Comparing the diagnostic and clinical utility of WGS and WES with standard genetic testing (SGT) in children with suspected genetic diseases: A systematic review and meta-analysis

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1.0 Abbreviations

ACMG – American College of Medical Genetics

CMA – Chromosomal microarray

EHR – Electronic Health Record

NBS – Newborn screening

NGS – Next-generation sequencing

P/LP – Pathogenic/Likely Pathogenic

SGT – Standard genetic testing

VUS – Variants of unknown significance

WGS – Whole-genome sequencing

WES – Whole-exome sequencing

2.0 Abstract

Importance: Rare genetic diseases are one of the leading causes of infant mortality worldwide. Whole-genome sequencing (WGS) and whole-exome sequencing (WES) are relatively new techniques for diagnosing genetic diseases, that classic newborn screening (NBS) fails to detect.

Objective: To systematically assess the diagnostic and clinical utility of WGS and WES, compared to standard genetic testing (SGT), in children with suspected genetic diseases, and discuss its impact on the expansion of NBS.

Data Sources: EMBASE, MEDLINE, PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and references of included full-text articles were searched until 21st October 2021.

Study Selection: Studies reporting the diagnostic yield or rate of change of management for WGS and/or WES were included. The meta-analysis included 43 of the original 1768 identified articles (2%).

Data Extraction and Synthesis: Data extraction followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline. The quality of included papers was assessed using QUADAS-2, and a meta-analysis was performed using a random-effects model to create pooled proportions and a pooled odds ratio.

Main Outcome(s) and Measure(s): Diagnostic utility, as determined by the diagnostic yield, which is defined as P/LP variants with strong or moderate associations with the presenting clinical phenotype of the affected patient, and that were reported to the patient's clinician. Clinical utility as defined by any change in clinical management (medically or surgically), determined through clinician questionnaires or Electronic Health Record reviews.

Results: A total of 43 studies were included, comprising 6168 children. The pooled diagnostic utility of WES (0.40, 95% CI 0.34-0.45, I^2=90%), was qualitatively greater than WGS (0.34, 95% CI 0.29-0.39, I^2=79%), and SGT (0.19, 95% CI 0.13-0.25, I^2=64%). The pooled clinical utility of WGS (0.74, 95% CI 0.56-0.89, I^2=93%), was qualitatively greater than WES (0.72, 95% CI 0.61-0.81, I^2=86%), while both were qualitatively greater than SGT (0.69, 95% CI 0.38-0.94).

Conclusions and Relevance: Our evidence suggests that WGS/WES should be considered the first-line test for genetic diseases. There is reason to believe that WGS and WES should be included as part of NBS, however, more studies are required to assess the cost-effectiveness of this approach.

4.0 Introduction

Genetic disorders, including monogenic diseases and chromosomal abnormalities, are one of the leading causes of infant mortality, particularly among those admitted to the neonatal and paediatric intensive care units.[1, 2] An estimated 400 million people worldwide are thought to suffer from a rare disease of which 80-85% are believed to have genetic origins. Approximately half of those affected by a rare disease are children, with 30% not surviving past their fifth birthday.[3, 4] It has been estimated that around 50% of patients with a genetic disorder are never diagnosed.[5] Although individually each genetic disease is rare, when combined, the estimated 6000-7000 diseases, are common and contribute significantly to infant morbidity, mortality, and healthcare costs.[6, 7]

Disease progression of genetic disorders within children can be rapid, and without early etiological diagnosis, intervention and management decisions made are uninformed and often ineffective, exacerbate symptoms or cause adverse effects, and lead to delays in starting appropriate treatment.[8-10] Therefore, a quick, accurate diagnosis for children is vital to improve outcomes, and reduce morbidity and mortality.[10]

Attaining a diagnosis for every child with a suspected genetic disease remains a significant challenge, due to the genetic and phenotypic variation of such diseases. Many countries have implemented newborn screening (NBS) programmes in an effort to reduce infant mortality associated with rare diseases, however, these programmes, where implemented, fail to recognise and screen for many rare genetic diseases. Although the WHO have published guidelines for the inclusion of a condition in NBS programmes, there remains to be large disparities between the conditions screened for in many countries and their individual states.[11-14] Any abnormalities detected during screening can provide an early indication of a rare disease, however, any rare diseases not detectable through analytes, such as some rare genetic diseases, cannot be screened for. Expanding the list of conditions for NBS to include other rare diseases, not detected through analytes, would ensure a broader range of conditions can be rapidly diagnosed and treated, improving outcomes and reducing infant morbidity and mortality.

Next-generation sequencing (NGS) technologies have rapidly advanced in recent years, and have shown great promise of new diagnostic potentials, due to their genetic and phenotypic approach. Whole-genome sequencing (WGS) and whole-exome sequencing (WES) allow for simultaneous analysis of numerous genes associated with genetic disorders, an approach that is not currently utilised within NBS.[15] The speed at which these approaches can analyse genomic data and identify pathogenic/likely pathogenic (P/LP) variants, makes them prime candidates for the expansion of NBS, due to their capabilities of rapid, early diagnoses of additional disorders that are not currently screened for, and would benefit from early detection and subsequent treatment. Here, we report a literature review and meta-analysis of the diagnostic and clinical utility of WGS and WES, compared with standard genetic testing (SGT), in children (≤18 years) with suspected genetic diseases, and discuss the impact this has on the expansion of the NBS programme through WGS and WES.

5.0 Methods

5.1 Data sources and record identification

On 21st October 2021, we searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PubMed, Scopus and Web of Science with the MeSH terms ("Infant" or "Infant, Newborn" or "Child"), and ("Whole Genome Sequencing" or "Whole Exome Sequencing" or "Genetic Testing" or "High-Throughput Nucleotide Sequencing"), and ("Critical Illness" or "Intensive Care Units" or "Intensive Care, Neonatal" or "Intensive Care Units, Pediatric" or "Intensive Care Units, Neonatal" or "Critical Care"), and relevant key terms. We manually searched the references of included papers for any missed eligible papers. There were no date, language, or literature type restrictions on searches. Papers identified through database searches were imported into EndNote X9 (Clarivate Analytics, Boston, MA) for duplication removal, title and abstract screening, and full-text review. Full search strategies are available within the appendix **(Appendix II)**.

5.2 Inclusion criteria and study eligibility

Studies that assessed the diagnostic utility or clinical utility (proportion of patients tested who had a change in clinical management upon receiving a diagnosis) of WGS and/or WES were eligible. Studies containing cohorts with specific disease types or clinical presentations, rather than a broad range of potential genetic diseases, probands over 18 years of age, already diagnosed or containing expired probands were excluded. Case reports, meeting/conference abstracts, and studies where full-texts were not available in English were also excluded. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement **(Appendix I, Table 1)**.[16]

5.3 Data extraction

Data extracted comprised of (1) the methodological information of the studies, including: first author, year of publication, objectives, sequencing method, sample size, and study country, (2) patient demographics, including: age of participants and rate of consanguinity, and (3) reported study outcomes, including: diagnostic yield, change in management, incidence of VUS, incidental findings, incidence of de novo variants, and turnaround time was extracted manually. Data was reviewed for completeness and accuracy by two authors with any disparities resolved by discussion and consensus. The PICOTS typology of the criteria for inclusion of studies in quantitative analyses was:

Patients: Data extraction was limited to critically ill children (aged less than 18 years) with a suspected genetic disease.

Intervention: WGS and/or WES

Comparator: Participants tested by WGS, WES and SGT were grouped and compared. SGT was treated as the Reference Standard.

Outcomes: Diagnostic utility and clinical utility. Diagnostic utility was determined by the diagnostic yield, which is defined as P/LP variants with strong or moderate associations with the presenting clinical phenotype of the affected patient, and that were reported to the patient's clinician.[17] Clinical utility was defined as any change in clinical management (medically or surgically) as determined through clinician questionnaires or Electronic Health Record (EHR) reviews. Incidental findings and variants of uncertain significance, where available, were also extracted.[18]

Timing: Where more than one paper reported results from the same study cohort, we extracted the most recent data for diagnostic and clinical utility.

Settings: There were no setting restrictions.

5.4 Quality assessment

Quality assessment involved evaluating the risk of bias for each included study using the QUADAS-2 tool, a validated tool for assessing the risk of bias in primary diagnostic accuracy studies.[19] The QUADAS-2 tool enables the classification of studies into low risk, high risk or unclear risk based on the following domains: patient selection (bias as a result of the selection of participants and representativeness of the sample), index test (bias as a result of the conduction and interpretation of the index test), reference standard (bias as a result of the conduction and interpretation of the reference standard), and flow and timing (bias as a result of the time interval and any interventions between the index test and reference standard). Applicability of studies was also evaluated for the first three domains in each study and judged as “yes, no, or unclear”, indicating a low, high, and unclear risk of bias, respectively.

5.5 Statistical analysis

Meta-analysis was conducted using the ‘metaprop’ and ‘metan’ commands in Stata version 15.[20] We transformed proportions from individual studies by stabilizing the between-study variance, using the Freeman-Tukey double arcsine transformation procedure, before computing the weighted overall pooled estimates, using the DerSimonian-Laird random-effect model, with an estimate of heterogeneity being taken from the inverse-variance fixed-effect model.[21] 95% confidence intervals are based on exact binomial procedures (Clopper-Pearson interval). The chi-squared test was used to assess between-study heterogeneity, with I^2 statistic values of 25%, 50%, and 75% interpreted as low, moderate, and severe heterogeneity, respectively.[22] Forest plots were used to summarize the individual study and pooled group meta-analysis statistics.

6.0 Results

6.1 Literature search results

WGS and WES are fast becoming commonplace methods for the diagnosis of genetic diseases. We compared the diagnostic and clinical utility of WGS and WES with that of SGT, including chromosomal microarray (CMA), Sanger sequencing, single-gene testing, panel testing, methylation studies, NBS, and others, as the standard of care for children with suspected genetic diseases. A total of 2635 records were identified through searches for studies assessing the use of WGS and WES in children with a wide range of suspected genetic diseases. Thirty-six of these records, comprising 5681 children, met the eligibility criteria. A further seven records were identified through manual searching of included records' reference lists, bringing the total number of eligible, included records to forty-three, comprising 6168 children.[10, 23-64] Of the forty-three included studies, thirty-eight were case studies; five were randomized controlled trials.[35, 38, 41, 47, 60] The process and outcome of the literature search are presented in detail in **Figure 1.**

Figure 1: Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram for Meta-analysis of diagnostic and clinical utility of WGS and WES.

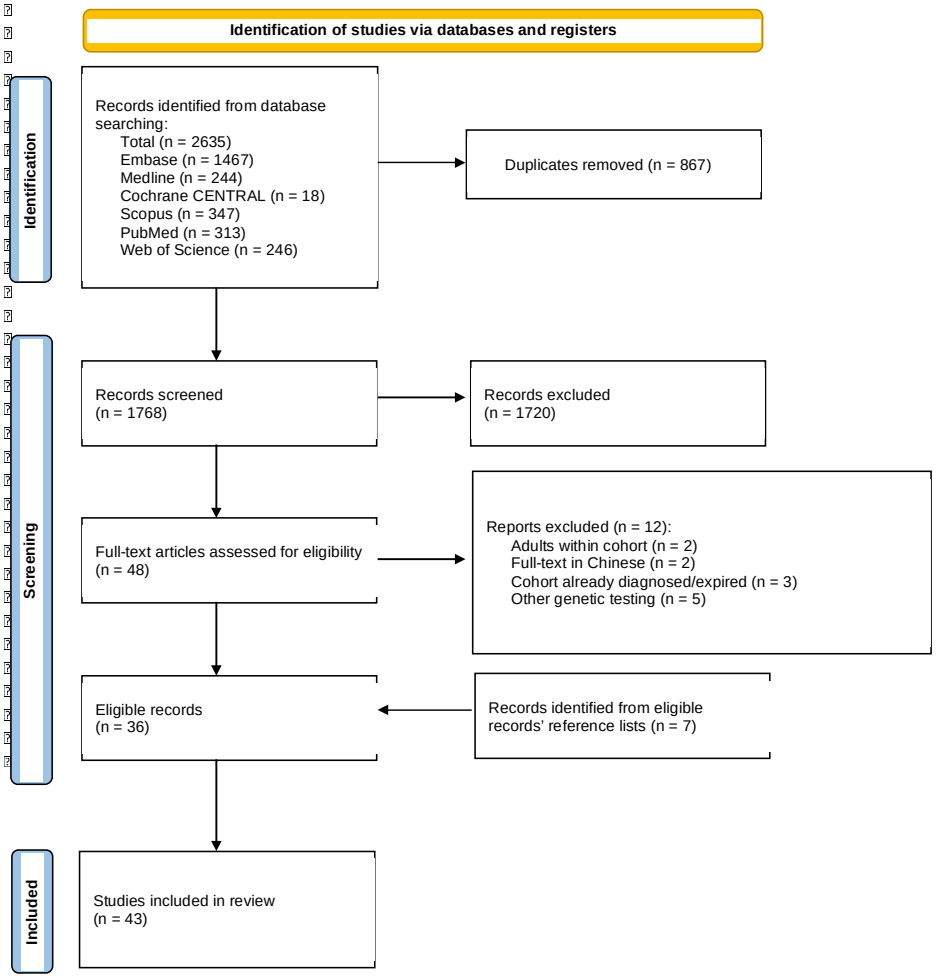

Figure 1: Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for meta-analysis of diagnostic and clinical utility of WGS and WES.

6.2 Meta-analysis results

Of the 43 included studies, 15/43 (35%) looked specifically at WGS, while 25/43 (53%) investigated WES. The characteristics of all forty-three included studies can be found in **Appendix I, Table 2**. The pooled diagnostic utility of WES was 0.40 (95% CI 0.34-0.45, 27 studies, 4238 children, I^2=90%), which was qualitatively greater than WGS (0.34, 95% CI 0.29-0.39, 17 studies, 1817 children, I^2=79%), and SGT (0.19, 95% CI 0.13-0.25, 6 studies, 669 children, I^2=64%) (Figure 2). The pooled clinical utility of WGS was 0.74 (95% CI 0.56-0.89, 13 studies, 467 children, I^2=93%), which was qualitatively greater than WES (0.72, 95% CI 0.61-0.81, 18 studies, 648 children, I^2=86%), and SGT (0.69, 95% CI 0.38-0.94, 2 studies, 12 children) (Figure 3). I^2 could not be assessed for SGT due to the small sample size of studies. Severe heterogeneity (I^2>75%) within WGS and WES groups precluded statistical comparisons. Among studies that provided complete data for the diagnostic utility of WGS or WES and SGT, the pooled odds of diagnosis were 2.93 times greater for WGS/WES (P<0.01) (Figure 4). 31/43 (72%) studies reported the heritability of detected variants, these included P/LP variants, variants deemed to be an incidental finding, and VUS. A total of 596/1381 (43%) were de novo variants. Some studies opted out of reporting incidental findings, while others only returned incidental findings to patients and families who had consented. Of the eighteen studies opting to report incidental findings, a total of 66/1221 (5%) participants received such findings.

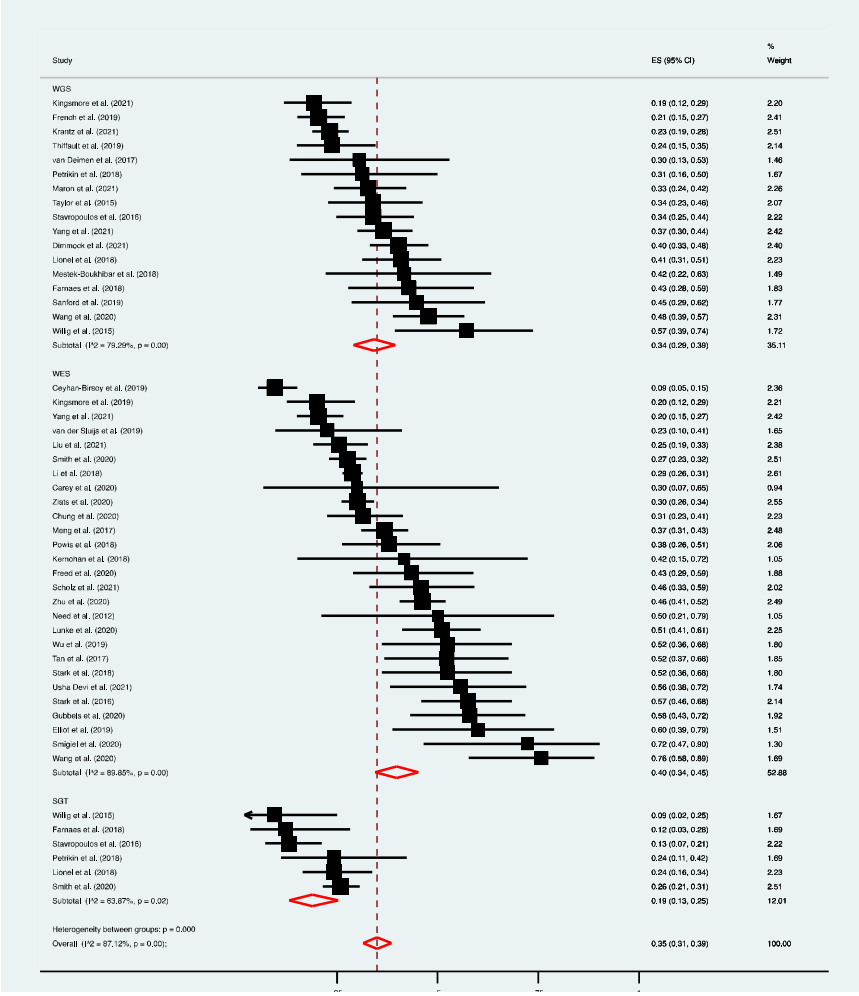

Figure 2: Forest plot of the diagnostic utility of WGS, WES, and standard genetic testing (SGT).

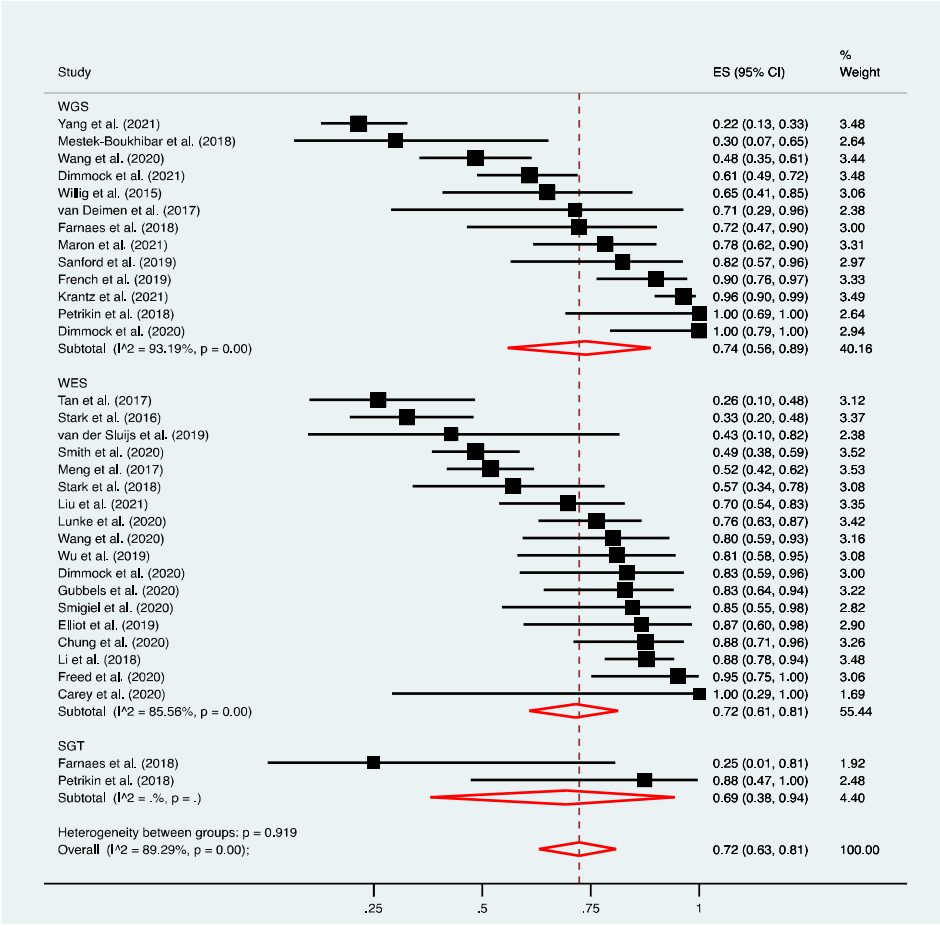

Figure 3: Forest plot of the clinical utility of WGS, WES, and standard genetic testing (SGT).

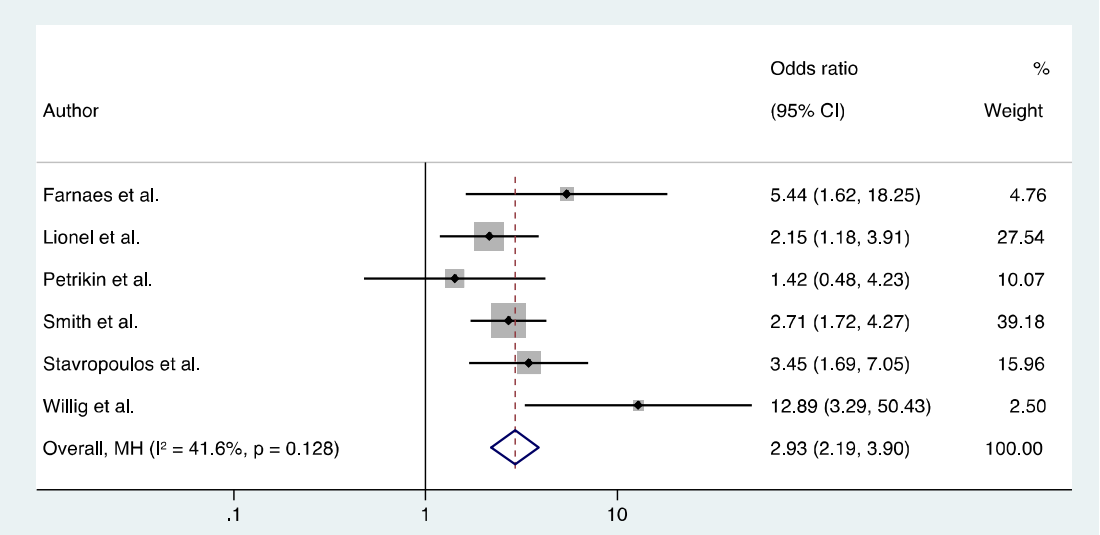

Figure 4: Forest plot of the odds ratio of WGS, WES, and standard genetic testing (SGT).

7.0 Discussion

Since the early 2010's, WGS and WES have gained recognition for the diagnosis of genetic diseases, however, widespread clinical use and thorough guidelines still do not exist. This systematic review identified thirty-six publications, comprising a total of 5540 children, reporting the diagnostic or clinical utility of WGS and WES. The pooled diagnostic utility showed that WES (0.40, 95% CI 0.34-0.45, I^2=90%), was qualitatively greater than WGS (0.34, 95% CI 0.29-0.39, I^2=79%), and SGT (0.19, 95% CI 0.13-0.25, I^2=64%). Only 6 (14%) included studies reported results of a comparator test, including CMA, Sanger sequencing, single gene tests, and gene panel testing. As such, comparisons of any statistical pooling were highly susceptible to confounding from factors; possible factors included: testing procedures, patient factors, such as consanguinity, eligibility criteria, or clinician input. This was evident within the severe levels of statistical heterogeneity between the study groups. These results suggest that CMA, Sanger sequencing, and other genetic tests, should no longer be considered the best genomic test for the diagnosis of children with suspected genetic disease, in terms of diagnostic utility; rather, WGS and WES should be considered the first-line genomic test.

While diagnostic utility is the primary measure of importance for a clinical diagnostic test, the clinical utility of WGS and WES is of high importance in order to improve the clinical outcomes of children with suspected genetic diseases. Forty-two (98%) of the included papers reported the diagnostic utility of WGS and/or WES, however, only thirty-one (72%) reported the clinical utility after diagnosis. The clinical utility of WGS and WES was measured in numerous ways throughout the studies, including clinician surveys, EHR reviews, or a combination of both. The heterogeneity within the clinical presentations and genetic origins of diseases, and the resulting numerous medical interventions, can result in a number of possible changes in medical management, thus increasing the difficulty of generalising measures of clinical utility. We defined clinical utility as any change in management within infants who have obtained a diagnosis from WGS, WES, or SGT, as determined through clinician survey and/or EHR review. Changes included further testing, transferral to palliative care, and withdrawal of support, but excluded genetic counselling and parental reproductive planning, as genetic counselling should be offered to all children and their families, regardless of diagnostic result, and reproductive planning for parents does not affect the diagnosed child's clinical status. The pooled clinical utility showed that WGS (0.74, 95% CI 0.56-0.89, I^2=93%), was qualitatively greater than WES (0.72, 95% CI 0.61-0.81, I^2=86%), while both were qualitatively greater than SGT (0.69, 95% CI 0.38-0.94). However, the results showed severe heterogeneity (I^2>75%) for WGS and WES, precluding a statistical comparison. Of the 6 (14%) papers to report results of a comparator test, only 2 (5%) reported outcomes of clinical management, which meant heterogeneity could not be calculated for the SGT group, and comparisons of statistical pooling would not be appropriate. Interestingly, some studies reported the clinical utility for all of the infants enrolled, including non-diagnosed patients, with some clinicians regarding WGS and WES to have a considerable negative predictive value, employing an informal Bayesian inferential reasoning, whereby negative genomic sequencing results revised the posterior probabilities of differential diagnoses. These studies suggest that, even after a non-diagnostic result, WGS and WES have some clinical utility, although changes in management were 10.1-fold more likely when results were positive (95% CI 4.7-22.4).[31, 35, 46-48, 50, 52, 57] Changes in management for non-diagnosed participants included cancellation of planned tissue biopsies, cessation of medications, subspecialist referrals, and screening recommendations, typically as a result of non-genetic diagnoses thought to be more likely.

If the overall diagnostic success of WGS and WES was 34% and 40%, respectively, and the overall clinical success of WGS and WES was the 74% and 72%, respectively, showing that WGS and WES were highly beneficial in the treatment, management, and therefore, survival of these children, then there is a strong case for standardising WGS/WES in newborns. Although it could be argued that WGS and WES should be used as the first-line genomic

test for children with suspected genetic diseases, rather than for all children as part of the NBS programme, in order to fully utilise the clinical utility of WGS/WES, they should be used as part of the NBS procedure, before any symptoms manifest and the risk of morbidity and mortality increases. Testing approaches of parent-child trios, duos, and singletons varied between papers; although these sub-group approaches were not analysed in this review, the testing of parent-child trios is considered to be superior to singleton and duo testing. This is thought to be due to the ability of trio testing allowing for heritability to be determined, more specifically, whether the variants detected were inherited through the parents or de novo mutations. Of the papers that reported the heritability of variants, de novo variants accounted for 596/1381 (43%) detected by WGS and WES in total. This included P/LP variants that led to diagnoses, variants deemed to be an incidental finding, and VUS. De novo variants are of significant importance, in the context of WGS and WES for all newborns, as preconception genetic screening would not detect these variants.

There were several limitations to this meta-analysis. We were limited to analysing WGS and WES on cohorts of unwell children with suspected genetic diseases. This was not truly representative of the target population WGS and WES would be used for NBS. During initial searches, only one study was identified that researched the use of WGS within healthy and unwell cohorts.[38] This paper was included in this study; however, the healthy cohort was omitted from data extraction and analysis due to not meeting the patient selection criteria, presenting a risk of bias, and source of heterogeneity. The field would benefit from further studies on the diagnostic and clinical utility of WGS and WES on an unbiased healthy cohort, to statistically determine if WGS and WES are worthwhile and cost-effective approaches to NBS. The highest level of evidence for clinical interventions is meta-analyses of RCTs (Level 1).[65] Our literature search identified only five published RCTs, with two looking at different outcomes from the same trial, while another compared time to receipt of results rather than comparing sequencing methods. Each RCT compared different index tests and reference standards, two looking WES vs WGS, one examining WGS vs SGT, and the other looking et WES vs. SGT. We were, therefore, unable to produce a high-level evidence meta-analysis of WGS and WES compared to SGT. Our review consisted mainly of published studies comprising a Level 2 (non-randomised controlled studies or quasi-experimental studies) and Level 3 evidence (non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies). We examined the diagnostic and clinical utility of WGS and WES compared to SGT. However, severe heterogeneity was present across all between-group analyses. This could largely be due to differing rates of consanguinity within the cohort, as well as “cherry-picking” of participants with certain clinical presentations considered to have a high likelihood of a genetic origin. The year of publication could have also played a part; WGS and WES are relatively new techniques whose methodologies and interpretations are expanding with time and further knowledge. The rates of severe heterogeneity could be better explored through a meta-regression to determine the impacts of certain confounding factors on heterogeneity. The meta-analysis did not include the cost-effectiveness of WGS and WES compared to SGT, either in terms of the patient’s diagnostic odyssey or the overall impact on the healthcare system.

8.0 Conclusion

In meta-analyses of 43 studies of children with suspected genetic diseases, the diagnostic utility of WES (0.40, 95% CI 0.34-0.45, I^2=90%), was qualitatively greater than WGS (0.34, 95% CI 0.29-0.39, I^2=79%), and SGT (0.19, 95% CI 0.13-0.25, I^2=64%). For the rate of clinical utility, WGS (0.74, 95% CI 0.56-0.89, I^2=93%), was qualitatively greater than WES (0.72, 95% CI 0.61-0.81, I^2=86%), while both were qualitatively greater than SGT (0.69, 95% CI 0.38-0.94). Additional studies are needed to examine the effectiveness of WGS and WES in cohorts of healthy children, particularly RCTs examining the diagnostic and clinical utility,

as well as the cost-effectiveness of using these sequencing techniques in this area, in order to truly determine if WGS and WES should become part of the NBS programme.

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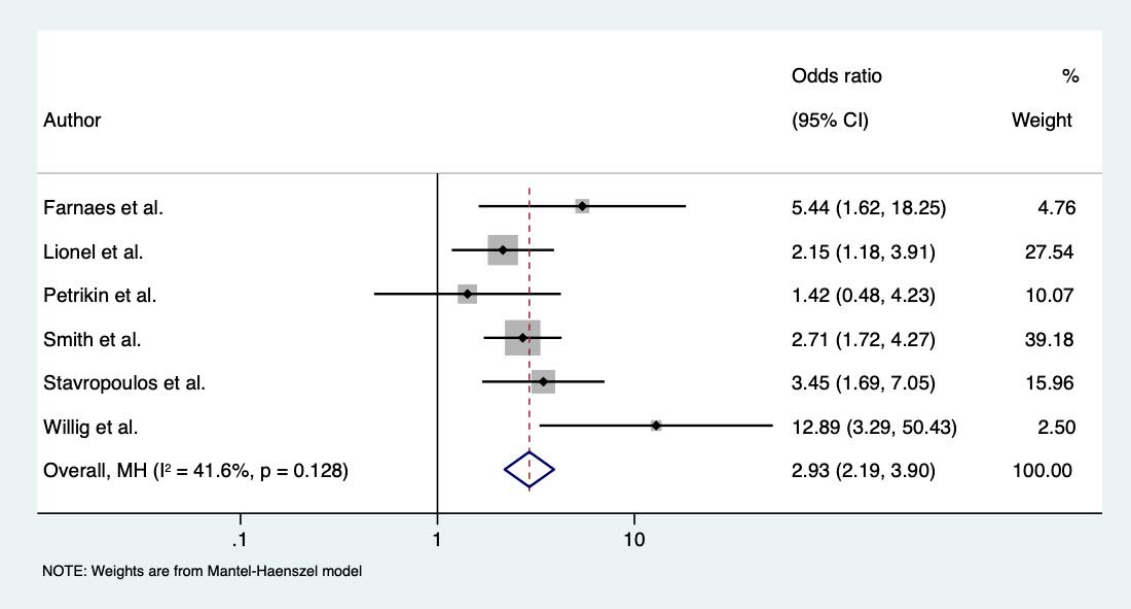


Figure 4: Forest plot of the odds ratio of WGS, WES, and standard genetic testing (SGT).

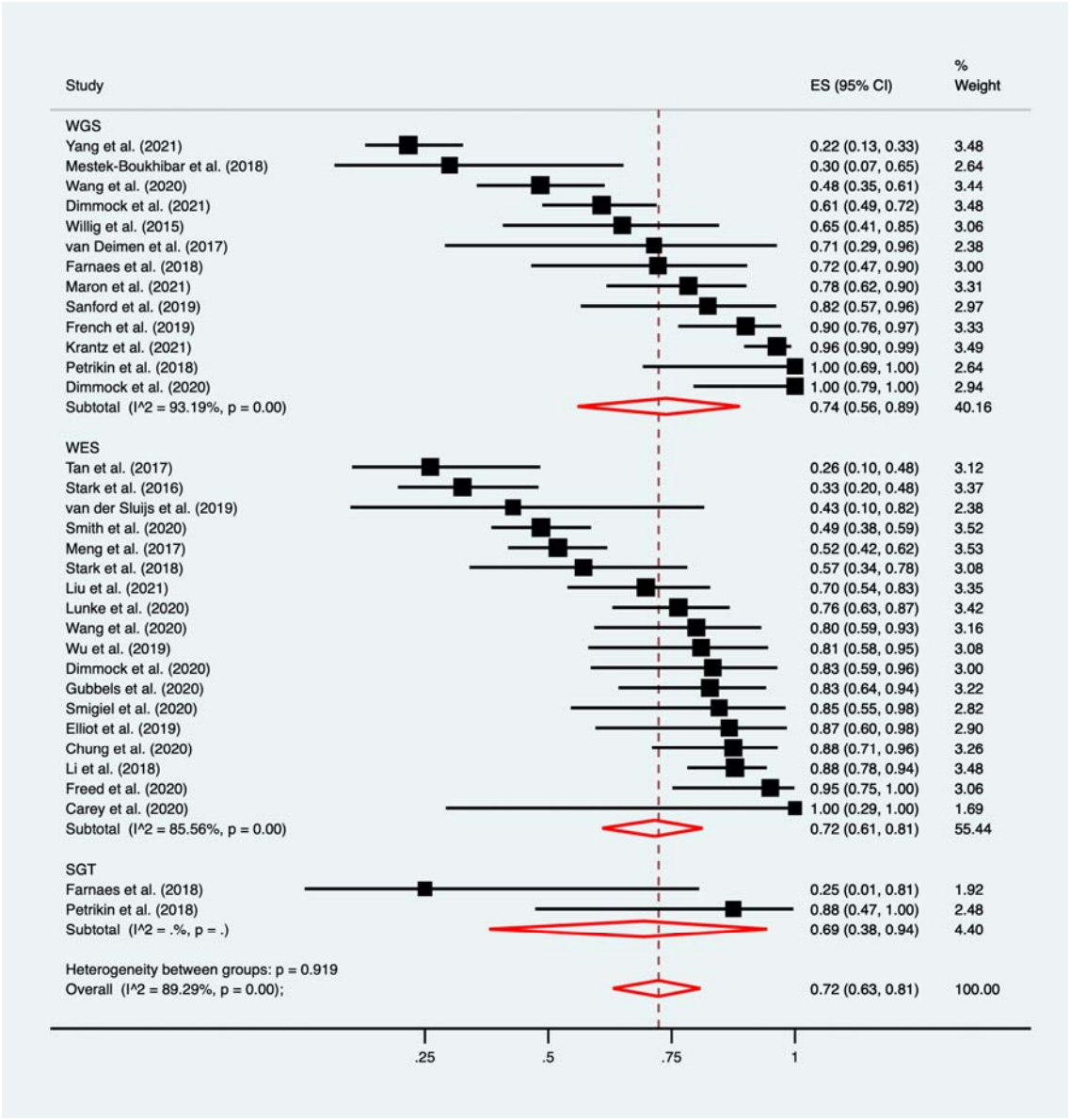


Figure 3: Forest plot of the clinical utility of WGS, WES, and standard genetic testing (SGT).

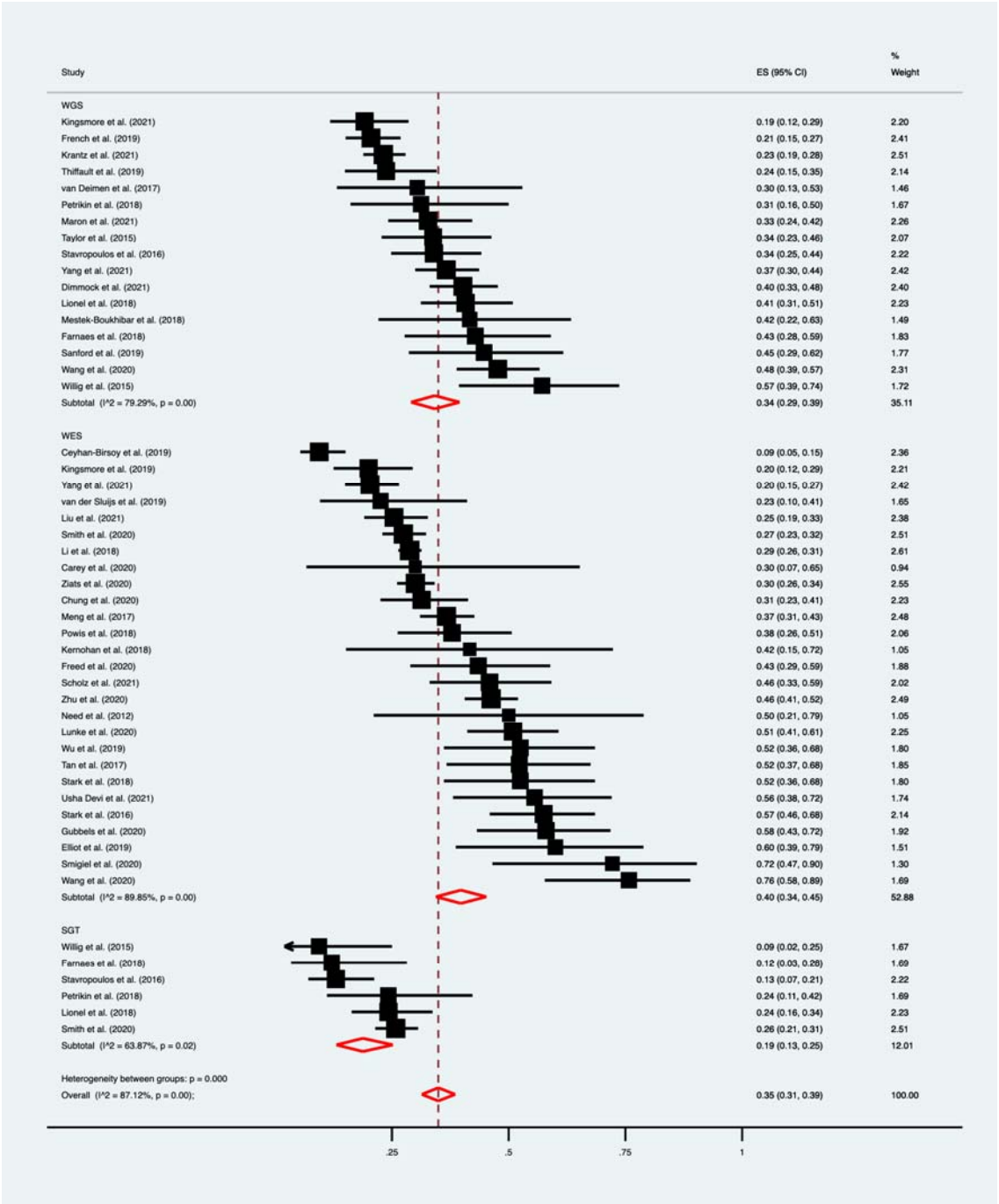


Figure 2: Forest plot of the diagnostic utility of WGS, WES, and standard genetic testing (SGT).

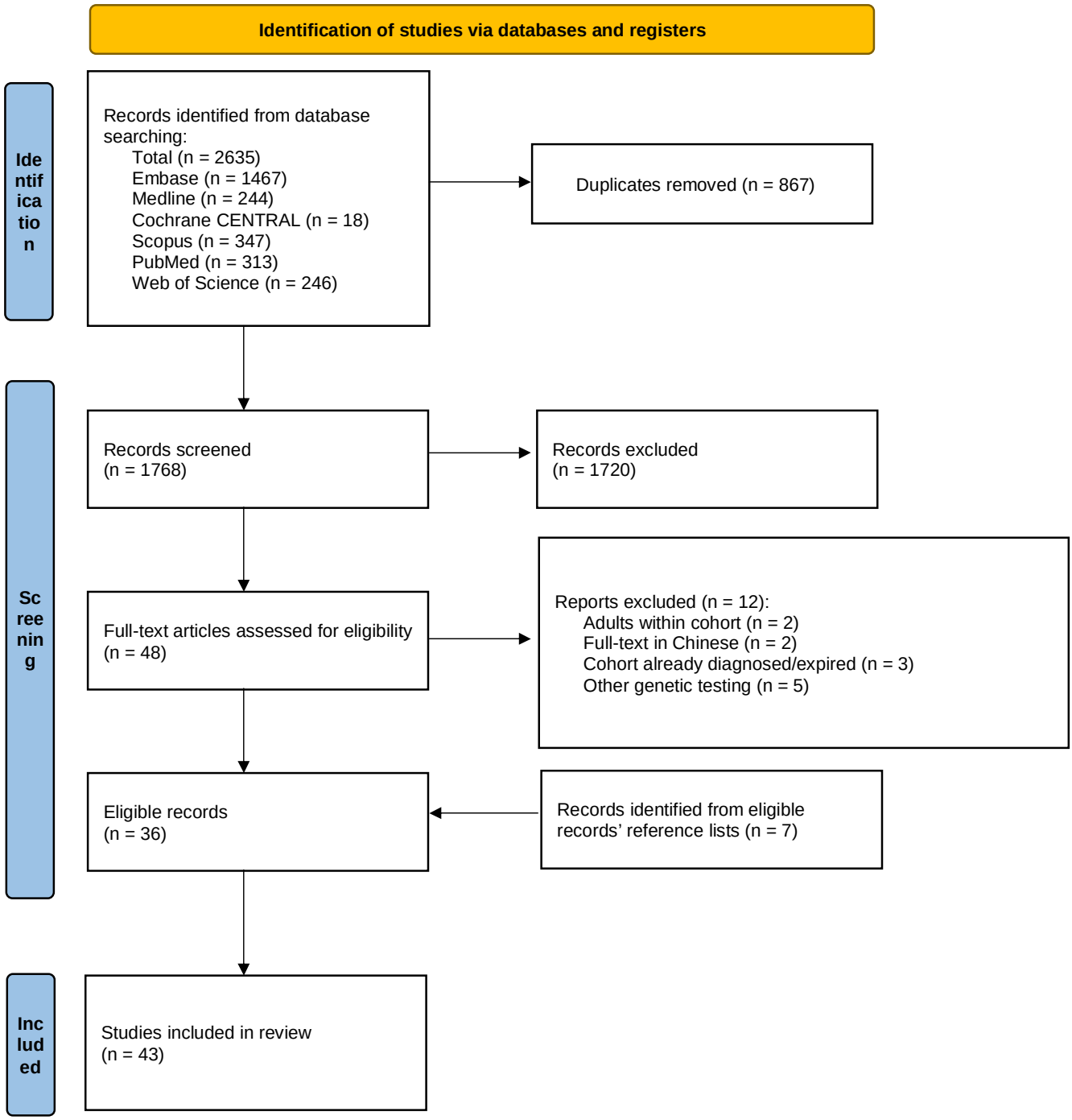


Figure 1: Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram for Meta-analysis of diagnostic and clinical utility of WGS and WES.

Citation	Site	Mode	Study Design	Study Outcomes	Total Study Size (no. of children)	Population
Carey et al, 2020	USA	rWES	Case series	Impact of rCES on the length of stay of pediatric patients admitted to PICU. Diagnostic yield of rCES, turnaround time, and clinical utility.	10	Patients under 6 years of age, with a predetermined ICD-10 concerning a new metabolic or neurologic disease, and an anticipated inpatient length of stay of at least 3 days, admitted at the Presbyterian Morgan Stanley Children's Hospital enrolled between October 2017 – December 2018.
Ceyhan-Birsoy et al, 2019	USA	WES	RCT	Diagnostic yield of WES on healthy and sick newborns compared to standard of care.	316	Patients under 42 days of age, born and admitted to the Well Newborn Nursery at Brigham and Women's Hospital or born and admitted to the NICU/PICU at Brigham Women's Hospital, Boston Children's Hospital, or Massachusetts General Hospital.
Chung et al, 2020	China	rWES	Case series	Assess the diagnostic capacity, TAT, clinical utility, and the costs associated with precision medicine interventions of rWES in predominantly Chinese infants and children with suspected monogenic disorders.	102	Critically ill pediatric patients urging for a diagnosis or whom would benefit from a timely diagnosis to support decisions in clinical management, from Queen Mary Hospital and the Hong Kong Children's Hospital, enrolled between June 2016 – February 2020
Dimmock et al, 2021	USA	rWGS	Case series	To evaluate the clinical and economic impact of rapid precision medicine based on rWGS as a first-line diagnostic test in the California Medicaid program.	184	Patients under 1 year of age and within one week of hospitalisation or had just developed an abnormal response to therapy, who was acutely ill, without a clear non-genetic etiology, from five tertiary care children's hospitals' NICU/PICU within California USA, enrolled between November 2018 – May 2020.
Dimmock et al, 2020	USA	urWGS rWGS rWES	RCT	Clinical utility and family-centered outcomes of acutely ill infants receiving urWGS, rWGS or rWES as a first-tier test.	213	Patients under 4 months of age, time from admission or time from development of a feature suggestive of a genetic condition < 96 hours, from the NICU/PICU/CVICU at Rady Children's Hospital, enrolled between

						29/06/2017 and 09/10/2018.
Elliott et al, 2019	CA	rWES	Case series	To establish and validate a pilot platform for rapid WES of critically ill babies with suspected genetic disorders. Diagnostic yield, turnaround time, clinical utility and economic feasibility of rWES as a first-tier clinical test for these patients. Identification of health service implementation issues related to rWES.	25	Patients admitted to the NICU at BC Women's Hospital with one or more of the following: unexplained seizures, metabolic disturbances, neurological abnormalities or depressed level of consciousness, multiple congenital anomalies, or significant physiological disturbance in keeping with a genetic disorder.
Farnaes et al, 2018	USA	rWGS	Case series	To compare the diagnostic yield, clinical utility, and healthcare utilization of rWGS and standard of care (including clinical genetic testing). Turnaround time of rWGS.	42	Patients under 1 year of age, admitted at Rady Children's Hospital with a suspected genetic disease but without an etiologic diagnosis, enrolled between 26/07/2016 and 08/03/2017.
Freed et al, 2020	USA	rWES	Case series	Diagnostic yield, turnaround time, and clinical utility of rWES in critically ill children with likely genetic disease.	46	Patients under 6 months of age, admitted at Seattle Children's Hospital ICU, critically ill with a suspected monogenic disorder and a recommendation of rWES by a consulting geneticist. Enrolled between October 2016 and July 2019.
French et al, 2019	UK	WGS	Case series	Establish WGS analysis pipeline in an ICU context, delivering clinical results in a timely manner. Determine the prevalence of genetic conditions within NICU/PICU populations and the clinical utility of diagnosis.	195	Children admitted to the NICU/PICU within the Cambridge University Hospitals Foundation Trust, with congenital anomalies, neurological symptoms including seizures, suspected metabolic disease, surgical necrotizing enterocolitis, extreme intrauterine growth retardation and unexplained critical illness of likely genetic etiology. Enrolled between December 2016 – September 2018.
Gubbels et al, 2020	USA	rWES	Case series	Impact of rWES in critically ill neonates, diagnostic yield, turnaround time and clinical utility.	50	Patients under 6 months of age, admitted to the NICU/CVICU/ICU at Boston Children's Hospital, Brigham and Women's Hospital and Massachusetts General Hospital, with hypotonia, seizures, a complex metabolic phenotype, and/or multiple congenital malformations and no likely alternative diagnosis. Enrolled between March 2017 and

						November 2018.
Kernohan et al, 2018	CA	WES	Case series	Diagnostic yield of WES compared to comprehensive panel testing.	12	Patients with an undiagnosed medical condition, who are currently admitted, or had been admitted in the past to the NICU at the Children's Hospital of Eastern Ontario and the Ottawa Hospital, General Campus, enrolled between January 2014 – December 2014.
Kingsmore et al, 2019	USA	urWGS rWGS rWES	RCT	Compare the analytic and diagnostic performance (diagnostic yield and turnaround time) of urWGS, rWGS and rWES.	213	Patients under 4 months of age, time from admission or time from development of a feature suggestive of a genetic condition < 96 hours, from the NICU/PICU/CVICU at Rady Children's Hospital, enrolled between 29/06/2017 and 09/10/2018.
Krantz et al, 2021	USA	WGS	RCT	To determine the effect of WGS on clinical management in a racially and ethnically diverse and geographically distributed population of acutely ill infants in the US.	354	Patients under 120 days of age, who were admitted to an intensive care unit with a suspected genetic disease. Several hospital from across the USA took part between 11/09/2017 and 30/04/2019.
Li et al, 2018	China	WES	Case series	Evaluate the diagnostic utility, clinical utility, turnaround time and overall performance of proband-only medical exome sequencing (POMES) as a cost-effective first-tier diagnostic test for pediatric patients with unselected conditions.	1323	Patients referred for genetic testing at Shanghai Children's Medical Center, enrolled between April 2015 – December 2016.
Liu et al, 2021	China	WES	Case series	To investigate the spectrum of monogenic disorders, the diagnostic yield and clinical utility of WES from a PICU in a large children's hospital in China.	169	Patients aged between 29 days and 18 years of age, with a suspected monogenic disease after consulting at least one geneticist from the PICU of Beijing Children's Hospital, enrolled between July 2017 – February 2020.
Lionel et al, 2017	CA	WGS	Case series	Compare the diagnostic utility of WGS, NGS gene panels and other conventional genetic testing methods in a pediatric population with diverse phenotypes.	103	Patients under 18 years of age, without a molecular genetic diagnosis from subspecialty outpatient clinics at The Hospital for Sick Children, enrolled between April 2013 – June 2015.
Lunke et al, 2020	AUS	urWES rWES	Case series	Evaluate the performance of ultra-rapid genomic diagnosis in a public healthcare system. Diagnostic yield, turnaround time, clinical utility and	108	Patients admitted to a participating NICU/PICU (from 12 tertiary hospitals in Australia, including 5 women's hospitals, 3 women's and children's hospitals, and 4

				proportion of laboratory reports returned prior to death or hospital discharge.		children's hospitals), referred to the clinical genetic service for a suspected monogenic condition, enrolled between March 2018 – February 2019.
Maron et al, 2021	USA	rWGS	Case series	Compare the diagnostic yield and clinical utility of rWGS and a novel targeted genomic sequencing platform.	113	Patients under 1 year of age, with a suspected, undiagnosed genetic disorder at Tufts Medical Center, Rady Children's Hospital, University of Pittsburgh Medical Center Children's Hospital, Mount Sinai Kravis Children's Hospital, North Carolina Children's Hospital, and Cincinnati Children's Hospital Medical Center, enrolled after July 2019.
Meng et al, 2017	USA	WES	Case series	Indications for testing, diagnostic yield, clinical use, turnaround time, molecular findings, patient age at diagnosis, and effect on medical management among a group of critically ill infants who were suspected to have genetic disorders.	278	Children under 100 days of age, at Texas Children's Hospital, referred for exome sequencing, between December 2011 – January 2017.
Mestek-Boukhibar et al, 2018	UK	rWGS	Case series	Establishment of a multidisciplinary Rapid Pediatric Sequencing team for case selection, trio WGS, rapid bioinformatics sequence analysis, phased analysis and reporting system to prioritize genes with a high likelihood of being causal.	24	Children with a suspected monogenic disease, enrolled between August 2015 – October 2017.
Need et al, 2012	USA	WES	Case series	Evaluate the use of NGS to provide genetic diagnoses in children with congenital anomalies and/or intellectual disabilities due to unexplained conditions presumed to be genetic.	12	Children with two or more of the following: unexplained intellectual disability and/or developmental delay, major congenital anomaly, multiple minor congenital anomalies, or facial dysmorphisms at the Duke University Medical Center.
Petrikin et al, 2018	USA	rWGS	RCT	Compare the rates of genetic diagnosis in NICU/PICU infants with possible genetic diseases at 28 days from enrollment by standard genetic tests alone versus standard genetic tests and trio rWGS.	65	Children under 4 months of age, admitted to the NICU/PICU at Children's Mercy, with illness of unknown etiology, enrolled between October 2014 – June 2016.
Powis et al, 2018	USA	WES	Case series	Determine the diagnostic rates, turnaround time, and features of neonatal patients undergoing	66	Children under 1 month of age undergoing diagnostic exome sequencing.

				diagnostic exome sequencing.		
Sanford et al, 2019	USA	rWGS	Case series	Evaluate NGS in pediatric critical care. Diagnostic yield, turnaround time and clinical utility.	38	Children between 4 months and 18 years of age, from the PICU at Rady Children's Hospital, with a suspected underlying monogenic disease, enrolled between July 2016 – May 2018.
Scholz et al, 2021	Germany	WES	Case series	Diagnostic yield of WES for monogenic diseases and identify phenotypes more likely associated with a genetic etiology in a cohort of critically ill premature and term-born infants in their first year of life.	61	Patients under 12 months of age, with a severe illness of unknown etiology, need for ICU admission or suspected underlying genetic disease, from the NICU/PICU of University Medical Center Hamburg-Eppendorf, enrolled between March 2017 – March 2020.
Smigiel et al, 2020	Poland	rWES	Case series	Evaluate the use of rWES as a diagnostic tool applied as a first-choice examination in critically ill children in the ICU. Diagnostic yield, turnaround time, and clinical utility/outcome.	18	Children in the ICU at Wroclaw Medical University, with severe unexplained neurological signs that started suddenly, enrolled between 2015 - 2016.
Smith et al, 2020	USA	WES	Case series	Diagnostic yield, survival, cost of care and clinical utility of exome sequencing compared no exome sequencing in a population of critically ill patients who had a suspected genetic etiology.	736	Children under 1 year of age, admitted to the ICU at Texas Children's Hospital, who have had an inpatient genetics consultation, and no definitive clinical diagnosis, enrolled between 01/12/2011 – 30/06/2017. The no-ES cohort was propensity score matched (based on clinical characteristics and Human Phenotype Ontology terms) with patients in the ES cohort.
Stark et al, 2018	AUS	rWES sWES	Case series	Implement and evaluate the outcomes of a rapid genomic program at two pediatric tertiary centers.	40	Children under 18 years of age, at the Royal Children's Hospital and Monash Children's Hospital, with likely monogenic disorders, enrolled between April 2016 – September 2017.
Stark et al, 2016	AUS	WES	Case series	Evaluate the diagnostic and clinical utility, and turnaround time of singleton whole-exome sequencing as a first-tier test in infants with suspected monogenic disease.	80	Children under 2 years of age, presenting with multiple congenital abnormalities and dysmorphic features, or other features strongly suggestive of monogenic disorders, at the Royal Children's Hospital, enrolled between February 2014 – May 2015.

Stavropoulos et al, 2016	CA	WGS	Case series	Diagnostic yield of WGS compared with conventional molecular testing.	100	Children under 18 years of age, with two or more structural malformations, or unexplained developmental delay/intellectual disability with or without clinical features, from The Hospital for Sick Children, enrolled between September 2013 – May 2014.
Tan et al, 2017	AUS	WES	Case series	Impact of WES in sequencing children suspected of having a monogenic disorder. Evaluate the cost-effectiveness if WES had been available at different time points in their diagnostic trajectory.	44	Children aged between 2 years and 18 years of age, at Royal Children's Hospital, with a suspected monogenic condition, remaining undiagnosed after clinical assessment, enrolled between 01/05/2015 – 30/11/2015.
Taylor et al, 2015	UK	WGS	Case series	Identify and quantify the effect on success of factors relating to the genetic architecture of a disease, experimental design and analytical strategy.	68	Children in whom WGS findings could have immediate clinical utility due to diagnosis, prognosis, treatment selection, or genetic counselling and reproductive choices recruited as a part of a collaboration between the Wellcome Trust Centre for Human Genetics at the University of Oxford, the Oxford NIHR Biomedical Research Centre and Illumina Inc. Enrolled after December 2010.
Thiffault et al, 2019	USA	WGS	Case series	Diagnostic yield and turnaround time of clinical genome sequencing in an unbiased pediatric cohort. Describe the clinical validation, patient metrics, ordering patterns, results, reimbursement, and physician retrieval of results.	80	Children with suspected genetic disorders, referred by their attending physician for clinical genome sequencing at Children's Mercy, enrolled between 12/08/2015 – 24/04/2017.
Usha Devi, 2021	India	CES	Case series	To study the utility of clinical exome sequencing using next generation sequencing in evaluating neonates with suspected genetic conditions.	36	Neonates with suspected genetic conditions/an atypical presentation of a suspected genetic condition, from the Level III NICU, Chennai, enrolled between August 2016 – August 2019.
van der Sluijs et al, 2019	NL	WES	Case series	Evaluate the use of exome sequencing as a diagnostic tool in children with a suspected genetic disorder. Diagnostic and clinical utility.	31	Children aged under 120 days, who received a clinical genetic consultation at the NICU/PICU in the Leiden University Medical Center, and had either of the following: isolated cardiac anomaly (mostly single ES), a combination of multiple congenital anomalies, or a congenital anomaly with dysmorphic features, in the absence of a

						clinical diagnosis, or delayed development or, e.g., persisting feeding problems at follow-up. Enrolled between September 2014 – September 2016.
van Diemen et al, 2017	NL	WGS	Case series	Turnaround time and diagnostic yield of rapid targeted genomic diagnostics for clinical application.	23	Children under 1 year of age, at University Medical Center Groningen, who are critically ill, and have one or more of the following: congenital anomalies and/or severe neurologic symptoms, such as intractable seizures, suggestive of a genetic cause of disease, enrolled between May 2014 – May 2016.
Wang et al, 2020	China	WGS	Case series	Establish an optimized trio genome sequencing (OTGS) analysis pipeline, evaluating the diagnostic utility and its influence on clinical management in infants from PICU/NICU.	130	Children from the PICU/NICU at the Children's Hospital of Fudan University, with one of the following: multisystem failure, congenital cardiac defect, recurrent infection, dysmorphia, metabolic crisis, failure to thrive or early onset developmental delay, families with an abnormal pregnancy history, enrolled between 01/06/2018 – 30/12/2018.
Wang et al, 2020	China	WES	Case series	Evaluate a rapid 24 hour trio-exome sequencing pipeline that permits early genetic diagnosis with a turnaround time of approx. 24 hours, at a fraction of the cost of rWGS. Diagnostic yield, turnaround time and clinical utility.	33	Children from the Children's Hospital of Fudan University, with a serious illness that progressed fast, but without a definite diagnosis, enrolled between May 2018 – June 2018.
Willig et al, 2015	USA	WGS	Case series	Comparison of the diagnostic rate, turnaround time, and types of molecular diagnoses of standard clinical genetic testing, as clinically indicated, versus rWGS.	35	Children aged under 4 months, from Children's Mercy, with an acute illness of suspected genetic cause, and no previous genetic diagnosis, enrolled between 11/11/2011 – 01/10/2014.
Wu et al, 2019	TW	WES	Case series	Assess the feasibility of WES as a tool to improve the efficacy of rare disease diagnosis for pediatric patients with severe illness. Diagnostic utility, turnaround time and clinical utility.	40	Children under 18 years of age, from the National Taiwan University Children's Hospital, who are critically ill, and suspected of having a genetic disease, or newborns who were suspected of having a serious genetic disease after newborn screening were referred for eligibility, enrolled between May 2017 – May 2018.

Yang et al, 2021	China	CES, WGS	Case series	Diagnostic and clinical utility of trio-rapid genome sequencing in critically ill infants.	202	Critically ill infants presenting with conditions suggestive of a genotypically heterogeneous disorder that other genetic testing strategies were unlikely to solve, from 13 member hospitals of the CNGP (China), enrolled between April 2019 – December 2019.
Zhu et al, 2020	China	WES	Case series	Molecular diagnostic yield of WES, investigate the underlying genetic conditions, and develop an ideal molecular diagnostic work-flow for Chinese NICU population suspected with a genetic etiology.	307	Children under 100 days of age, at various Shanghai Jiao Tong University School of Medicine Hospitals, with suspected genetic causes of illness, enrolled between January 2016 – December 2018.
Ziats et al, 2020	USA	WES	Case series	Determine how ES is changing pediatric clinical practice and furthering our understanding of pathogenesis of many genetic diseases. Diagnostic utility of ES.	523	Children referred to the Michigan Medicine Pediatric Genetics clinic for any reason and who underwent WES as part of their diagnostic workup, enrolled between 01/10/2012 – 30/04/2018.

Table X: Included Study Characteristics

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 (supplementary)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7

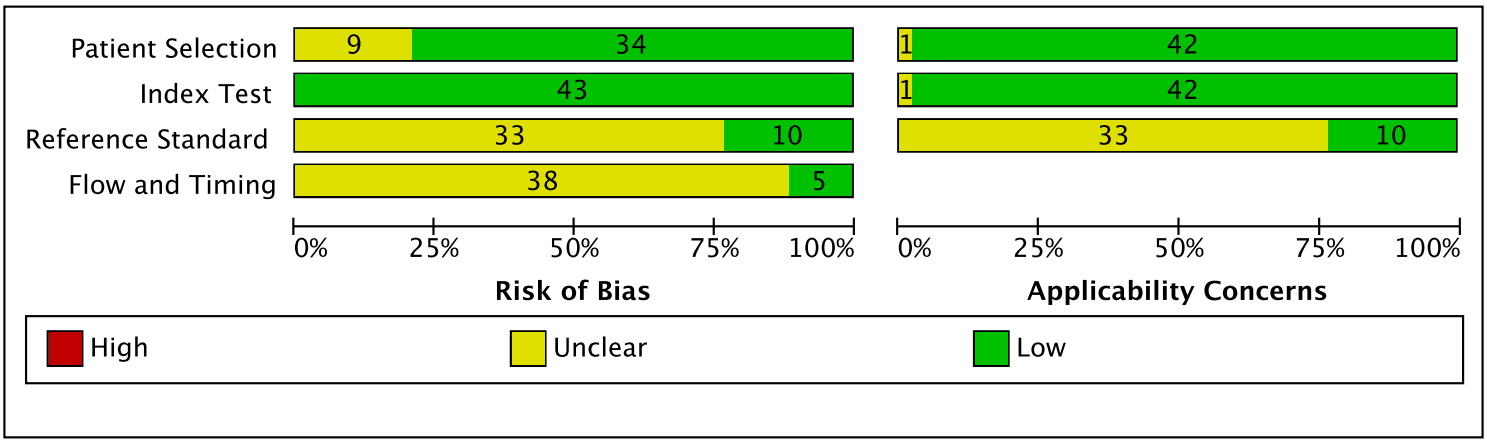
PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	11
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	10/11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/



P: seriously ill children, infants, newborns with suspected genetic disorders
I: whole exome sequencing, whole genome sequencing
C: single-gene testing/standard newborn screening
O: genetic/clinical diagnosis, time to diagnosis, change in treatment/management

Concept 1: children, infant, newborn

- MeSH terms: “Infant”[Mesh] OR “Infant, Newborn”[Mesh] OR "Child"[Mesh]
- Key search terms: child*[tw] OR infant[tw] OR newborn[tw]

Concept 2: whole genome sequencing, whole exome sequencing

- MeSH terms: “Whole Genome Sequencing”[Mesh] OR “Whole Exome Sequencing”[Mesh] OR “Genetic Testing”[Mesh] OR "High-Throughput Nucleotide Sequencing"[Mesh]
- Key search terms: WGS[tw] OR rWGS[tw] OR urWGS[tw] OR WES[tw] OR rWES[tw] OR “whole genome seqeunc*”[tw] OR “whole exome sequenc*”[tw]

Concept 3: critically ill, ICU, NICU, PICU

- MeSH terms: “Critical Illness”[Mesh] OR “Intensive Care Units”[Mesh] OR "Intensive Care, Neonatal"[Mesh] OR "Intensive Care Units, Pediatric"[Mesh] OR "Intensive Care Units, Neonatal"[Mesh] OR "Critical Care"[Mesh]
- Key search terms: “critically ill”[tw] OR ICU[tw] OR NICU[tw] OR PICU[tw]

PubMed Search

#1 “Infant”[Mesh] OR “Infant, Newborn”[Mesh] OR "Child"[Mesh] OR child*[tw] OR infant[tw] OR newborn[tw] OR baby[tw] OR neonate[tw]

#2 “Whole Genome Sequencing”[Mesh] OR “Whole Exome Sequencing”[Mesh] OR “Genetic Testing”[Mesh] OR "High-Throughput Nucleotide Sequencing"[Mesh] OR WGS[tw] OR rWGS[tw] OR urWGS[tw] OR WES[tw] OR rWES[tw] OR “whole genome seqeunc*”[tw] OR “whole exome sequenc*”[tw] OR “whole-genome sequenc*”[tw] OR “whole-exome sequenc*”[tw] OR “genomic sequenc*”[tw] OR “exome sequenc*”[tw] OR “genome sequenc*”[tw] OR TES[tw] OR TGS[tw] OR miseq[tw] OR hiseq[tw] OR “ion torrent”[tw] OR “clinical exome sequenc*”[tw] OR CES[tw]

#3 “Critical Illness”[Mesh] OR “Intensive Care Units”[Mesh] OR "Intensive Care, Neonatal"[Mesh] OR "Intensive Care Units, Pediatric"[Mesh] OR "Intensive Care Units, Neonatal"[Mesh] OR "Critical Care"[Mesh] OR “critically ill”[tw] “critical illness”[tw] OR “gravely ill”[tw] OR “severely ill”[tw] OR ill[tw] OR unwell[tw] OR sick[tw] OR ICU[tw] OR NICU[tw] OR PICU[tw]

#4 #1 AND #2 AND #3

Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to October Week 3 2021

#1 exp whole genome sequencing/
#2 exp whole exome sequencing/
#3 "whole genome sequenc*".ti,ab,mp.
#4 "whole-genome sequenc*".ti,ab,mp.
#5 "whole exome sequenc*".ti,ab,mp.
#6 "whole-exome sequenc*".ti,ab,mp.
#7 "genomic sequenc*".ti,ab,mp.
#8 wgs.ti,ab,mp.
#9 wes.ti,ab,mp.
#10 rwgs.ti,ab,mp.
#11 urwgs.ti,ab,mp.
#12 rwes.ti,ab,mp.
#13 "exome sequenc*".ti,ab,mp.
#14 "genome sequenc*".ti,ab,mp.
#15 tes.ti,ab,mp.
#16 tgs.ti,ab,mp.
#17 miseq.ti,ab,mp.
#18 hiseq.ti,ab,mp.
#19 "ion torrent".ti,ab,mp.
#20 "clinical exome sequenc*".ti,ab,mp.
#21 ces.ti,ab,mp.
#22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
#23 exp child/
#24 exp infant/
#25 exp newborn/
#26 child*.ti,ab,mp.
#27 infant.ti,ab,mp.
#28 newborn.ti,ab,mp.
#29 baby.ti,ab,mp.
#30 neonate.ti,ab,mp.
#31 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
#32 exp Critical Illness/
#33 exp intensive care unit/
#34 exp intensive care units, neonatal/
#35 exp pediatric intensive care unit/
#36 exp intensive care/
#37 "critical illness".ti,ab,mp.
#38 "critically ill".ti,ab,mp.
#39 "gravely ill".ti,ab,mp.
#40 "severely ill".ti,ab,mp.
#41 ill.ti,ab,mp.
#42 unwell.ti,ab,mp.
#43 sick.ti,ab,mp.
#44 exp critical care/
#45 icu.ti,ab,mp.
#46 nicu.ti,ab,mp.

#47 picu.ti,ab,mp.
#48 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
#49 22 and 31 and 48

Scopus Search

#1 TITLE-ABS-KEY(child* OR infant OR newborn OR baby OR neonate)
#2 TITLE-ABS-KEY("whole genome sequenc*" OR "whole-genome sequenc*" OR "whole exome sequenc*" OR "whole-exome sequenc*" OR "genomic sequenc*" OR {WGS} OR {rWGS} OR {urWGS} OR {WES} OR {rWES} OR "exome sequenc*" OR "genome sequenc*" OR {TES} OR {TGS} OR {miseq} OR {hiseq} OR "ion torrent" OR "clinical exome sequenc*" OR {CES})
#3 TITLE-ABS-KEY("critically ill" OR "critical illness" OR "gravely ill" OR "severely ill" OR ill OR unwell OR sick OR ICU OR NICU OR PICU)
#4 #1 AND #2 AND #3

Web of Science Search

#1 ts=child*
#2 ts=infant
#3 ts=newborn
#4 ts=baby
#5 ts=neonate
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 ts="whole genome sequenc*"
#8 ts="whole-genome sequenc*"
#9 ts="whole exome sequenc*"
#10 ts="whole-exome sequenc*"
#11 ts="genomic sequenc*"
#12 ts=WGS
#13 ts=rWGS
#14 ts=urWGS
#15 ts=WES
#16 ts=rWES
#17 ts="exome sequenc*"
#18 ts="genome sequenc*"
#19 ts=TES
#20 ts=TGS
#21 ts=miseq
#22 ts=hiseq
#23 ts="ion torrent"
#24 ts="clinical exome sequenc*"
#25 ts=CES
#26 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27 ts="critically ill"

#28 ts="critical illness"
#29 ts="gravely ill"
#30 ts="severely ill"
#31 ts=ill
#32 ts=unwell
#33 ts=sick
#34 ts=ICU
#35 ts=NICU
#36 ts=PICU
#37 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38 #6 AND #26 AND #37

EMBASE search 1980 to 2021 Week 41

#1 exp whole genome sequencing/
#2 exp whole exome sequencing/
#3 "whole genome sequenc*".ti,ab,mp.
#4 "whole-genome sequenc*".ti,ab,mp.
#5 "whole exome sequenc*".ti,ab,mp.
#6 "whole-exome sequenc*".ti,ab,mp.
#7 "genomic sequenc*".ti,ab,mp.
#8 wgs.ti,ab,mp.
#9 wes.ti,ab,mp.
#10 rwgs.ti,ab,mp.
#11 urwgs.ti,ab,mp.
#12 rwes.ti,ab,mp.
#13 "exome sequenc*".ti,ab,mp.
#14 "genome sequenc*".ti,ab,mp.
#15 tes.ti,ab,mp.
#16 tgs.ti,ab,mp.
#17 miseq.ti,ab,mp.
#18 hiseq.ti,ab,mp.
#19 "ion torrent".ti,ab,mp.
#20 "clinical exome sequenc*".ti,ab,mp.
#21 ces.ti,ab,mp.
#22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
#23 exp child/
#24 exp infant/
#25 exp newborn/
#26 child*.ti,ab,mp.
#27 infant.ti,ab,mp.
#28 newborn.ti,ab,mp.
#29 baby.ti,ab,mp.
#30 neonate.ti,ab,mp.
#31 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
#32 exp Critical Illness/

#33 exp intensive care unit/
#34 exp newborn intensive care/
#35 exp pediatric intensive care unit/
#36 exp intensive care/
#37 "critical illness".ti,ab,mp.
#38 "critically ill".ti,ab,mp.
#39 "gravely ill".ti,ab,mp.
#40 "severely ill".ti,ab,mp.
#41 exp critically ill patient/
#42 ill.ti,ab,mp.
#43 unwell.ti,ab,mp.
#44 sick.ti,ab,mp.
#45 icu.ti,ab,mp.
#46 nicu.ti,ab,mp.
#47 picu.ti,ab,mp.
#48 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
#49 22 and 31 and 48

Cochrane library – Cochrane Central Register of Controlled Trials (Issue 10 of 12, October 2021)

#1 MeSH descriptor: [Infant] explode all trees
#2 MeSH descriptor: [Infant, Newborn] explode all trees
#3 MeSH descriptor: [Child] explode all trees
#4 child*
#5 infant
#6 newborn
#7 baby
#8 neonate
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 MeSH descriptor: [Whole Genome Sequencing] explode all trees
#11 MeSH descriptor: [Whole Exome Sequencing] explode all trees
#12 MeSH descriptor: [Genetic Testing] explode all trees
#13 MeSH descriptor: [High-Throughput Nucleotide Sequencing] explode all trees
#14 WGS
#15 rWGS
#16 urWGS
#17 WES
#18 rWES
#19 "whole genome sequenc*"
#20 "whole-genome sequenc*"
#21 "whole exome sequenc*"
#22 "whole-exome sequenc*"
#23 "genomic sequenc*"
#24 "exome sequenc*"
#25 "genome sequenc*"

#26 TES
#27 TGS
#28 miseq
#29 hiseq
#30 "ion torrent"
#31 "clinical exome sequenc*"
#32 CES
#33 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34 MeSH descriptor: [Critical Illness] explode all trees
#35 MeSH descriptor: [Intensive Care Units] explode all trees
#36 MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees
#37 MeSH descriptor: [Intensive Care Units, Pediatric] explode all trees
#38 MeSH descriptor: [Critical Care] explode all trees
#39 "critically ill"
#40 "critical illness"
#41 "gravely ill"
#42 "severely ill"
#43 ill
#44 unwell
#45 sick
#46 ICU
#47 NICU
#48 PICU
#49 #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
#50 #9 AND #33 AND #49