Genetics in Medicine (2023) 25, 100896

ELSEVIER

Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

SYSTEMATIC REVIEW

Meta-analysis of the diagnostic and clinical utility of exome and genome sequencing in pediatric and adult patients with rare diseases across diverse populations

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ARTICLE INFO

Article history:
Received 13 December 2022
Received in revised form
7 May 2023
Accepted 10 May 2023
Available online 13 May 2023

Keywords:
Genomic diversity
Meta-analysis
Rare disease
Exome sequencing
Genome sequencing

ABSTRACT

Purpose: This meta-analysis aims to compare the diagnostic and clinical utility of exome sequencing (ES) vs genome sequencing (GS) in pediatric and adult patients with rare diseases across diverse populations.
Methods: A meta-analysis was conducted to identify studies from 2011 to 2021.
Results: One hundred sixty-one studies across 31 countries/regions were eligible, featuring 50,417 probands of diverse populations. Diagnostic rates of ES (0.38, 95% CI 0.36-0.40) and GS (0.34, 95% CI 0.30-0.38) were similar ($P = .1$). Within-cohort comparison illustrated 1.2-times odds of diagnosis by GS over ES (95% CI 0.79-1.83, $P = .38$). GS studies discovered a higher range of novel genes than ES studies; yet, the rate of variant of unknown significance did not differ ($P = .78$). Among high-quality studies, clinical utility of GS (0.77, 95% CI 0.64-0.90) was higher than that of ES (0.44, 95% CI 0.30-0.58) ($P < .01$).
Conclusion: This meta-analysis provides an important update to demonstrate the similar diagnostic rates between ES and GS and the higher clinical utility of GS over ES. With the newly published recommendations for clinical interpretation of variants found in noncoding regions of the genome and the trend of decreasing variant of unknown significance and GS cost, it is expected that GS will be more widely used in clinical settings.

The Article Publishing Charge (APC) for this article was paid by the Hong Kong Genome Institute.

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doi: https://doi.org/10.1016/j.gim.2023.100896

Introduction

The rapid advancement and translational application of next-generation sequencing technologies in genomic medicine over the past decades is a significant milestone that could potentially revolutionize the diagnostic odyssey of patients with rare diseases (RDs).[1] RDs are conditions affecting <40 in 100,000 individuals in a population, with limited medical knowledge regarding their diagnoses and treatments.[2] Given the decreasing cost of sequencing a human genome in recent years (<$1000 in 2021 as suggested by the National Human Genome Research Institute), genomic technologies are now feasible and affordable for implementation and integration in routine clinical services and health care systems.[3,4] However, accessibility of these technologies varies within and across populations and countries. It is challenging for medical practitioners to allocate and deliver health care services and resources safely and equitably to patients with RD without relevant guidelines and supporting evidence.[5,6]

During the past decade, there has been a rapid shift toward the use of exome sequencing (ES) and genome sequencing (GS) as the first-line diagnostic test for patients with suspected genetic diseases. The growing number of ES and GS studies in RDs demonstrated an improvement in diagnostic rate by allowing concomitant examination of genes more comprehensively compared with conventional genetic tests, such as gene panels and chromosomal microarray analysis (CMA).[7-9] Coupled with a higher capability to discover novel genes for the establishment of a causal relationship between genotype and phenotype (3 times higher than conventional methods), ES and GS hold a greater promise for elucidating the etiology of RDs.[10] A previous meta-analysis by Clark et al[11] in 2018 compared the diagnostic rate and clinical utility of ES and GS with CMA in children with RDs, suggesting the potential for ES or GS as the first-line diagnostic tests to replace conventional CMA in the pediatric population. Despite many ES and GS studies being published and identified internationally, most are focused on children and the White populations. There is a lack of evidence and guidelines for the use of ES and GS across age groups and populations to guide health care providers. Although ES allows variations in the protein-coding region of any gene to be identified, it has its limitations in detecting noncoding variants (NCVs) and structural variations (SVs).[12] Additional or alternative methods are required when there is growing evidence of disorders caused by NCVs and SVs (eg, trinucleotide repeat in the 5′ untranslated region of the *FMR1* gene for fragile X syndrome). In contrast, GS has higher sensitivity in SV detection and the capability to detect NCVs with more uniform coverage, genotype quality, and a lower rate of false-positive variants, which in principle, allows the detection of all disease relevant genomic variants beyond the exome. Nevertheless, as the quantity and complexity of genetic information rises, the number of variants of unknown significance (VUS) and the associated uncertainties regarding its clinical relevance increase as well, hindering the widespread application in the clinical setting. With the newly published guidelines for the clinical interpretation of NCV, several studies suggested that GS will eventually supersede ES and other genetic tests in a clinical setting.[13-15] Recently, Souche et al[16] has provided recommendations for the use of GS in diagnostics for RDs, from quality control and validation of laboratory procedures, bioinformatics pipelines, and variant interpretation to ethical concerns of reporting test results. With GS' diagnostic superiority to detect NCVs and SVs simultaneously, as well as single-nucleotide variations for monogenic and oligogenic diseases, they also provided the rationale to shift toward GS.

Since majority of the RDs are chronically debilitating and life threatening, early and rapid adoption of ES or GS could potentially impact diagnosis-predicated clinical management, often referred to as clinical utility, which may, in turn, improve patient's clinical outcome. Shickh et al[17] conducted a systematic review in 2019 to review clinical utility of ES and GS, providing evidence that ES and GS have a greater potential to improve patient's clinical management compared with standard genetic tests, particularly in patients with neurologic and acute indications. Similarly, meta-analysis by Clark et al[11] demonstrated the significantly higher clinical utility of GS compared with CMA. Nevertheless, evidence to compare clinical utility between ES and GS remains extremely scarce in literature. A higher diagnostic and clinical utility will not only end the diagnostic trajectory and improve patients' health outcomes but it will also have economic implications on health care systems. Previous systematic review by Schearze et al[18] highlighted the limited health economic evidence in literature to support the widespread use of ES and GS in clinical setting. In the era of budget and resource constraints, the evaluation of cost-effectiveness of providing ES and GS has a principal role in informing efficient and effective health care resource allocation.

Given the drastically increased number of ES and GS publications in the past few years and the recent successful launch of large-scale RDs sequencing programs focusing on diverse populations (eg, The 100,000 Genomes Project led by Genomics England), it is important to evaluate and understand the existing evidence of ES vs GS to guide their use by clinicians in clinical settings.[19-21] To the best of knowledge, there is no existing meta-analysis that compares the diagnostic rate and clinical utility of ES and GS across pediatric and adult populations as well as the number of VUS and health economic outcomes associated with these technologies. There is an urgent need to fill the literature gap by conducting a meta-analysis to provide empirical evidence on the diagnostic rate and clinical utility of ES and GS in pediatric and adult patients across diverse populations.

Materials and Methods

Data sources and search strategy

This meta-analysis was conducted according to the Meta-analyses of Observational Studies in Epidemiology

(MOOSE) and Preferred Reporting Items for Systematic Reviews and the Meta-analyses (PRISMA) guidelines.[22,23] Search terms and Medical Subject Headings (MeSH) related to ES or GS and RDs were used to identify relevant articles in PubMed and Embase between 2011 and 2021. Additional articles were also manually identified by examining reference lists of previously published systematic reviews and meta-analyses. Details of the MOOSE Checklist and search strategy can be found in Supplemental Table 1 and 2, respectively.

Study selection criteria and data extraction

Studies that reported the diagnostic rate of ES or GS were eligible. Diagnostic rate is defined as the percentage of individuals with identified causal variant that could explain patient phenotype, based on evidence, such as mode of inheritance, previous reporting, and functional evidence. Additional study outcomes, including clinical utility, rate of VUS, number of novel genes, health economics data, and diagnostic rate from ES reanalysis, were extracted whenever available. Clinical utility is defined as the percentage of individuals experiencing changes to clinical management following a diagnosis by ES or GS, including, but not limited to, surveillance, referral to specialists, hospitalization, and indication or contraindication of investigations, procedures, surgeries, and medications. Genetic counseling and reproductive planning were not included as part of clinical utility because they were assumed to apply to all types of diagnostic tests. Rate of VUS is defined as the proportion of number of probands with VUS to the total number of probands in the cohort. Health economics data included any assessment or evaluation of cost outcomes, including, but not limited to, cost-effectiveness analysis, cost-utility analysis, cost of care, cost of previous tests, cost-to-diagnosis, cost-savings from changes in clinical management, cost of sequencing methods (singleton vs trio), and participants' out-of-pocket costs. We limited the eligibility to cohorts with a broad range of RDs and undiagnosed diseases. Cohorts of patients with global developmental delay, intellectual disability, or indications of neurologic diseases were also included because these are common presentations for a variety of RDs and genetic diseases. Since there are existing guidelines that are specific for the interpretation of mitochondrial and somatic variants in mitochondrial diseases and cancers, in which they rely on phasing and genotyping that are limited by the current short-read GS technology, cohorts focusing on mitochondrial diseases and cancers were excluded to minimize data heterogeneity that is caused by different interpretation standards. Cohorts focusing on specific diseases or those that affect only 1 body system were also excluded because they may contribute to a higher diagnostic rate with a higher likelihood of genetic etiology. Studies of any age groups, including infant (age 0-12 months), children (age 1-18 years), and adult (>18 years) cohorts were eligible. Other variables were extracted whenever available, including study country/region, population descriptor, sequencing manner (rapid/nonrapid), sequencing family structure (singleton/trio), rate of consanguinity, and unit cost of ES/GS.

Study country/region was identified based on recruitment site. Population descriptor was identified from the original studies, which refers to how the original studies reported their patient race, ethnicity, or ancestry in the cohorts. For studies that reported their cohort to be of >1 race/ethnicity/ancestry or provided detailed breakdown of patient race/ethnicity/ancestry (usually >1 population descriptor in the demographics table), they were categorized as "multiple populations."

Screening of titles, abstracts, full text, and data extraction were performed by 2 researchers independently. Discrepancies were identified and resolved through multiple panel discussions with 2 additional independent investigators. Details of the study inclusion and exclusion criteria were listed in the PICOTS table (Supplemental Table 3).

Quality assessment

Methodological quality of each original study was assessed using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool, which was designed to assess the quality of primary diagnostic accuracy studies and is recommended by the Cochrane Collaboration Diagnostic Accuracy Working Group.[24,25] The tool evaluates the risk of bias across 4 domains: patient sample, index test, reference standard, and study flow and timing. Risk of bias was qualitatively assessed based on signaling questions and was judged as "high," "low," or "unclear." Studies with "low" bias across all domains were deemed as "high-quality" studies. Concerns regarding applicability of the study to the research question were also rated using the same scale for patient sample, index test, and reference standard. Quality of studies was assessed by 2 researchers independently; discrepancies were identified, discussed, and resolved. Risk of bias and applicability of studies were summarized in bar plots.

Statistical analysis

Characteristics of included studies were summarized using descriptive statistics. A random-effects model with the Clopper-Pearson confidence limits was used to obtain pooled estimate and 95% CIs for the meta-analysis. Raw proportions of the diagnostic rate and rate of clinical utility of each ES and GS cohorts were computed and pooled to fit the model. For each comparison, only the relevant subsets of patients reported were retained. Subgroup analyses were conducted to minimize the severe heterogeneity between studies. Subgroup analyses were performed based on age group (infants, children, and adults), indications for testing, sequencing manner,

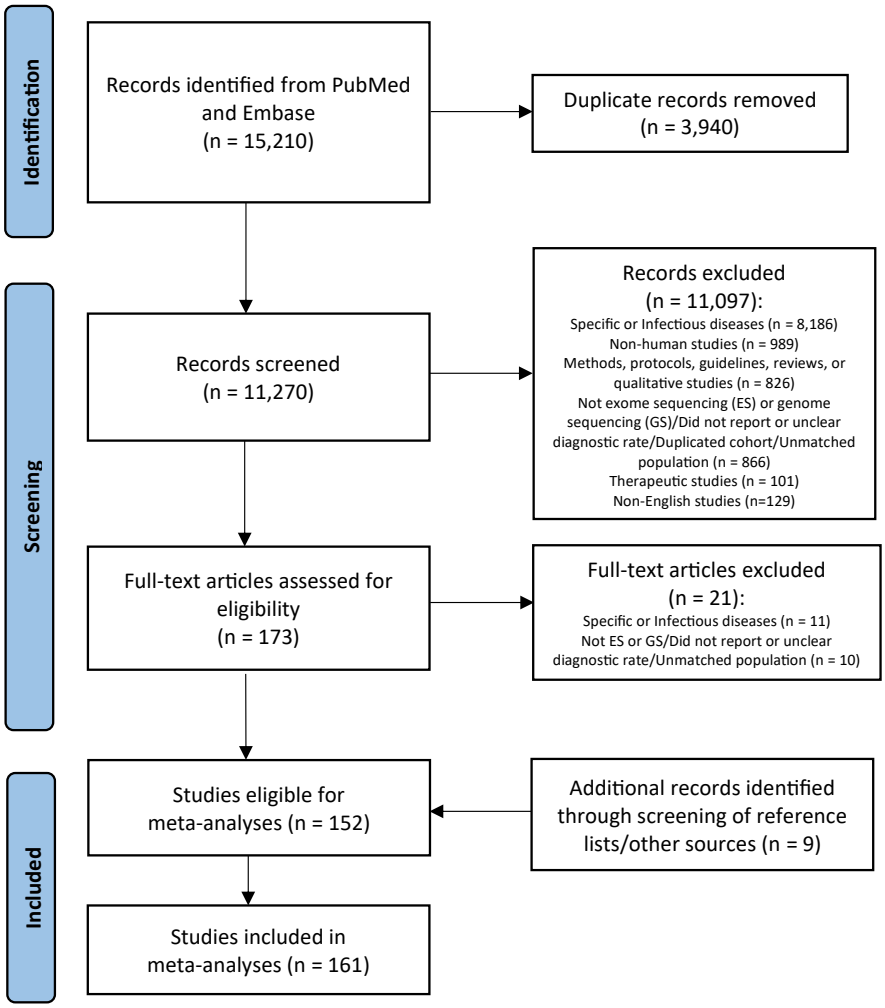

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of meta-analysis articles inclusion. ES, exome sequencing; GS, genome sequencing.

sequencing family structure, and whether variant classification was assessed using the American College of Medical Genetics and Genomics (ACMG) guideline. For within-cohort comparisons, an inverse-weighted random-effects model was used to estimate pooled odds ratios (ORs). OR is a measure of association between exposure and outcome (diagnostic rate/rate of clinical utility) and is used to compare the relative odds of occurrence of the outcome of interest, given exposure to the variable of interest. OR >1 indicates a higher odds of outcome for the exposure; OR <1 indicates a lower odds of outcome for the exposure; and OR = 0 indicates odds of outcome not affected by the exposure. Between-study heterogeneity was assessed using between-study variance (τ2), I^2 statistic, and Cochran's Q-test. Meta-regression was used to explore the association between diagnostic rate/rate of clinical utility and continuous variables, including number of probands, rate of consanguinity, and year of study publication. Association between rate of VUS and year of study publication was also evaluated using meta-regression. Sensitivity analysis was performed among "high-quality studies" assessed by QUADAS-2. Forest plots and bubble plots were used to summarize the findings of meta-analysis and meta-regression. The significant level was set at $P < .05$ for 2 tails for all analyses. All statistical analyses were performed using STATA version 17.[26]

Unit cost estimates for ES and GS testing were extracted. In cases which the cost year was not stated, the latest date at which the costing must have been conducted was used (eg, date of manuscript submission). Cost estimates were converted to US dollars and were adjusted for inflation using the GDP implicit price deflators to uprate the cost to 2021 prices.

Results

A total of 15,210 records were identified by searches from PubMed and Embase, of which 3940 were duplicates, leaving 11,270 records for screening (Figure 1). Following title and abstract screening, 173 full-text articles were assessed, 152 of these fulfilled inclusion criteria. Hand-searching of reference lists retrieved an additional 9

Table 1 Characteristics of included ES and GS studies

Study	Year	Country/ Region	RD	Number of Proband	Rapid/ Nonrapid	Age (median/ mean)	Age Group	ES/ GS	Population Descriptor	Diagnostic Rate[a]	Singleton/ Trio	Rate of Clinical Utility[b]	Rate of Consanguinity	Number of Novel Genes	VUS Rate[c]	Cost Analysis?	Type of Cost Analysis	Unit Cost in USD (2021 prices)[d]
Yang et al[27]	2021	China	Diverse	2,303	Nonrapid	N/A	Infant	ES	N/A	12%	S	47%	0%	N/A	N/A	N	N/A	N/A
Brockman et al[28]	2021	United States	Diverse	99	Nonrapid	40.1 y	All	GS	Multiple populations	16%	Both	N/A	N/A	N/A	35%	N	N/A	N/A
de Ligt et al[29]	2012	Netherlands	NDD	100	Nonrapid	N/A	All	ES	N/A	16%	T	N/A	N/A	24	N/A	N	N/A	N/A
Klee et al[30]	2021	United States	Diverse	1101	Nonrapid	18 y	All	ES	N/A	16%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Posey et al[31]	2016	United States	Diverse	486	Nonrapid	N/A	Adult	ES	Multiple populations	17%	S	N/A	5%	N/A	N/A	N	N/A	N/A
Hou et al[32]	2020	United States	Diverse	1190	Nonrapid	54 y	Adult	GS	Multiple populations	17%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Guo et al[33]	2021	United States	Neuro	427	Nonrapid	N/A	Adult	ES	N/A	18%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Baker et al[34]	2019	United States	Diverse	300	Nonrapid	N/A	All	ES	N/A	20%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
East et al[35]	2021	United States	Diverse	176	Nonrapid	Ped: 5 y Adult: 35 y	All	GS	Multiple populations	20%	T	N/A	N/A	N/A	24%	N	N/A	N/A
Dai et al[36]	2021	China	NDD	35	Nonrapid	N/A	Ped	ES	Chinese	20%	N/A	N/A	N/A	N/A	N/A	N	N/A	N/A
Bertoli-Avella et al[37]	2021	Saudi Arabia	Diverse	1007	Nonrapid	N/A	All	GS	Multiple populations	21%	Both	N/A	51%	N/A	24%	N	N/A	N/A
French et al[38]	2019	United Kingdom	Diverse	195	Rapid	NICU: 12 d Other: 24 mo	Ped	GS	N/A	21%	Both	58%	N/A	N/A	N/A	N	N/A	N/A
Eratne et al[39]	2021	Australia	Neuro	160	Nonrapid	52 y	All	ES	N/A	21%	N/A	68%	N/A	N/A	N/A	N	N/A	N/A
Taylor et al[40]	2015	United Kingdom	Diverse	156	Nonrapid	N/A	All	GS	N/A	21%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Bruel et al[41]	2019	France	Diverse	313	Nonrapid	9 y	All	ES	Multiple populations	23%	S	N/A	4%	17	8%	N	N/A	N/A
van der Sluijs et al[42]	2019	Netherlands	Diverse	31	Nonrapid	3 d	Infant	ES	N/A	23%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Dimmock et al [e43,44]	2020	United States	Diverse	213	Rapid	5 d	Infant	ES/GS	Multiple populations	24%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Splinter et al[45]	2018	United States	Diverse	360	Nonrapid	29 y	All	ES/GS	Multiple populations	24%	N/A	N/A	N/A	15	N/A	Y	Cost of care	N/A
Thiffault et al[46]	2019	United States	Diverse	80	Nonrapid	6.9 y	Ped	GS	N/A	24%	Both	N/A	3%	N/A	6%	N	N/A	N/A
Zhu et al[47]	2015	United States	Diverse	119	Nonrapid	N/A	N/A	ES	Multiple populations	24%	T	14%	8%	N/A	N/A	N	N/A	N/A
Yang et al[48]	2014	United States	Diverse	2,000	Nonrapid	6 y	All	ES	N/A	25%	N/A	N/A	2%	N/A	N/A	N	N/A	N/A
Yang et al[49]	2013	United States	Diverse	250	Nonrapid	N/A	Ped	ES	N/A	25%	N/A	48%	N/A	N/A	N/A	N	N/A	N/A
Wang et al[50]	2020	China	NDD	95	Nonrapid	N/A	Ped	ES/GS	Chinese	25%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Liu et al[51]	2021	China	Diverse	169	Nonrapid	10.5 mo	Ped	ES	N/A	25%	Both	70%	N/A	N/A	N/A	N	N/A	N/A
Smedley et al[19]	2021	United Kingdom	Diverse	2,183	Nonrapid	35 y	All	GS	Multiple populations	25%	Both	25%	3%	579	10%	Y	Cost of care	N/A
Nambot et al[52]	2018	France	Diverse	416	Nonrapid	10.5 y	All	ES	N/A	25%	S	N/A	9%	N/A	9%	N	N/A	N/A
Prasad et al[53]	2018	United States	NDD	53	Nonrapid	N/A	Ped	ES	N/A	26%	N/A	57%	N/A	N/A	N/A	N	N/A	N/A
Lee et al[54]	2014	United States	Diverse	814	Nonrapid	N/A	All	ES	N/A	26%	Both	N/A	6%	N/A	28%	N	N/A	N/A
Chérot et al[55]	2017	France	NDD	216	Nonrapid	N/A	All	ES	N/A	26%	Both	N/A	8%	N/A	N/A	N	N/A	N/A
Bowling et al[56]	2017	United States	NDD	371	Nonrapid	N/A	All	ES/GS	N/A	26%	N/A	N/A	N/A	N/A	N/A	N	N/A	N/A
Basel-Salmon et al[57]	2019	Israel	Diverse	114	Nonrapid	N/A	Ped	ES	N/A	26%	Both	N/A	14%	N/A	N/A	N	N/A	N/A
Abe-Hatano et al[21]	2021	Japan	NDD	45	Nonrapid	N/A	Ped	GS	Japanese	27%	T	N/A	N/A	N/A	N/A	N	N/A	N/A
Wang et al[58]	2021	China	Diverse	588	Nonrapid	N/A	Infant	ES/GS		27%	Both	N/A	N/A	N/A	4%	N	N/A	N/A
Smith et al[59]	2020	United States	Diverse	368	Nonrapid	N/A	Infant	ES	Multiple populations	27%	Both	49%	N/A	N/A	N/A	Y	Cost of care	N/A
Sainio et al[60]	2021	Finland	Neuro	100	Nonrapid	49 y	Adult	ES	Predominantly Finnish	27%	S	N/A	0%	N/A	18%	Y	Cost of previous tests	N/A
Kim et al[61]	2019	Korea	Diverse	52	Nonrapid	6.7 y	All	ES	N/A	29%	T	N/A	N/A	N/A	N/A	N	N/A	N/A
Hu et al[62]	2018	China	Diverse	1323	Nonrapid	5.25 y	Ped	ES	Chinese	29%	S	45%	N/A	N/A	N/A	Y	Cost-to-diagnosis	N/A
Lazaridis et al[63]	2016	United States	Diverse	51	Nonrapid	21 y	All	ES	N/A	29%	N/A	N/A	N/A	N/A	N/A	Y	Cost-to-diagnosis	$7839 (T)
Vissers et al[64]	2017	Netherlands	Neuro	150	Nonrapid	5.6 y	Ped	ES	N/A	29%	Both	N/A	N/A	N/A	N/A	Y	Cost-to-diagnosis	$2240 (S) $4355 (T)
Monroe et al[65]	2016	Netherlands	NDD	17	Nonrapid	3 y	Ped	ES	N/A	29%	T	N/A	0%	N/A	N/A	Y	CEA	$4492 (S)
Retterer et al[66]	2016	United States	Diverse	3040	Nonrapid	11.4 y	All	ES	N/A	29%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A

(continued)

Table 1 Continued

Study	Year	Country/ Region	RD	Number of Proband	Rapid/ Nonrapid	Age (median/ mean)	Age Group	ES/ GS	Population Descriptor	Diagnostic Rate[a]	Singleton/ Trio	Rate of Clinical Utility[b]	Rate of Consanguinity	Number of Novel Genes	VUS Rate[c]	Cost Analysis?	Type of Cost Analysis	Unit Cost in USD (2021 prices)[d]
Sawyer et al[67]	2016	Canada	Diverse	362	Nonrapid	3 y	All	ES	Canadian	29%	Both	6%	21%	N/A	N/A	N	N/A	N/A
Ziats et al[68]	2020	United States	Diverse	523	Nonrapid	21.5 mo	All	ES	N/A	30%	N/A	N/A	N/A	N/A	N/A	N	N/A	N/A
Valencia et al[69]	2015	United States	Diverse	40	Nonrapid	7 y	All	ES	Multiple populations	30%	Both	100%	N/A	N/A	N/A	N	N/A	N/A
Carey et al[70]	2020	United States	Neuro	10	Rapid	N/A	Ped	ES	Multiple populations	30%	T	100%	N/A	N/A	N/A	N	N/A	N/A
Farwell et al[71]	2015	United States	Diverse	500	Nonrapid	11.21 y	All	ES	N/A	30%	Both	N/A	N/A	N/A	9%	N	N/A	N/A
Bowling et al[72]	2021	United States	Diverse	367	Nonrapid	31 d	Infant	GS	Multiple populations	30%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Ewans et al[73]	2018	Australia	Diverse	37	Nonrapid	N/A	All	ES	N/A	30%	Both	9%	N/A	N/A	N/A	Y	CEA	$1319 (S) $3462 (T)
Costain et al[74]	2020	Canada	Diverse	49	Nonrapid	7 y	Ped	GS	Multiple populations	31%	Both	73%	10%	3	N/A	N	N/A	N/A
Petrikin et al[75]	2018	United States	Diverse	32	Rapid	25 d	Infant	GS	Multiple populations	31%	T	100%	3%	N/A	N/A	N	N/A	N/A
Trujillano et al[76]	2017	Multiple	Diverse	1000	Nonrapid	N/A	All	ES	Multiple populations	31%	Both	N/A	45%	N/A	N/A	N	N/A	N/A
Chung et al[77]	2020	Hong Kong	Diverse	102	Rapid	3.4 y	Ped	ES	Predominantly Chinese	31%	Both	88%	2%	N/A	N/A	Y	Cost-savings from changes in clinical management	$1285
Trinh et al[78]	2019	Germany	NDD	4351	Nonrapid	7.75 y	All	ES	N/A	31%	N/A	N/A	43%	N/A	78%	N	N/A	N/A
Medne et al[79]	2021	United States	Diverse	354	Nonrapid	15 d	Infant	GS	Multiple populations	31%	T	75%	N/A	N/A	N/A	N	N/A	N/A
Fitzgerald et al[80]	2015	United Kingdom	NDD	1133	Nonrapid	5.5 y	Ped	ES	Predominantly Northwest European	31%	T	N/A	4%	12	N/A	N	N/A	N/A
Quaio et al[81]	2020	Brazil	Diverse	500	Nonrapid	N/A	All	ES	Brazilian	32%	T	49%	1%	N/A	0%	N	N/A	N/A
Taylor et al[82]	2019	United Kingdom	Diverse	76	Nonrapid	6 y	All	ES	N/A	32%	Both	N/A	N/A	N/A	N/A	Y	Cost estimation of multi-disciplinary team process	$1077
Iglesias et al[83]	2014	United States	Diverse	115	Nonrapid	N/A	All	ES	Multiple populations	32%	Both	35%	11%	4	N/A	N	N/A	N/A
Powis et al[84]	2020	United States	Diverse	41	Rapid	N/A	Ped	ES	Multiple populations	32%	N/A	N/A	N/A	1	N/A	N	N/A	N/A
Blake B et al[85]	2021	United States	Neuro	22	Nonrapid	20 y	All	GS	N/A	32%	T	N/A	9%	N/A	50%	N	N/A	N/A
Thevenon et al[86]	2016	France	NDD	43	Nonrapid	14 y	All	ES	N/A	33%	T	29%	12%	1	N/A	N	N/A	N/A
Nair et al[87]	2018	Lebanon	Diverse	167	Nonrapid	N/A	Ped	ES	Lebanese	34%	S	N/A	41%	N/A	N/A	N	N/A	N/A
Stavropoulos et al[7]	2016	Canada	Diverse	100	Nonrapid	5.5 y	Ped	GS	N/A	34%	S	44%	8%	N/A	N/A	N	N/A	N/A
Reuter et al[88]	2019	United States	Diverse	66	Nonrapid	14.6 y	All	ES	Multiple populations	35%	Both	61%	N/A	N/A	N/A	N	N/A	N/A
Thuriot et al[89]	2018	Canada	Diverse	51	Nonrapid	N/A	All	ES	N/A	35%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Bick et al[90]	2017	United States	Diverse	22	Nonrapid	6.9 y	All	GS	N/A	36%	N/A	75%	N/A	4	N/A	N	N/A	N/A
Tran Mau-Them et al[91]	2021	France	Diverse	324	Nonrapid	N/A	N/A	ES	N/A	36%	N/A	N/A	N/A	19	N/A	Y	Cost of singleton vs trio ES	$500
Wu et al[92]	2021	China	Diverse	202	Nonrapid	N/A	Infant	ES / GS	Chinese	37%	Both	N/A	N/A	N/A	10%	Y	Cost-savings from changes in clinical management	N/A
Bhatia et al[93]	2021	Singapore	Diverse	196	Nonrapid	N/A	All	ES / GS	Multiple populations	37%	Both	27%	N/A	N/A	8%	N	N/A	N/A
Meng et al[94]	2017	United States	Diverse	278	Nonrapid	28.5 d	Infant	ES	N/A	37%	Both	52%	N/A	N/A	N/A	N	N/A	N/A
Jiao et al[95]	2019	China	Neuro	172	Nonrapid	29.7 mo	Ped	ES	N/A	37%	Both	>8%	0%	N/A	N/A	N	N/A	N/A
Powis et al[96]	2018	United States	Diverse	66	Nonrapid	N/A	Infant	ES	Multiple populations	38%	T	N/A	2%	1	N/A	N	N/A	N/A
Bergant et al[97]	2018	Serbia	Diverse	1059	Nonrapid	N/A	All	ES	N/A	38%	N/A	N/A	N/A	2	N/A	N	N/A	N/A

(continued)

Table 1 Continued

Study	Year	Country/ Region	RD	Number of Proband	Rapid/ Nonrapid	Age (median/ mean)	Age Group	ES/ GS	Population Descriptor	Diagnostic Rate[a]	Singleton/ Trio	Rate of Clinical Utility[b]	Rate of Consanguinity	Number of Novel Genes	VUS Rate[c]	Cost Analysis?	Type of Cost Analysis	Unit Cost in USD (2021 prices)[d]
Aaltio et al[3]	2021	Finland	Neuro	48	Nonrapid	5.4 y	Ped	ES	N/A	38%	S	N/A	0%	N/A	N/A	Y	CEA	$1628
Grunseich et al[98]	2021	United States	Neuro	66	Nonrapid	48 y	All	ES	N/A	39%	N/A	N/A	N/A	N/A	N/A	N	N/A	N/A
Anazi et al[99]	2017	Saudi Arabia	NDD	232	Nonrapid	N/A	Ped	ES	N/A	39%	N/A	N/A	82%	3	N/A	N	N/A	N/A
Pode-Shakked et al[100]	2021	Israel	Diverse	280	Nonrapid	9.3 y	All	ES	Jewish	39%	T	N/A	4%	N/A	26%	N	N/A	N/A
Dimmock et al[101]	2021	United States	Diverse	184	Rapid	N/A	Infant	GS	Multiple populations	40%	T	78%	N/A	N/A	11%	Y	Cost-savings from changes in clinical management	$9492
Stranneheim et al[102]	2021	Sweden	Diverse	3219	Nonrapid	N/A	All	GS	Swedish	40%	Both	N/A	N/A	17	N/A	N	N/A	N/A
Tan et al[103]	2019	Australia	Diverse	30	Nonrapid	21.5 mo	All	ES	N/A	40%	Both	N/A	N/A	N/A	N/A	Y	Cost of singleton vs trio ES	$878
Shieh et al[104]	2021	United States	Diverse	50	Nonrapid	N/A	All	GS	N/A	40%	N/A	N/A	N/A	N/A	N/A	N	N/A	N/A
Córdoba et al[105]	2018	Argentina	Neuro	40	Nonrapid	23 y	All	ES	Argentine	40%	N/A	N/A	N/A	N/A	N/A	Y	Cost of previous tests	$1099
Mahfouz et al[106]	2020	United Arab Emirates	Diverse	51	Nonrapid	N/A	Ped	ES	Predominantly Emirati	41%	Both	62%	43%	N/A	N/A	N	N/A	N/A
Mak et al[107]	2018	Hong Kong	Diverse	104	Nonrapid	4.1 y	All	ES	Chinese	41%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Lionel et al[8]	2018	Canada	Diverse	103	Nonrapid	N/A	Ped	GS	Multiple populations	41%	S	N/A	9%	N/A	N/A	Y	Cost of previous tests	N/A
Srivastava et al[108]	2014	United States	NDD	78	Nonrapid	8.6 y	All	ES	N/A	41%	T	66%	12%	N/A	41%	N	N/A	N/A
Xiang et al[109]	2021	China	NDD	17	Nonrapid	5.6 y	Ped	ES	N/A	41%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Dong et al[110]	2020	China	NDD	1090	Nonrapid	N/A	Ped	ES	Chinese	41%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Zhu et al[111]	2020	China	Diverse	257	Nonrapid	8 d	Infant	ES	Chinese	42%	Both	N/A	1%	N/A	N/A	N	N/A	N/A
Mahler et al[112]	2019	Germany	NDD	50	Nonrapid	2.5 y	Ped	ES	Multiple populations	42%	T	81%	18%	N/A	N/A	N	N/A	N/A
Kim et al[113]	2019	Korea	NDD	108	Nonrapid	With Dx: 4 y W/o Dx: 4.6 y	Ped	ES	N/A	42%	Both	N/A	N/A	N/A	30%	N	N/A	N/A
Mestek-Boukhibar et al[114]	2018	United Kingdom	Diverse	24	Rapid	15.9 mo	Ped	GS	N/A	42%	T	30%	N/A	N/A	N/A	N	N/A	N/A
Kernohan et al[115]	2018	Canada	Diverse	12	Nonrapid	N/A	Infant	ES	N/A	42%	T	N/A	N/A	4	N/A	N	N/A	N/A
Yeung et al[116]	2020	Australia	Diverse	92	Nonrapid	19.8 mo	Ped	ES	N/A	42%	S	74%	N/A	N/A	N/A	Y	CEA	$2227
Gilissen et al[117]	2014	Netherlands	NDD	50	Nonrapid	N/A	All	GS	N/A	42%	T	N/A	N/A	8	N/A	N	N/A	N/A
Xiao et al[118]	2018	China	NDD	33	Nonrapid	3 y	Ped	ES	N/A	42%	N/A	N/A	6%	N/A	N/A	N	N/A	N/A
Mena et al[119]	2020	Dominican Republic	Diverse	40	Nonrapid	5 y	All	ES	Dominicans	43%	T	N/A	N/A	N/A	33%	N	N/A	N/A
Farnaes et al[120]	2018	United States	Diverse	42	Rapid	62 d	Infant	GS	Multiple populations	43%	Both	72%	2%	N/A	N/A	Y	Cost-savings from changes in clinical management	$9102
Monies et al[121]	2017	Saudi Arabia	Diverse	347	Nonrapid	N/A	N/A	ES	Indigenous Arabs	43%	Both	N/A	45%	75	N/A	N	N/A	N/A
Cloney et al[122]	2021	Australia	Diverse	144	Nonrapid	N/A	Ped	ES/GS	N/A	43%	T	N/A	7%	N/A	N/A	N	N/A	N/A
Seo et al[123]	2020	Korea	Diverse	330	Nonrapid	11.9 y	All	ES	N/A	43%	S	2%	0%	N/A	59%	N	N/A	N/A
Baldridge et al[124]	2017	United States	Diverse	155	Nonrapid	6 y	All	ES	Multiple populations	43%	T	12%	4%	N/A	N/A	Y	Out-of-pocket costs	N/A
Monies et al[125]	2019	Saudi Arabia	Diverse	2219	Nonrapid	N/A	All	ES	Saudi Arabian	43%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Zhang et al[126]	2021	China	Diverse	1360	Nonrapid	4.7 y	All	ES	Chinese	44%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Lee et al[127]	2021	Taiwan	Neuro	214	Nonrapid	71.7 mo	Ped	GS	N/A	44%	S	23%	N/A	N/A	N/A	N	N/A	N/A
Gao et al[128]	2019	China	NDD	54	Nonrapid	15 mo	Infant	ES	N/A	44%	T	N/A	N/A	N/A	N/A	N	N/A	N/A
Marques Matos et al[129]	2019	Portugal	Neuro	34	Nonrapid	18 y	All	ES	N/A	44%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Sanford et al[130]	2019	United States	Diverse	38	Rapid	2.96 y	Ped	GS	Multiple populations	45%	Both	82%	N/A	N/A	N/A	N	N/A	N/A
Bourchany et al[131]	2017	France	NDD	29	Nonrapid	5.8 y	All	ES	N/A	45%	S	17%	10%	N/A	N/A	N	N/A	N/A
Soden et al[132]	2014	United States	NDD	100	Rapid	83.8 mo	Infant	ES/GS	N/A	45%	T	N/A	5%	N/A	N/A	Y	Cost of previous tests	N/A
Scholz et al[133]	2021	Germany	Diverse	61	Nonrapid	68 d	Infant	ES	N/A	46%	Both	75%	13%	N/A	N/A	N	N/A	N/A
Kamolvisit et al[134]	2021	Thailand	Diverse	54	Rapid	3 mo	All	ES	Thai	46%	Both	96%	0%	N/A	N/A	N	N/A	N/A

(continued)

Table 1 Continued

Study	Year	Country/ Region	RD	Number of Proband	Rapid/ Nonrapid	Age (median/ mean)	Age Group	ES/ GS	Population Descriptor	Diagnostic Rate[a]	Singleton/ Trio	Rate of Clinical Utility[b]	Rate of Consanguinity	Number of Novel Genes	VUS Rate[c]	Cost Analysis?	Type of Cost Analysis	Unit Cost in USD (2021 prices)[d]
Eaton et al[135]	2020	Canada	Diverse	116	Nonrapid	N/A	N/A	ES	Canadian	46%	Both	N/A	60%	13	18%	N	N/A	N/A
Hong et al[136]	2019	China	Diverse	17	Nonrapid	4.4 mo	Infant	ES	Chinese	47%	N/A	N/A	N/A	N/A	47%	N	N/A	N/A
Liu et al[137]	2021	China	Diverse	58	Nonrapid	2.2 y	Ped	ES	N/A	47%	Both	41%	N/A	N/A	10%	N	N/A	N/A
Kosaki et al[138]	2020	Japan	Diverse	360	Nonrapid	N/A	All	ES	Japanese	48%	S	54%	N/A	N/A	N/A	Y	Cost-to-diagnosis	N/A
Wang et al[139]	2020	China	Diverse	130	Rapid	N/A	Infant	GS	Chinese	48%	N/A	48%	N/A	N/A	9%	N	N/A	$1686 per family (OTGS) $1623 per family (ES)
Al-Dewik et al[140]	2019	Qatar	Diverse	509	Nonrapid	N/A	All	ES	Multiple populations	48%	T	N/A	65%	11	N/A	N	N/A	N/A
Nolan et al[141]	2016	United States	Neuro	50	Nonrapid	7.4 y	Ped	ES	Multiple populations	48%	T	50%	7%	N/A	N/A	Y	Cost of previous tests	N/A
Alfares et al[142]	2017	Saudi Arabia	Diverse	454	Nonrapid	N/A	All	ES	Saudi Arabian	49%	Both	N/A	72%	N/A	N/A	N	N/A	N/A
Kuperberg et al[143]	2016	Israel	Neuro	57	Nonrapid	7 y	Ped	ES	N/A	49%	T	18%	5%	N/A	N/A	N	N/A	N/A
Liu et al[144]	2021	China	NDD	94	Nonrapid	24.7 mo	Ped	ES	N/A	49%	Both	N/A	N/A	N/A	N/A	N	N/A	N/A
Denomme-Pichon et al[145]	2021	France	Neuro	37	Nonrapid	27 d	Ped	GS	N/A	49%	T	N/A	11%	N/A	22%	N	N/A	N/A
Brunet et al[146]	2021	Multiple	NDD	231	Nonrapid	5.3 y	All	ES	N/A	50%	T	N/A	1%	6	3%	N	N/A	N/A
Need et al[147]	2012	United States	Diverse	12	Nonrapid	N/A	All	ES	Multiple populations	50%	T	N/A	N/A	N/A	N/A	N	N/A	N/A
Lunke et al[148]	2020	Australia	Diverse	108	Rapid	28 d	Ped	ES	Predominantly Australian	51%	T	76%	24%	2	N/A	N	N/A	N/A
Strauss et al[149]	2018	United States	Diverse	72	Nonrapid	6.9 y	All	ES	Old Order Amish and Mennonite	51%	T	N/A	N/A	5	N/A	N	N/A	N/A
Hengel et al[150]	2020	Multiple	Neuro	83	Nonrapid	N/A	N/A	ES	Palestinian and Israeli Arabs	51%	N/A	10%	72%	N/A	N/A	N	N/A	N/A
Eldomery et al[151]	2017	United States	Diverse	74	Nonrapid	N/A	N/A	ES	N/A	51%	Both	N/A	N/A	8	N/A	N	N/A	N/A
Marinakis et al[152]	2021	Greece	Diverse	257	Nonrapid	N/A	Ped	ES	N/A	51%	S	N/A	N/A	N/A	3%	N	N/A	N/A
Chen et al[153]	2021	Taiwan	NDD	49	Nonrapid	6 y	Ped	ES	N/A	51%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Sobering et al[154]	2020	United States	Diverse	27	Nonrapid	N/A	All	ES	Multiple populations	52%	Both	N/A	4%	N/A	7%	N	N/A	N/A
Freed et al[155]	2020	United States	Diverse	46	Rapid	297 d	Ped	ES	N/A	52%	T	52%	N/A	N/A	N/A	N	N/A	N/A
Guo et al[156]	2021	China	NDD	21	Nonrapid	45.4 mo	Ped	ES	N/A	52%	T	N/A	N/A	N/A	N/A	N	N/A	N/A
Tan et al[157]	2017	Australia	Diverse	44	Nonrapid	28 mo	All	ES	N/A	52%	S	26%	N/A	N/A	N/A	Y	CEA	$1659
Hiraide et al.[158]	2021	Japan	NDD	101	Nonrapid	4 y	All	ES	Japanese	53%	T	N/A	N/A	N/A	N/A	N	N/A	N/A
Stark et al[159]	2018	Australia	Diverse	40	Rapid	28 d	Ped	ES	N/A	53%	S	57%	20%	N/A	N/A	Y	CEA	$3347
Wu et al[160]	2019	Taiwan	Diverse	40	Nonrapid	2.2 y	Ped	ES	N/A	53%	T	81%	N/A	N/A	N/A	N	N/A	N/A
Salvatore et al[161]	2020	Italy	Diverse	13	Nonrapid	N/A	All	ES	N/A	54%	T	N/A	31%	N/A	N/A	N	N/A	N/A
Tan et al[162]	2019	Australia	Diverse	13	Nonrapid	15 d	Infant	ES	N/A	54%	S	N/A	N/A	N/A	N/A	N	N/A	N/A
Dillon et al[163]	2018	Australia	Diverse	145	Nonrapid	N/A	Ped	ES	N/A	54%	S	N/A	16%	N/A	N/A	Y	Cost-to-diagnosis	$1691
Muthaffar OY[164]	2020	Saudi Arabia	Neuro	26	Nonrapid	4.8 y	Ped	ES	Saudi Arabian	54%	S	N/A	69%	N/A	23%	N	N/A	N/A
Beuschel et al[165]	2021	United States	Diverse	24	Rapid	149.7 d	Ped	GS	N/A	54%	S	84%	N/A	N/A	25%	N	N/A	N/A
Mergnac et al[166]	2021	France	Diverse	128	Nonrapid	6.5 y	Ped	ES	N/A	55%	N/A	N/A	N/A	N/A	15%	N	N/A	N/A
Usha Devi et al[167]	2021	India	Diverse	36	Nonrapid	13.5 d	Infant	ES	Indian	56%	S	30%	36%	N/A	14%	N	N/A	N/A
Stojanovic et al[168]	2020	Serbia	NDD	88	Nonrapid	N/A	Ped	ES	N/A	56%	S	16%	1%	N/A	9%	N	N/A	N/A
Willig et al[169]	2015	United States	Diverse	35	Rapid	26 d	Infant	GS	N/A	57%	T	65%	3%	N/A	N/A	N	N/A	N/A
Stark et al [e170,171]	2016	Australia	Diverse	80	Nonrapid	8 mo	Infant	ES	N/A	58%	S	33%	21%	N/A	N/A	Y	CEA of ES reanalysis; CUA of clinical management changes	N/A
Gubbels et al[172]	2020	United States	Diverse	50	Rapid	13 d	Infant	ES	N/A	58%	T	83%	N/A	2	N/A	N	N/A	N/A
Yavarna et al[173]	2015	Qatar	Diverse	149	Nonrapid	N/A	All	ES	Predominantly Arabs	60%	T	N/A	74%	N/A	N/A	N	N/A	N/A
Weiss et al[174]	2018	Israel	Diverse	34	Nonrapid	N/A	All	ES	N/A	62%	T	N/A	56%	10	N/A	N	N/A	N/A
Liu et al[175]	2019	China	Diverse	16	Nonrapid	N/A	All	GS	Chinese	63%	T	N/A	N/A	2	N/A	N	N/A	N/A

(continued)

Table 1 Continued

Study	Year	Country/ Region	RD	Number of Proband	Rapid/ Nonrapid	Age (median/ mean)	Age Group	ES/ GS	Population Descriptor	Diagnostic Rate[a]	Singleton/ Trio	Rate of Clinical Utility[b]	Rate of Consanguinity	Number of Novel Genes	VUS Rate[c]	Cost Analysis?	Type of Cost Analysis	Unit Cost in USD (2021 prices)[d]
Järvelä et al[176]	2021	Finland	NDD	39	Nonrapid	N/A	All	ES	Finnish	64%	T	N/A	8%	N/A	10%	N	N/A	N/A
Scocchia et al[177]	2019	Mexico	Diverse	60	Nonrapid	7.6 y	Ped	GS	N/A	68%	Both	49%	N/A	N/A	N/A	N	N/A	N/A
Tarailo-Graovac et al[178]	2016	Canada	Neuro	41	Nonrapid	5.9 y	All	ES	Multiple populations	68%	Both	44%	0%	2	N/A	N	N/A	N/A
Wang et al[179]	2020	China	Diverse	33	Rapid	56 d	Infant	ES	N/A	70%	T	43%	N/A	N/A	N/A	N	N/A	N/A
Śmigiel et al[180]	2020	Poland	Diverse	18	Rapid	N/A	Infant	ES	N/A	72%	S	61%	N/A	2	N/A	N	N/A	N/A
Range				10- 4351						12-72%		2-100%	0 - 82%	1-579	0-78%			ES singleton: $500- 2240
Total/Mean		31		49,180						39%		52%	18%		21%			

CEA, cost-effectiveness analysis; *CUA*, cost-utility analysis; *Diverse*, diverse indications; *dx*, diagnostic rate; *ES*, exome sequencing; *GS*, genome sequencing; *moN*. no; *N/A*, not applicable; *NDD*, neurodevelopmental disorder; *Neuro*, neurologic indications; *NICU*, neonatal intensive care unit; *OTGS*, optimal trio genome sequencing, *Ped*, pediatric; *RD*, rare diseases; *S*, singleton; *T*, trio; *USD*, US dollar; *VUS*, variants of unknown significance; *W/o*, without; *Y*, yes.

[a]The reported proportion of the number of probands with molecular diagnosis to the number of probands tested.

[b]Excluding genetic counseling and reproductive planning.

[c]The proportion of the number of probands with VUS to the total number of probands in the cohort.

[d]Cost estimates were converted to US dollars and adjusted for inflation using the GDP implicit price deflators to uprate the cost to 2021 prices.

[e]Outcomes are merged with another publication of the same cohort.

relevant publications. Overall, 161 studies, featuring 159 cohorts and 50,417 probands, met eligibility and were included in data analysis.[3,7,8,19,21,27-182]

Study and patient characteristics

The 159 cohorts were diverse in their patient representations (Table 1, Supplemental Table 4). These articles were published between 2012 and 2021 and originated from 31 countries/regions around the world, with 38% from North America (n = 60), 31% from Asia (n = 50), 21% from Europe (n = 34), 7% from Australia (n = 11), 1% from South America (n = 2), and 1% from multiple regions (n = 2). The study populations consisted of exclusively pediatric patients (including infants and children) (50%; n = 80), exclusively adult patients (3%; n = 4), a mixture of pediatric and adult patients (43%; n = 69), or the age distribution was not described by the authors (4%; n = 6). Majority of cohorts had diverse indications for testing (70%; n = 111). Thirty cohorts (19%) included patients with neurodevelopmental disorders (NDDs), and 18 cohorts (11%) included patients with neurological indications. The sample size varied from 10 to 4351 probands. Thirty-one of the cohorts (19%) focused on GS, 117 on ES (74%), 9 (6%) reported both ES and GS, and 2 (1%) exclusively focused on reanalysis of ES.[181,182]

Diagnostic rate of ES and GS

The pooled diagnostic rate of ES was 0.38 (95% CI 0.36-0.40, 126 studies, n = 38,277, I^2 = 95%), qualitatively greater than that of GS (0.34, 95% CI 0.30-0.38, 40 studies, n = 11,207, I^2 = 95%). However, difference between the 2 was not statistically significant (Supplemental Figure 1, P = .10). Only 9 studies, featuring 2269 probands, compared ES and GS within the cohorts. The odds of a diagnosis by GS was 1.2 times greater than that of ES (95% CI 0.79-1.83, I^2 = 68%, P = .38) (Supplemental Figure 2).[43,45,50,56,58,92,93,122,132]

Subgroup comparisons of diagnostic rate

The overall pooled diagnostic rate among pediatric patients (including infants and children) (0.40, 95% CI 0.37-0.43, 79 studies, n = 13,796, I^2 = 91%) was significantly higher than that of adult patients (0.18, 95% CI 0.16-0.19, 4 studies, n = 2203, I^2 = 0%) (Supplemental Figure 3, P < .01), regardless of whether it was analyzed using ES (Supplemental Figure 4) or GS (Supplemental Figure 5). It was found that the diagnostic rate among infants only (0.41, 95% CI 0.35-0.46, 27 studies, n = 5,924, I^2 = 94%) was also significantly higher compared with that of adult patients (P < .01). A total of 10 studies, comprising 1905 probands, compared diagnostic rate among pediatric vs adult patients within cohorts.[28,68,71,81-83,86,88,134,154] Nine studies made use of ES, and 1 made use of GS as their sequencing technology. Pediatric patients had 1.6-times odds of a diagnosis compared with

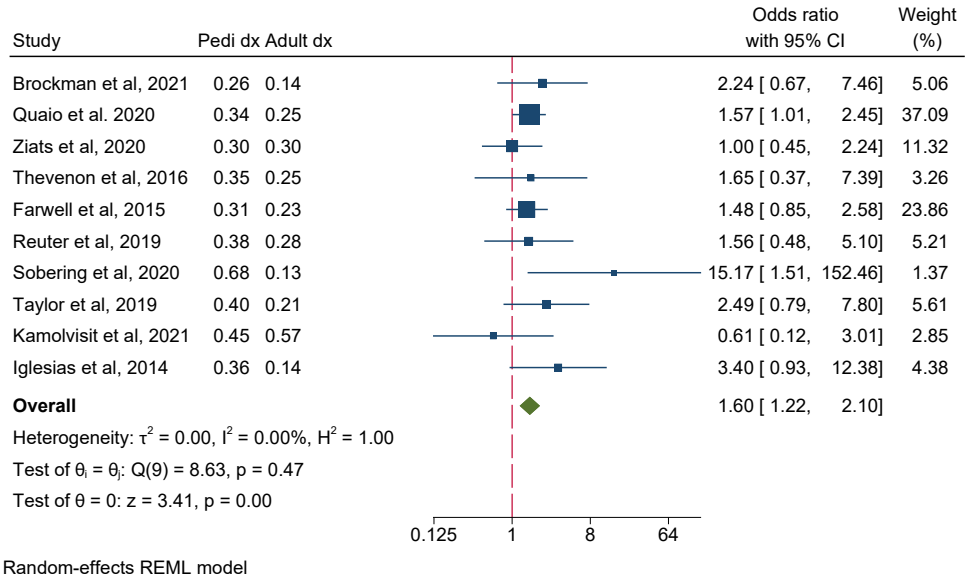

Figure 2 Comparison of pediatric and adult diagnostic rate within studies. CI, confidence interval; dx, diagnostic rate; Pedi, Pediatrics; REML, restricted maximum likelihood.

that of adult patients (95% CI 1.22-2.10, $I^2 = 0\%$, $P < .01$) (Figure 2). Limited data for adult cohorts (4 studies) precluded further statistical comparisons.

Based on different indications for testing, the pooled diagnostic rates were found to be the highest in studies with neurologic indications among both ES (0.39, 95% CI 0.32-0.46, 15 studies, $n = 1464$, $I^2 = 87\%$) and GS (0.43, 95% CI 0.38-0.49, 3 studies, $n = 273$, $I^2 = 0\%$) studies (Supplemental Figures 6 and 7). Based on this observation, the diagnostic rates of ES and GS were further compared among studies of neurology cohorts ($n = 18$ studies). The pooled diagnostic rate of GS was found to be higher than that of ES among patients with neurologic indications (Supplemental Figure 8, $P = .31$).[3,39,60,64,70,85,95,98,105,127,129,141,143,145,150,156,164,178]

A total of 21 cohorts reported that ES/GS was sequenced in a rapid manner, with an average turnaround time of 2 to 4 weeks.[38,43,70,75,77,84,101,114,120,130,132,134,139,148,155,159,165,169,172,179,180] Ten of them were sequenced using rapid ES (rES), 9 of them were sequenced using rapid GS (rGS), and the remaining 2 reported both rGS and rES. Among both ES and GS studies, rapid sequencing (0.44, 95% CI 0.38-0.50, 21 studies, $n = 1519$, $I^2 = 82\%$) achieved a significantly higher diagnostic rate than nonrapid sequencing (0.37, 95% CI 0.35-0.39, 136 studies, $n = 47,661$, $I^2 = 95\%$) (Supplemental Figure 9, $P = .02$).[3,7,8,19,21,27-43,45-170,172-180]

In 79 studies, comprising 15,917probands, trio testing (0.43, 95% CI 0.39-0.46, 46 studies, $n = 5493$, $I^2 = 85\%$) yielded a higher pooled diagnostic rate compared with singleton testing (0.39, 95% CI 0.34-0.44, 33 studies, $n = 10,424$, $I^2 = 97\%$) (Supplemental Figure 10). Meta-analysis was performed in 18 studies (10,646 probands) that compared the diagnostic rate of ES/GS by using both singleton and trio testing within the same study. In these studies, the odds of diagnosis using trios was 1.16 times greater than that of using singletons (95% CI 0.89-1.50, $I^2 = 69\%$, $P = .27$) (Supplemental Figure 11).[28,37,46,51,54,58,64,66,82,102,111,126,129,134,137,144,154,162]

Among the 131 cohorts that classified variants according to the ACMG guideline, the pooled diagnostic rate of ES was 0.39 (95% CI 0.36-0.41, 103 studies, $n = 34,850$, $I^2 = 96\%$), and the diagnostic rate of GS was 0.34 (95% CI 0.29-0.38, 36 studies, $n = 7678$, $I^2 = 94\%$), both similar to the overall diagnostic rates of ES (0.38, 95% CI 0.36-0.40, 126 studies, $n = 38,277$, $I^2 = 95\%$) and GS (0.34, 95% CI 0.30-0.38, 40 studies, $n = 11,207$, $I^2 = 95\%$).

Clinical utility of ES and GS

Overall, 62 of 157 cohorts (40%) reported on rate of clinical utility (Table 1). Diagnosis-predicated clinical management occurred in 2% to 100% of patients receiving a diagnosis. Meta-analysis of ES and GS groups, demonstrated that the pooled clinical utility of GS (0.61, 95% CI 0.50-0.73, 16 studies, $n = 3686$, $I^2 = 94\%$) was higher than that of ES (0.48, 95% CI 0.40-0.56, 47 studies, $n = 8869$, $I^2 = 97\%$) (Supplemental Figure 12, $P = .07$).[7,19,27,38,39,43,47,49-51,53,59,62,67,69,70,73-75,77,79,81,83,86,88,90,93-95,101,106,108,112,114,116,120,123,124,127,130,131,133,134,137,138,141,143,148,150,155,157·159,160,165,167-170,172,177-180]

Subgroup comparisons of clinical utility

Among 16 infant cohorts ($n = 4099$), the proportion of infants receiving a change in clinical management by GS was 0.74 (95% CI 0.60-0.88, 6 studies, $n = 777$, $I^2 = 89\%$), significantly higher than that of ES (0.53, 95% CI 0.39-0.66, 10 studies, $n = 3322$, $I^2 = 93\%$) (Supplemental Figure 13, $P = .04$).[27,43,59,75,79,94,101,120,133,139,167,169,170,172,179,180]

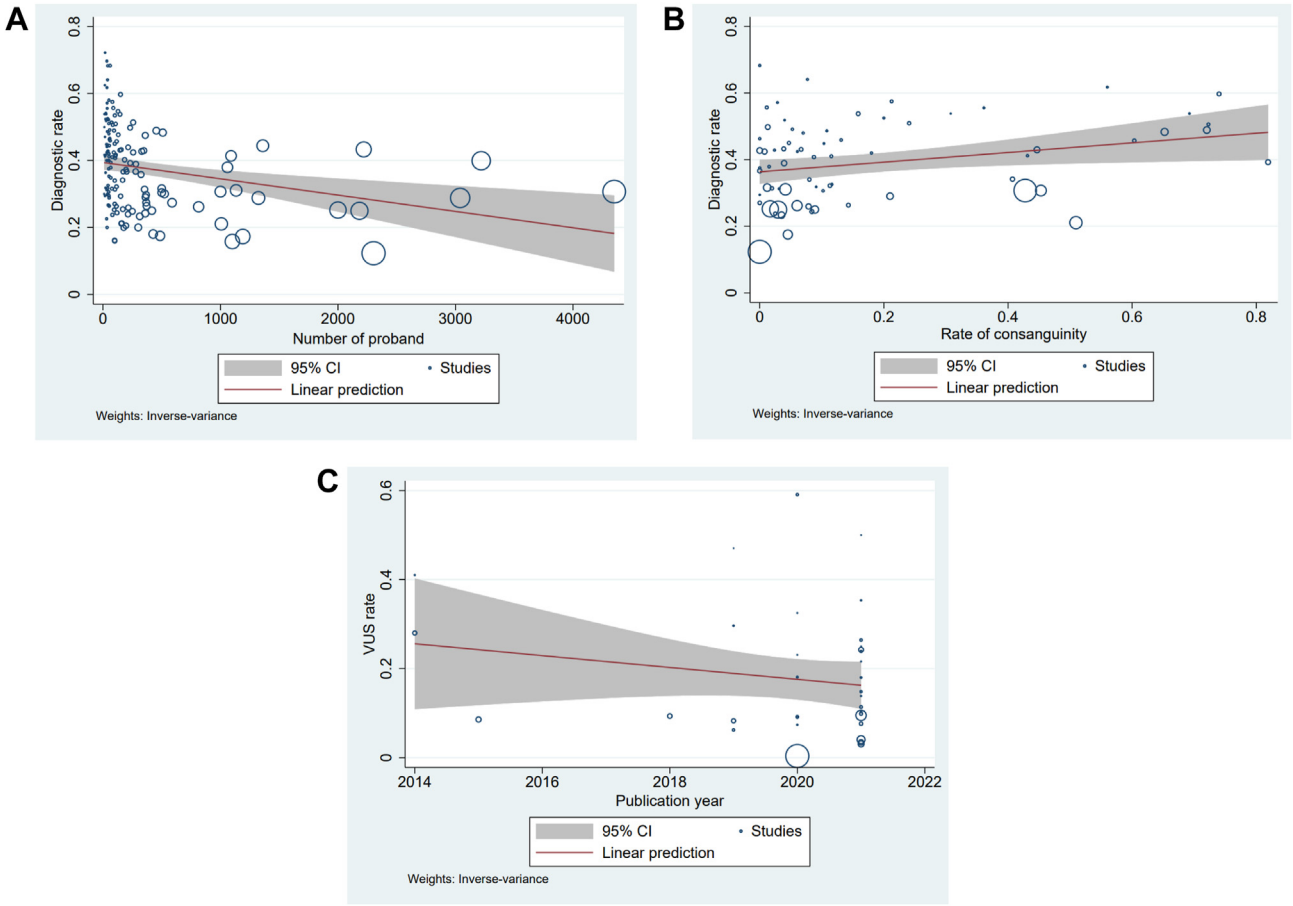

Figure 3 **Meta-regression plots.** A. The association between diagnostic rate and the number of probands. B. The association between diagnostic rate and the rate of consanguinity. C. The association between publication year and rate of VUS. CI, confidence interval; VUS, variant of unknown significance.

Meta-analysis of rapid vs nonrapid ES/GS groups revealed that rapid sequencing (0.72, 95% CI 0.63-0.82, 18 studies, $n = 1165$, $I^2 = 88\%$) achieved a significantly higher clinical utility than nonrapid sequencing (0.44, 95% CI 0.36-0.52, 44 studies, $n = 11{,}319$, $I^2 = 97\%$) ($P < .01$), regardless of whether ES or GS was performed (Supplemental Figure 14). In 34 cohorts featuring 7049 probands, trio testing (0.59, 95% CI 0.46-0.71, 19 studies, $n = 1968$, $I^2 = 95\%$) had a significantly higher rate of clinical utility compared with singleton testing (0.40, 95% CI 0.29-0.52, 15 studies, $n = 5081$, $I^2 = 96\%$) (Supplemental Figure 15, $P = .04$). Limited data in clinical utility of the ES and GS arms precluded further subgroup analyses.

Analysis of heterogeneity of diagnostic rate and clinical utility

Studies varied in size from 10 to 4351 probands. Meta-regression showed a modest relationship between study size and diagnostic rate. On average, an increase of 1000 subjects decreased diagnostic rate by 4.9% (Figure 3, $P = .001$). The rate of consanguinity varied from 0% to 82% ($n = 69$). Meta-regression revealed a positive correlation between consanguinity and diagnostic rate, indicating that an increase of 1% in the rate of consanguinity increased the rate of diagnosis by 14.5% (Figure 3, $P = .021$). Studies were published between 2012 and 2021. Meta-regression demonstrated a mild positive association between publication year and diagnostic rate, with an annual increase of 0.5% in diagnostic rate (Supplemental Figure 16, $P = .318$).

Meta-regression demonstrated a negative association between sample size and clinical utility, indicating that an increase of 1000 subjects decreased the rate of clinical utility by 10.2%, though this was not statistically significant (Supplemental Figure 17, $P = .208$). Year of study publication was associated with a positive correlation with the rate of clinical utility, showing an increase of 2.6% each year (Supplemental Figure 17, $P = .104$).

Diagnostic and clinical utility of ES and GS among high-quality studies

To examine whether the overall findings are robust, meta-analysis of diagnostic rate and clinical utility of ES and GS were performed only among high-quality studies, assessed using QUADAS-2. A total of 22 studies

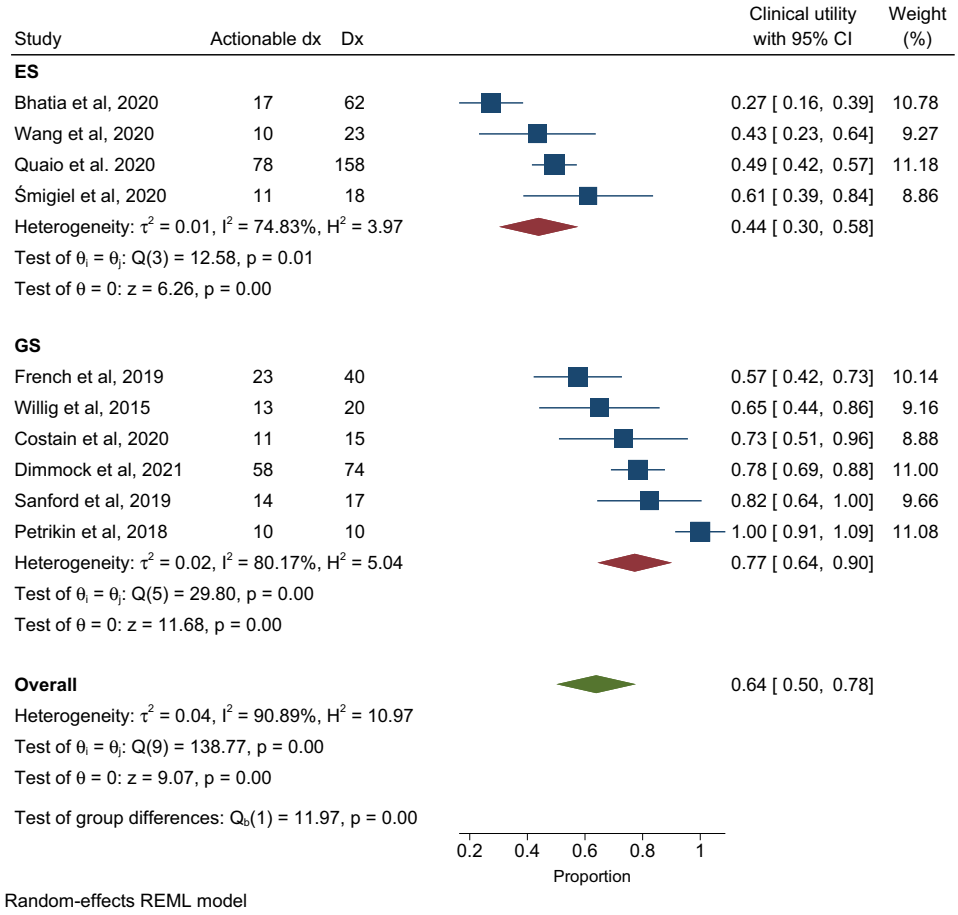

Figure 4 Comparison of rate of clinical utility among high-quality ES and GS studies. Dx, number of diagnoses; ES, exome sequencing; GS, genome sequencing; REML, restricted maximum likelihood.

were assessed to have low risk of bias across all 4 domains, and low concern regarding applicability, which were deemed to be "high-quality" studies (Supplemental Figure 18).[37,38,72,74-76,81,84,92,93,100,101,105,128,130,145,151,153,169,173,179,180] Among these 22 studies comprising 4580 probands, no significant difference in diagnostic rate was observed between ES (0.43, 95% CI 0.35-0.51, 13 studies, $n = 2612$, $I^2 = 94\%$) and GS (0.34, 95% CI 0.28-0.41, 11 studies, $n = 2{,}170$, $I^2 = 88\%$) (Supplemental Figure 19, $P = .09$). Ten of these studies reported data on clinical utility, featuring 1280 probands. GS was found to achieve a significantly higher rate of clinical utility (0.77, 95% CI 0.64-0.90, 6 studies, $n = 533$, $I^2 = 80\%$) compared with ES (0.44, 95% CI 0.30-0.58, 4 studies, $n = 723$, $I^2 = 75\%$) (Figure 4, $P < .01$).

Reporting of VUS and novel genes

Among 131 cohorts that classified variants using ACMG criteria, 35 cohorts reported the rate of VUS, of which the rate of VUS ranged from <1% to 59% for ES and 6% to 50% for GS. Rate of VUS by ES and GS did not differ significantly (Supplemental Figure 20, $P = .78$).[19,28,35,37,41,46,52,54,60,71,81,85,100,101,108,113,119,123,135-137,139,145,146,152,154,164-168,176] In addition, meta-regression demonstrated a trend of decreasing rate of VUS from 2014 to 2021, showing a decrease of 1.3% each year, though this was not statistically significant (Figure 3, $P = .272$).

A total of 29 cohorts reported the number of novel genes associated with the disease, of which the number of novel genes discovered by ES ranged from 1 to 75 (22 studies, 5038 probands), whereas the number of novel genes discovered by GS ranged from 2 to 579 (6 studies, 5539 probands) (Table 1). Severe heterogeneity in methodology and reporting precluded further statistical comparisons.

Reporting of costs between ES and GS studies

Only 7 studies performed a formal economic evaluation to evaluate both costs and outcomes (Table 1), of which, 6 of them performed a cost-effectiveness analysis of ES over standard conventional diagnostic pathways, with all of them concluding that ES is cost saving.[3,65,73,116,157,159] The remaining one included a cost-utility analysis to evaluate the changes in quality-adjusted life-years due to patient management changes, concluding that clinical management changes due to ES were cost-saving; it also modeled the cost-effectiveness of ES data reanalysis compared with

standard diagnostic care, demonstrating ES reanalysis at 18 months was more cost-effective than reanalyzing data every 6 months.[171] Interestingly, all of these 7 studies were from high-income countries, with 5 studies from Australia and the remaining 2 from The Netherlands and Finland.

A total of 17 studies reported unit cost estimates, of which cost estimates for a single ES test ranged from $500 to $2240 and for a trio ranged from $1623 to $7839 (Table 1). None of the GS studies provided unit cost estimates for singleton/trio GS. Two studies provided cost estimates for rES, ($1285 and $3347 per test), and 2 studies provided cost estimates for rGS ($9102 and $9492 per test). Few cost analyses presented data transparently and many publications did not state which components were included in their unit cost estimates.

Comparison of ES reanalysis and GS

A total of 9 ES studies comprising 1748 probands were reanalyzed, of which 7 reported both initial and reanalysis outcomes and 2 reported exclusively on ES reanalysis (Supplemental Table 4).[34,52,57,73,118,122,171,181,182] Among those reported, primary ES data were reanalyzed 1 month to 3.4 years after the initial negative results, achieving an additional diagnostic rate of 1% to 16%. Diagnostic rate between ES reanalysis (0.43, 95% CI 0.36-0.50, 9 studies, $n = 2361$, $I^2 = 89\%$) and GS (0.34, 95% CI 0.30-0.38, 40 studies, $n = 11{,}207$, $I^2 = 95\%$) was significantly different (Supplemental Figure 21, $P = .04$). Limited data precluded further statistical comparisons.

Discussion

Previous meta-analyses and systematic reviews have recommended the use of ES and GS over conventional diagnostic methods for etiologic diagnosis of patients with suspected monogenic disorders, yet evidence to compare ES and GS does not exist. The magnitude and types of the impact of ES vs GS were corroborated by evidence across 31 countries/regions in the past decade, combined as a meta-analysis of 161 publications comprising 159 cohorts and 50,417 affected probands. This study serves as the most comprehensive evaluation of the diagnostic and clinical utility of ES vs GS in both pediatrics and adults across diverse populations to date. Our study provides an important update in literature, highlighting similar diagnostic rates between ES and GS and a higher clinical utility of GS over ES.

GS examines all exons and 90% of the genome, which offers the potential to identify disease-causing copy number variants and SVs, repeat expansions, and nonexonic regulatory and splicing variations, and may improve variant calling in homologous sequences.[16] On the contrary, ES examines exons only (approximately 1%-2% of the genome), which limits its ability to detect NCV and SV, as demonstrated by previous studies.[16] Nevertheless, diagnostic rate of GS did not differ significantly from that of ES, in both primary analysis and among high-quality studies in the current meta-analysis. This aligns with the findings from a previous meta-analysis of 28 ES/GS studies in children that was published in 2018.[11] Similarity in diagnostic rate could potentially be explained by the much broader use of ES over GS in the past decade, as illustrated by the number of ES and GS studies (117 vs 31 studies) identified, possibly because of the substantial cost difference between the two. Nevertheless, current meta-analysis of 9 studies featuring within-cohort comparisons showed 1.2 times greater odds of a diagnosis by GS over ES (95% CI 0.79-1.83, $I^2 = 68\%$, $P = .38$). Existing evidence also illustrated the capability of GS to achieve molecular diagnoses for cases undiagnosed by ES.[37,92,183] In particular, Wu et al[92] compared the diagnostic sensitivity of exome and genome sequencing and showed that 10 of 74 (14%) diagnoses were missed by ES because of disease-causing deep intronic, NCVs and SVs. In addition, previous studies have demonstrated the power of GS to screen for short tandem repeat (STR) expansions with the help of STR analysis methods. In a cohort of 11,631 undiagnosed patients from the 100,000 Genomes Project led by Genomics England, assessment of STR expansions using GS led to identification of neurological repeat expansion disorders in 68 patients who were previously undiagnosed under standard genetic tests.[14] These include STR genes located in the 5′ region (ie, *C9orf72*, *FMR1*, and *PPP2R2B*), 3′ region (ie, *DMPK*), and intron 1 (ie, *FXN*) that could only be identified with the help of GS. With GS' capability to detect the most common repeat expansions as well as the testing of copy number variants and SNVs, it offers the potential to achieve a molecular diagnosis in most patients with heterogeneous disorders who have not been diagnosed using locus-specific testing. With the newly published recommendations for clinical interpretation of variants found in noncoding regions of the genome, it would improve the ability to fully interpret NCV identified by GS, which, in turn, would lead to new diagnoses and catalyze the discovery of novel disease mechanisms.[15]

The successful application of ES and GS has accelerated the speed of novel gene discoveries over the past decade, with discoveries almost tripled those made by conventional methods since 2013.[184] Discovering the causal link between genotype and phenotype not only helps the understanding of gene function and regulation and thus increases diagnostic successes but also facilitates the understanding of biological mechanisms, which may facilitate the development of targeted and novel treatment. The current meta-analysis has identified a higher range of novel genes discovered by GS compared with ES. Among those reported, cohort-wide burden testing using 57,000 genomes from the 100,000 Genomes Project discovered the largest number of novel genes. A total of 579 novel genes were identified, which helped to establish 19 new disease-gene associations and 3 new disease genes.[19] Importantly, such novel discoveries have allowed immediate clinical actionability, such as the

identification of a novel *CHM* promoter variant causing loss of gene expression in a patient with suspected choroideremia, in which the diagnosis has enabled eligibility for a gene-replacement trial.[19] With GS' potential to accelerate novel gene discoveries, it is expected that GS will eventually supersede ES in terms of its diagnostic capability and clinical actionability, especially with its increased use in clinical settings, facilitated by the decrease in GS cost.[13-15]

The establishment of gene-disease association can facilitate reclassifying of VUS to likely pathogenic and pathogenic variants. Even with the higher diagnostic potential of GS over ES and a higher range of novel genes being discovered by GS studies, the rate of VUS between GS and ES does not differ significantly. Importantly, as illustrated by the meta-regression between rate of VUS and year of study publication, there was a trend of decreasing VUS prevalence from 2014 to 2021, with a reduction of 1.3% each year. This might be contributed by the recent advancement in the interpretation of variations in both coding and noncoding regions of the genome and growing knowledge of the field as well as the active input from clinicians and patients for reinterpretation and reanalysis of data within a recommended timeframe of 1 to 2 years to achieve a diagnosis.[118,171] Although the included studies classified VUS according to the ACMG recommendations, these results should be interpreted with caution because of severe heterogeneity in VUS reporting. Some laboratories reported VUS that are considered causative of the patients' phenotypes, whereas others reported VUS that are located in the candidate genes regardless of whether the gene function has been well established.[185] This remains one of the major issues that require consensus from laboratories, clinicians, genetic counselors, patients, and policy makers to avoid ethical issues for better practices.

Lack of diversity in genomic research has been highlighted in multiple studies and systematic review previously.[17,186,187] The underrepresentation of populations other than White individuals would limit the usefulness of genomic technologies, including ES and GS, complicating interpretation of genetic testing results. The current meta-analysis included studies from 31 countries/regions, featuring patients of diverse populations, such as Arabs, Australian, Brazilian, Chinese, Finnish, German, Indian, Japanese, Korean, Thai, etc, increasing inclusiveness of patient diversity. Diagnostic rates were generally higher in Middle Eastern patients (Table 1), potentially explained by the higher rate of consanguinity in these populations, which increases the population incidence of homozygous recessive genetic diseases. For example, diagnostic rates were found to be 49% to 60% in cohorts of Arab individuals, with the rate of consanguinity being 69% to 82%.[142,150,164,173] In fact, meta-regression of 69 studies showed a significant positive association between rate of consanguinity and rate of diagnosis, indicating that an increase of 1% in the rate of consanguinity would increase the rate of diagnosis by 14.5% ($P = .021$).

Previous meta-analysis by Clark et al[11] has demonstrated a negative association between rate of consanguinity and the number of de novo variants. Sequencing of parent-child trios is often recommended to facilitate the detection of de novo variants and phasing of compound heterozygous variants during interpretation to increase diagnostic rate. It also offers the potential to upgrade VUS to likely pathogenic and pathogenic variants via segregation analysis. Meta-analysis of 18 within-cohort comparisons demonstrated 1.2 odds of diagnosis among trio-testing over singleton-testing. Existing evidence also illustrated the capability of trio-sequencing to achieve molecular diagnoses in previous unsolved ES cases that were sequenced as singletons.[48,76]

With 50% to 75% of the RDs being pediatric onset and are often chronically debilitating, previous cohort studies and meta-analyses have predominantly focused on infants and children.[3,7,11,74,77,148,157,165] Our study findings demonstrated the significantly higher pooled diagnostic rate among infants and children compared with adults, regardless of whether it was sequenced using ES or GS, further supporting previously published evidence.[28,71,81,82,88] Although only 4 studies of adult cohorts were identified, application of ES and GS in adult patients also showed promising results, achieving a diagnostic rate of 0.17 to 0.27.[31-33,60] On the other hand, many cohorts have focused on patients with neurologic indications, potentially supported by the known higher diagnostic rate achieved among this population.[9,17,82,88] Unsurprisingly, current study findings also illustrated higher diagnostic rate among patients with neurologic indications. Importantly, this meta-analysis provides empirical evidence to demonstrate the significantly higher diagnostic rate of rapid ES/GS sequencing compared with nonrapid sequencing, illustrating the higher potential to diagnose patients in acute clinical settings by returning results in a rapid manner.

With a rapid genetic diagnosis made by ES and GS, more evidence from literature could be gathered about the underlying disease to inform the next steps in clinical management, which helps to accelerate discussion and the decision-making process between clinicians and the patient by reducing uncertainty. Current study findings demonstrated the power of ES and GS in influencing clinical management in 2% to 100% of the diagnosed patients in 62 cohorts through different types of management changes, including, but not limited to, surveillance, referral to specialists, diet and lifestyle changes, hospitalization, and indication or contraindication of investigations, procedures, surgeries, and medications. In the meta-analysis by Clark et al[11] that included 4 GS studies and 12 ES studies with data on clinical utility, 27% (95% CI 17%-40%) and 17% (95% CI 12%-24%) of children with genetic diagnoses had subsequent changes in their clinical management, respectively. Our meta-analysis provided evidence to further support the higher pooled clinical utility of GS (0.61, 95% CI 0.50-0.73) over ES (0.48, 95% CI 0.40-0.56). Meta-analysis also revealed that rapid sequencing in both ES

and GS achieved a significantly higher clinical utility than nonrapid sequencing ($P < .01$), illustrating the potentials of rapid management changes in acutely ill patients with a shorter turnaround time. Nevertheless, even after excluding cases in which the only management changes were ending the diagnostic odyssey or genetic counseling about recurrence risk and reproductive planning, the range of clinical utility across studies was broad (2%-100%), reflecting the inconsistent definitions used in literature. This would, in turn, reduce the quality of evidence to support the higher clinical utility of GS over ES. Nonetheless, current subgroup meta-analysis of 10 high-quality ES and GS studies indicated a significant difference of 0.33 in clinical utility between GS (0.77, 95% CI 0.64-0.90) and ES (0.44, 95% CI 0.30-0.58) ($P < .01$), reinforcing the higher potential of GS over ES in affecting patient's clinical management. Our findings also illustrated a much higher pooled clinical utility of both ES and GS compared with previous evidence by Clark et al (studies identified up to 2017), indicating increased knowledge and technological improvements over the years. This was supported by the positive association observed between the rate of clinical utility and year of study publication, showing an increase of 2.6% each year as illustrated by the meta-regression.

In addition to the impact on patient's clinical management and clinical outcomes, application of ES and GS was shown to have economic implications for the health system by avoiding unnecessary procedures and hospitalizations and reducing health care costs.[77,92,101,120,159] Despite the clinical and economic potential of ES and GS, universal application in health systems is yet to be implemented, mainly hindered by the high unit costs of ES and GS. In the era of resource and budget constraints, it is important to assess the economic impact of ES and GS to inform health care planning and resource allocation. Yet, cost-effectiveness evidence of ES and GS is limited in literature, as highlighted by the current meta-analysis and a previous systematic review by Schwarze et al.[18] Only 7 studies from Australia, Finland, and The Netherlands identified in the current meta-analysis were full economic evaluations that compared ES and conventional diagnostic methods, with all of them concluding that ES is cost saving and should be applied early in the diagnostic pathway.[3,65,73,116,157,159,171] Health care systems in these 3 countries provide universal health care coverage to their citizens, potentially explaining the need for cost-effectiveness evidence to inform health care decision making. GS studies that included cost-analysis in the current study estimated the cost of previous diagnostic tests, cost of care, and cost savings generated from changes in clinical management[8,19,92,101,120,132]; none of them performed formal cost-effectiveness analysis. Whether GS is a cost-effective diagnostic test compared with ES and other conventional methods depends upon the value of obtaining an additional diagnosis or its impact on clinical management, particularly because the unit cost of GS may be offset by the downstream cost saving that it generates, such as from the avoidance of investigations and procedures. Traditionally GS is about 2 to 3 times more expensive than ES, but the cost of GS has decreased substantially in the past decade, with the cost per human genome falling below $1000 since 2019 as suggested by the National Human Genome Research Institute.[4] With the similar diagnostic rate of ES and GS as illustrated by the current meta-analysis, the drop in GS cost would potentially increase its application in clinical setting because of its diagnostic superiority over ES in detecting variants in noncoding regions of the genome.

With compelling evidence on the diagnostic and clinical utility of ES and GS, health systems and governments around the world have started to implement ES and GS in routine clinical care and in Genome Projects in their respective regions, aiming to enhance clinical application of genomic medicine for precision medicine.[184,188] Genomics England in the United Kingdom has launched the 100,000 Genomes Project in 2013, and it has been a huge success in providing grounds for the Genomic Medicine Service of National Health System England to be the first to offer GS as part of routine clinical care for patients with undiagnosed RDs. In the near future, genomic data from global Genome Projects would potentially enhance the ability of RD diagnosis and management and would provide empirical evidence for the translation and application of ES and GS into clinical practice. Such large-scale sequencing initiatives across diverse range of patient groups would also provide grounds to identify novel disease-gene associations and generate meaningful cost-effectiveness estimates, providing empirical evidence to inform clinical management and allocate health care resources at a national level. Importantly, availability of genomic data across races and ethnicities would together improve genomic diversity and equity of access globally.

The current meta-analysis serves as the most comprehensive evaluation of the diagnostic and clinical utility of ES vs GS to date and attempts to extend the body of evidence to outcomes of VUS rate, novel genes, and cost-effectiveness across both pediatric and adult populations. Nevertheless, several limitations were acknowledged in this study. First, pooled diagnostic rates were based on published face values, and diagnoses were not recalculated and reclassified according to the strength of evidence of gene-disease associations. Second, study comparisons should be interpreted with caution because high heterogeneity among cohorts was observed despite performing multiple subgroup analyses. Nonetheless, analysis among high-quality studies through stringent and robust quality assessment revealed similar diagnostic rates between GS and ES and higher clinical utility of GS over ES. Third, the absence of data and data heterogeneity in evaluating and reporting VUS, cost-effectiveness evidence, and ES reanalysis data preclude further statistical comparisons, limiting the usefulness and generalizability to different clinical and geographical settings. Future studies of ES and GS on outcomes of VUS and health economics in a transparent manner are urgently required to allow more informed decision making in this context. Fourth, meta-analyses were performed based on the overall number of ES/GS studies to include more

evidence from literature. Subgroup comparisons were not made between studies that have performed clinical/medical exome/genome sequencing (CES/MES/CGS/MGS) vs whole-exome sequencing/whole-genome sequencing, though diagnostic rates between CES/MES and whole-exome sequencing and between CGS/MGS and whole-genome sequencing, were found to be similar, both concluding similar diagnostic rates between ES and GS. Finally, the current study did not focus on the interpretation of mitochondrial and somatic variants in mitochondrial diseases and cancers. There are existing guidelines specific for the interpretation of mitochondrial DNA and somatic variants, which rely on phasing and genotyping that are limited by the current short-read GS technology. In the long-run, long-range sequencing and DNA modification technology will be supplemented to GS to enhance the rate of diagnosis and clinical utility.

Conclusion

The magnitude and types of impact of ES and GS were corroborated by 161 publications from 31 countries/regions, combined as a meta-analysis. This study demonstrates a similar diagnostic rate of ES and GS and a higher clinical utility of GS over ES in pediatric and adult patients across diverse populations. With the newly published recommendations for clinical interpretation of variants found in non-coding regions of the genome and the trend of decreasing VUS and GS cost, it is expected that GS will be more widely used in clinical settings.

Data Availability

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

Acknowledgment

The authors would like to thank Dr Su-vui Lo, Chief Executive Officer, of the Hong Kong Genome Institute for the instrumental leadership and guidance.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Conceptualization: C.C.Y.C., B.H.Y.C.; Data Curation: C.C.Y.C., S.P.Y.H., N.Y.T.N., P.H.L.D.; Formal Analysis: C.C.Y.C., S.P.Y.H.; Funding Acquisition: A.T.W.C., B.H.Y.C.; Investigation: C.C.Y.C., S.P.Y.H., A.T.W.C., B.H.Y.C.; Methodology: C.C.Y.C., S.P.Y.H., N.Y.T.N., P.H.L.D.; Project Administration: C.C.Y.C., A.T.W.C., B.H.Y.C.; Resources: A.T.W.C., B.H.Y.C.; Supervision: A.T.W.C., B.H.Y.C.; Visualization: C.C.Y.C., S.P.Y.H.; Writing-original draft: C.C.Y.C., S.P.Y.H.; Writing-review and editing: N.Y.T.N., P.H.L.D., A.T.W.C., B.H.Y.C.

Ethics Declaration

Ethics approval is not required for this meta-analysis.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2023.100896) contains supplementary material, which is available to authorized users.

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