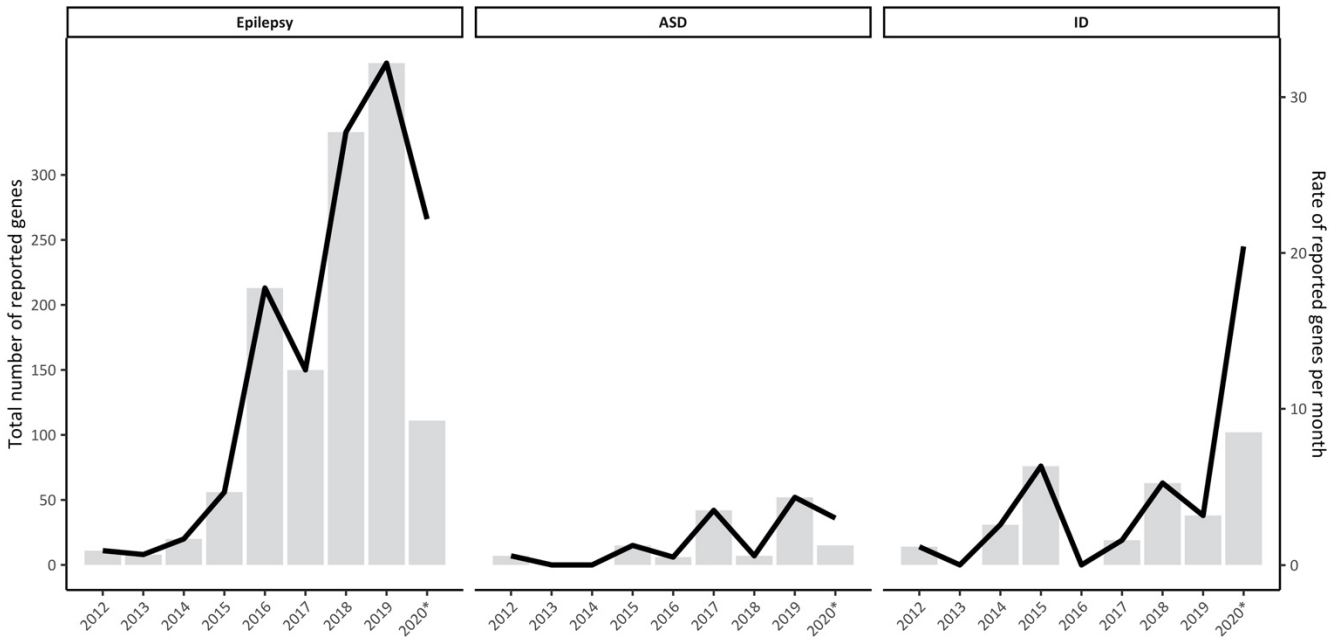
1.4.4. Figure S25. Funnel plot of all Any Age studies



Grey dots = Original studies.

2. Reported genes

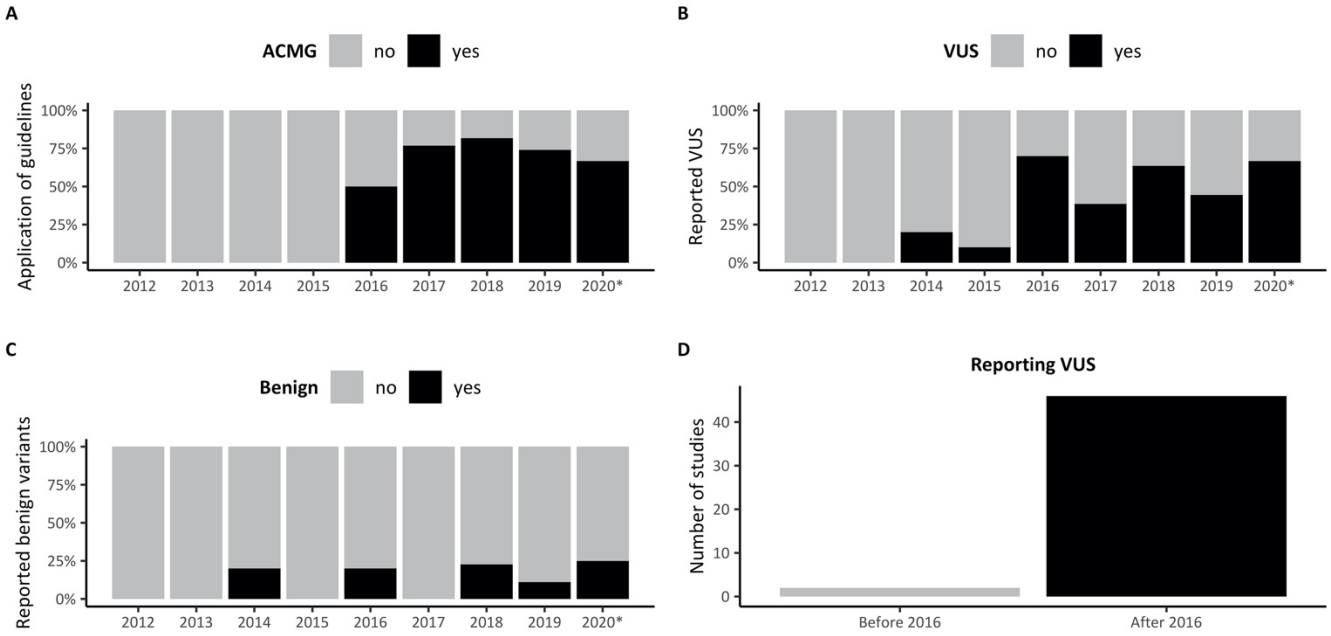
2.1. Figure S26. Number and rate of genes with pathogenic variant



The bars represent the number of genes with pathogenic variants. The line represents the rate of genes per month and year. The number of identified genes increased rapidly in recent years for epilepsy. For ASD and ID the number of reported genes with pathogenic v*ariants is low. Abbreviations: ASD = autism spectrum disorder, ID = intellectual disability,* * = Data were collected until May 20, 2020.

3. Variant interpretation, VUS, and benign variants

3.1. Figure S27. Level of variant interpretation and reporting as well as the proportion of the studies which reported VUS and benign variants



Data analyzed from 103 studies. ***A*** *Since the introduction of the ACMG guidelines in 2015, there is a clear trend in adopting these in clinical sequencing studies beginning in 2016.* ***B*** *Reporting VUS becomes more common practice over time.* ***C*** *Benign variants are still being reported rather infrequently to date; their potential clinical use is considered low.* ***D*** *The number of studies reporting VUS has increased significantly after the introduction of the ACMG guidelines (OR = 38.6, P = 5.2×10^{-14}).*

*Abbreviation: * = Data were collected until May 20, 2020.*

4. References of all studies included in meta-analysis

4.1. Table S1. List of all 103 studies

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