Washington State Health Care Authority

Whole Exome Sequencing

Draft Evidence Report

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Health Technology Assessment Program (HTA)

Washington State Health Care Authority

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This evidence report is based on research conducted by the RTI-University of North Carolina Evidence-based Practice Center through a contract between RTI International and the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents. The findings and conclusions do not represent the views of the Washington HCA and no statement in this report should be construed as an official position of Washington HCA.

The information in this report is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
CI	Confidence interval
CMA	Chromosomal microarray analysis
CNV	Copy number variants
CPG	Clinical practice guidelines
ES	Executive summary
HTA	Health technology assessment
NR	Not reported
NS	Not significant
QALY	Quality-adjusted life year
U.K.	United Kingdom
U.S.	United States
WES	Whole exome sequencing
WGS	Whole genome sequencing

Executive Summary

Structured Abstract

Purpose: To conduct a health technology assessment (HTA) on the efficacy, safety, and cost of whole exome sequencing (WES).

Data Sources: PubMed and Embase from inception through March 14, 2019; clinical trial registry; government, payor, and clinical specialty organization websites; hand searches of systematic reviews.

Study Selection: Using a priori criteria, we selected English-language primary research studies that were conducted in very highly developed countries that reported clinical utility (i.e., changes in medical management resulting from diagnosis), health outcomes, safety outcomes (such as secondary findings), or cost outcomes. We selected trials, cohort studies (controlled or uncontrolled), or case series with 5 or more participants. To address a separate contextual question on diagnostic yield, we also identified studies from our search that reported this outcome.

Data Extraction: One research team member extracted data and a second checked for accuracy. Two investigators independently assessed risk of bias of included studies. We rated the certainty of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Data Synthesis: We flagged 99 studies for the contextual question on diagnostic yield. On average, 38% of patients for whom WES is performed receive a diagnosis. Annual reanalysis of WES data increases the diagnostic yield. Diagnostic yield was highest among patients with phenotypes exclusively or predominantly of genetic origin, such as childhood onset muscle disorders.

We included 57 studies that reported 1 or more clinical utility, health, safety, or cost outcome. A diagnosis from WES resulted in a change in clinical management of 12% to 100% across 18 studies that enrolled diverse phenotypes and 0% to 31% across 5 studies enrolling participants with epilepsy. Seven studies reported on diverse health outcomes. Four studies among hospitalized pediatric patients reported mortality, which ranged from 17% to 57%. Management changes based on WES resulted in improved seizure control or behavior management in 0% to 3% of patients with epilepsy. The pooled proportion of patients with a medically actionable secondary finding was 4% across 13 studies; most patients and families did not experience psychosocial harms from receiving negative or uncertain WES results. The cost of a WES test ranged from $1,000 to $15,000 across 15 studies. In both single-phenotype and diverse-phenotype populations, testing pathways that included WES identified more diagnoses and either cost less or cost somewhat more (highest reported estimate was $8,599 more) per additional diagnosis. Pathways with earlier WES testing were more likely to be cost-savings compared to pathways that used WES later in the testing pathway or used WES as a last-resort strategy.

Limitations: Most of the evidence is from uncontrolled, retrospective, observational studies.

Conclusions: WES increases diagnostic yield over standard diagnostic testing. A diagnosis from WES changes clinical management for some patients, but our certainty in the estimate of this frequency is very low. The evidence regarding the impact of WES testing on health and most safety outcomes is limited, though we have low certainty that the proportion of patients tested who receive a medically actionable secondary finding is about 4%. WES may be cost-effective in terms of diagnostic success, but our certainty is very low.

ES 1. Background

We designed this health technology assessment (HTA) to assist the State of Washington's independent Health Technology Clinical Committee with determining coverage for whole exome sequencing (WES).

ES 1.1 Condition Description

Whole exome sequencing (WES) may be indicated for testing for a wide range of genetic diseases. This test is most commonly used when a patient is suspected of having a genetic disorder, but the signs or symptoms are not recognizable as a specific genetic condition. This test is also used when the patient's phenotype could be consistent with multiple genetic disorders. A variant in the sequence of a gene may or may not affect the gene's function or result in symptoms. Variants that cause malformation, dysfunction, or disorders are termed pathogenic variants. Indications that a symptom or phenotype may be related to a pathogenic genetic variant include dysmorphic features, multiple anomalies, unexplained neurocognitive impairment, multifocal presentation, earlier or more severe onset of common symptoms, or a family history of similarly affected individuals.[1,2] Although genetic conditions are often thought of has having onset during infancy or childhood, many genetic disorders first become symptomatic in adulthood. Further, some conditions with pediatric onset may not be diagnosed until adulthood.

Because WES sequences the entire exome, it may also identify genetic disorders other than those that cause the patient's phenotype, some of which require specific medical management. For example, the identification of a pathogenic mutation in the BRCA2 gene would prompt early, frequent screening for breast cancer or other preventive measures.[1] In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended specifically looking for pathogenic and likely pathogenic variants in 56 genes for which medical management guidelines were available, in order to standardize the reporting of secondary findings.[2]

ES 1.2 Disease Burden

There are more than 6,000 human genetic diseases.[3] Although genetic diseases are individually rare, they collectively affect approximately 1 in 17 individuals.[4] One study estimated that the range of total inpatient charges for United States (U.S.) pediatric patients related to suspected genetic diseases in 2012 was US$ 14 to US$ 57 billion—11% to 46% of all pediatric inpatient charges.[5]

ES 1.3 Technology Description

WES identifies the DNA base-pair sequences of the protein-coding regions of the genome.[6] WES is primarily used to identify small changes in base-pair sequences that disrupt protein function and cause disease; however, improved bioinformatics has increased the ability to identify chromosomal copy number variants (i.e., larger deletions or duplications involving larger stretches of DNA) from sequenced data and also changes in the mitochondrial genome. Diagnostic WES testing is ordered by a physician or other health care professional and is conducted in a clinical diagnostic laboratory to aid in the diagnosis of a patient. Parents' or siblings' genes may be sequenced to help interpret identified variants (Trio WES).

WES uses next-generation sequencing (NGS) technologies; NGS makes many copies of the target genome, then cuts them into random sequences, and simultaneously sequences the resulting fragments. After this sequencing step, WES requires a series of bioinformatics analyses to interpret the sequencing. These analyses are described in detail in ***Section 1.3*** of the full report. A clinical laboratory report for WES usually includes all pathogenic or likely pathogenic variants identified in genes associated with the clinical phenotype of the patient and their interpretation as primary findings, and any ACMG-defined medically actionable variants as secondary findings.

The use of WES within clinical practice is still evolving in terms of how and where it is used within a diagnostic testing pathway for individual patients. Typically, WES is used when a monogenic disorder is suspected but when the patient's phenotype does not suggest a specific disorder for testing. WES can replace most single and multi-gene panel testing, but up until recently could not replace chromosomal microarray analysis (CMA) for the detection of copy number variants.

ES 1.4 Regulatory Status

The U.S. Food and Drug Administration (FDA) approves the sequencing platforms which are used to conduct clinical NGS, including WES. FDA approval is based on the demonstration of analytic validity, in other words that the sequencing machines correctly sequence DNA specimens. The FDA does not regulate WES as a diagnostic test, which involves both the sequencing component and the bioinformatics and variant interpretation component. WES is conducted by laboratories that are accredited by the Clinical and Laboratory Improvement Act (CLIA) to conduct high complexity testing. Because of the equipment and software involved (particularly for the bioinformatics platform), this test is generally only conducted in laboratories associated with large, tertiary medical centers or commercial genetics laboratories.

ES 1.5 Policy Context

The State of Washington HCA selected this topic for review because of high concerns for safety and medium concerns for efficacy and cost.

ES 2. Methods

This section describes the methods we used to conduct this HTA.

ES 2.1 Research Questions and Analytic Framework

We developed the following research questions to guide the systematic evidence review of primary research studies:

Key Question 1: Effectiveness (Clinical Utility)

1a. In what proportion of patients does testing with WES result in a clinically actionable finding (i.e., the diagnosis resulting from WES leads to something that can be treated, prevented, or mitigated)?

1b. In what proportion of patients does testing with WES result in an actual change to the patient's medical management (medication or therapies, follow-up testing, medical monitoring) or genetic counseling (reproductive risks or risks of other family members)?

1c. What is the effect of testing pathways that include WES on medical management or genetic risk counseling compared to testing pathways that do not include WES?

Key Question 2: Effectiveness (Health Outcomes)

2a.: What are the health outcomes, including mortality, among patients who have WES testing?

2b: What are the health outcomes, including mortality, of patients who receive testing pathways that include WES compared to alternative testing pathways with or without WES?

Key Question 3: Safety and Harms

3a: How many patients receive erroneous results after WES testing, either false positive or false negative results? What harms are caused by these test results and how many patients experience these harms?

3b: What harms are caused by uncertain WES results or a lack of diagnosis after WES testing?

3c: How many patients receive reports on ACMG-defined medically actionable variants after WES testing? What harms do they experience, and how many patients experience these harms?

3d: How frequently do WES results cause harm to family relationships?

Key Question 4: Cost

4a: What is the cost of WES testing?

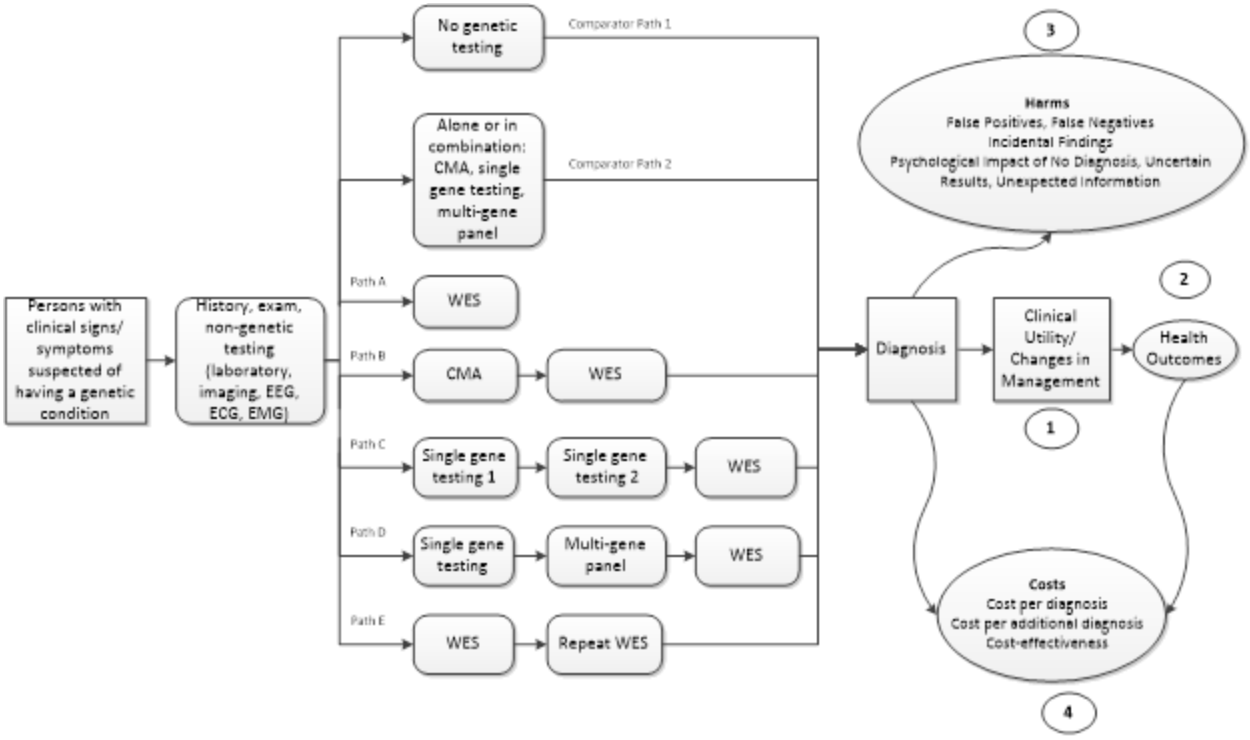
4b. What is the cost per diagnosis of pathways that include WES testing?

4c: What is the cost per additional diagnosis, comparing a pathway with WES to an alternative pathway with or without WES?

4d: What is the cost-effectiveness of testing with WES?

We also created the analytic framework, shown in ***ES-Figure 1***, to guide our review.

Figure ES-1. Analytic framework for HTA on whole exome sequencing



Abbreviations: CMA=chromosomal microarray; ECG=electrocardiography; EEG=electroencephalography; EMG=electromyography; WES=whole exome sequencing

In addition, we addressed the following contextual questions, which were not systematically reviewed and therefore are not shown in the analytic framework.

Contextual Question 1: What is the diagnostic yield of WES either alone or as part of a testing pathway and what are the factors (e.g., phenotypes being tested, testing platforms and bioinformatics analysis used) that contribute to variation in diagnostic yields?

Contextual Question 2: How often does WES return variants of uncertain clinical significance and what impact does repeat bioinformatics analysis have on diagnostic yield?

ES 2.2 Data Sources and Search

We searched MEDLINE® (via PubMed), Embase, and a clinical trials registry for relevant English-language studies from inception to March 14, 2019. We searched the Centers for Medicare and Medicaid Services and FDA websites, selected payer and health care professional society websites, and websites of other organizations. We used medical subject headings (MeSH terms) and text words associated with whole exome fusion. The detailed search strategy is in ***Appendix B.***

ES 2.3 Study Selection

Two reviewers independently screened titles and abstracts and full-text articles based on the following study inclusion criteria (complete details are in ***Table 1*** of the Full Technical Report).

- **Population:** adults or children with suspected genetic disease
- **Intervention:** WES used in a clinical diagnostic context either alone or as part of a testing strategy that includes other clinical laboratory, imaging, or other diagnostic investigations.
- **Comparator(s):** Standard clinical diagnostic investigation (i.e., usual care), single gene or multi-gene panel testing, chromosomal microarray analysis (CMA), and WES used in different places within the testing pathway. However, we did not require studies to have a comparator testing strategy.
- **Outcomes:** clinical utility (results could or were used to change clinical management, further diagnostic testing, or risk counseling or testing of family members, including reproductive counseling); health outcomes (mortality, length of survival, morbidity, cognitive ability, functional outcomes); safety and harms (misdiagnosis, proportion with ACMG-defined medically actionable variants, psychosocial harms, and employment or insurance discrimination), and cost outcomes (cost of WES test, cost per patient of strategy with WES, cost per diagnosis, cost per additional diagnosis[compared to other strategies], cost effectiveness).
- **Setting(s):** Inpatient or outpatient clinical settings from countries with a development rating designated as *very high* on the United Nations Human Development Index.
- **Study Design:** Single-arm or controlled clinical trials or observational cohort studies with more than 10 participants, case control studies, case series (between 5 to 10 participants), cost-benefit analyses, cost-utility analyses, cost-effectiveness analyses, modeling studies, and qualitative research studies (for safety and harms outcomes only).
- **Other:** English-language, published in 2010 or later (WES was not used clinically before this time)

ES 2.4 Data Abstraction and Risk of Bias Assessment

Two team members extracted relevant study data into a structured abstraction form, and the lead investigator checked those data for accuracy. Two team members conducted independent risk of bias assessments on all included studies. Risk of bias was assessed as *high*, *some concerns*, or *low* for each separate outcome domain: clinical utility, health outcomes, and safety outcomes. We assessed the risk of bias for cost outcomes with the Quality of Health Economic Studies Instrument.[7]

ES 2.5 Data Synthesis and Quality of Evidence Assessment

We qualitatively synthesized study characteristics and results for each research question in tabular and narrative formats. We used Stata (version 15) to conduct quantitative pooling of the diagnostic yield estimate for contextual question 1. We were not able to conduct quantitative syntheses for any of the key questions because of the clinical and methodological heterogeneity in this evidence base. We graded the certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8] With GRADE, the certainty of evidence can be graded as *very low*, *low*, *moderate*, or *high* based on imprecision, inconsistency, and study limitations. We note that the GRADE framework was initially developed for RCTs of interventions; it may not be well suited for assessing the strength of evidence for genetic testing.

ES 3. Results

ES 3.1 Literature Yield

We included a total of 57 studies from 60 publications published between 2014 and 2019. Thirty studies provided evidence on clinical utility (KQ1), 7 studies provided evidence on health outcomes (KQ2), 26 studies provided evidence on safety outcomes (KQ3), and 17 studies provided evidence on cost outcomes (KQ4).

ES 3.2 Contextual Questions on Diagnostic Yield

Four systematic reviews[9-12] and 99 individual studies (see ***Appendix F***) provided information on the diagnostic yield of WES. Some studies enrolled patients with diverse phenotypes, while others enrolled patients with a single phenotype (e.g., epilepsy). The degree of diagnostic testing prior to WES testing that was received by participants enrolled in these studies varied; most all had received some initial diagnostic evaluation (specialty consultation,[13-25] laboratory, imaging). Many had also received some genetic testing (e.g., single or multi-gene panels, CMA).

We calculated the pooled estimate for diagnostic yield from the 99 individual studies as 38% (95% CI, 35.7% to 40.6%). We calculated the pooled diagnostic yield of traditional testing pathways (4 studies[16,20,26,27]) as 21% (95% CI, 5.6% to 36.4%) and the diagnostic yield of gene panels (6 studies[26,28-32]) as 27% (95% CI, 13.7% to 40.5%). The likelihood of a genetic cause and therefore the diagnostic yield of WES varied by patient age and phenotype. The diagnostic yield decreased as the age of participants increased: 42% among infants, 38% among children, and 20% among adults. There were 7 disorders or groups of related disorders for which there were

more than 2 studies of diagnostic yield. The diagnostic yield for these disorders ranged from 29% for participants with an intellectual or developmental disability to 48% for those with limb-girdle muscular dystrophy.

Reanalysis of WES data using updated variant call algorithms and newly discovered pathogenicity information increases diagnostic yield. Among the 8 studies that examined the yield from reanalysis, 17% of previously undiagnosed patients were diagnosed by reanalysis of existing WES data.[13,21,33-38]

ES 3.3 Key Question 1: Effectiveness (Clinical Utility)

Thirty studies (reported in 33 publications) reported on clinical utility outcomes.[13-16,18,19,22,24,25,27,28,32,34,39-58] Most studies were single-arm observational cohort studies and 16 were conducted in the U.S. Fifteen studies were rated as having a high risk of bias, and 17 as having some risk of bias. Eight studies had all or some industry-funding, but this characteristic was not uniformly reported by all studies. Enrollment in 29 studies was limited by age group: 3 studies[28,40,56] only included infants, 13 only included children, and 1[50] only included adults. The remaining 12 studies included both adults and children.[18,32,34,39,41-46,48,57] Eighteen of the included studies performed WES on patients with diverse phenotypes. The remaining studies enrolled single-phenotype participants. Five studies included patients with epilepsy,[27,28,32,34,58] and 7 studies included patients with another phenotype: familial hypercholesterolemia,[50] intellectual developmental disorder,[44] malignant infantile osteopetrosis,[53] kidney transplant,[48] young onset nephrolithiasis,[41] neurodevelopmental disorders,[25] and short stature.[51]

The key findings are:

- Among studies that enrolled patients with diverse phenotypes (18 studies):
    - A WES diagnosis changed clinical management for between 12% to 100%
    - A WES diagnosis changed medication for between 5% to 25%
    - A WES diagnosis resulted in counseling and genetic testing for family members for between 4% and 97%
- Among studies that enrolled patients with epilepsy (5 studies):
    - A WES diagnosis changed clinical management for between 0% to 31%
    - A WES diagnosis changed medication for between 0% to 20%
- Among studies that enrolled patients with a single phenotype (7 studies), all reported some changes in clinical management following a WES diagnosis, but the data was too heterogenous to synthesize into a single range.

We assessed the certainty of evidence related to all clinical utility outcomes as *very low* because of study designs, study limitations, inconsistency, and imprecision.

ES 3.4 Key Question 2: Effectiveness (Health Outcomes)

Seven studies reported on health outcomes.[22,32,34,40,53,56,58] One study was a case series,[53] 1 study was a controlled observational cohort,[22] and the rest were single-arm observational cohort studies. Three studies were conducted in the U.S.[40,56,58] Two studies had some industry funding,[22,56] and 4 studies had no industry funding.[32,34,40,58] Two studies did not specifically list any study funders.[32,58] Three studies only included probands under the age of 18,[22,53,58] and 2 studies only included infants.[40,56] Two studies included both adults and children.[32,34] Three of the included studies performed WES on probands with diverse phenotypes,[22,40,56] and 3 studies included probands with epilepsy.[32,34,58] The remaining study included only probands with a clinical diagnosis of malignant infantile osteopetrosis.[53]

The key findings are:

- Mortality ranged from 17% to 57%, but the studies that reported mortality were conducted among infants in NICUs or hospitalized children with acute illness.
- Among patients with epilepsy, management changes resulting from WES diagnosis improved seizure control or behavior management in 0% to 3% of study participants.

We were unable to assess the certainty of evidence related to health outcomes because of very serious limitations in the study designs and reporting of outcomes.

ES 3.5 Key Question 3: Safety and Harms

Twenty-six studies provided evidence on the harms associated with WES.[20,24,40,42,43,50,54,58-76] Twenty-one quantitative studies[20,24,40,42,43,54,58,60,61,63-66,69-76] were single-arm observational cohort studies. Twelve had a low risk of bias,[42,54,60,63,64,66,69-74] 7 had some risk of bias,[20,24,40,43,61,65,75] and 2 had a high risk of bias.[58,76] The single-modeling study[75] was rated as having some risk of bias. We did not assess the risk of bias for the 4 qualitative research studies.[59,62,67,68] Four studies received some industry funding[40,60,63,66] and 4 were completely funded by industry[50,61,64,71]; the rest either had no industry funding of this information was not reported. Twenty studies were conducted in the U.S.

The key findings are:

- Two percent of patients diagnosed using standard testing were not diagnosed by WES. The patients not diagnosed with WES had genetic variants that were not diagnosed well by WES technology at the time the study was done.
- We calculated the pooled percent of patients with an ACMG-defined medically actionable variant to be 4% (95% CI, 2.4% to 5.3%) across 13 studies that provided data suitable for use in pooling. Of the remaining studies, 4 reported 0% with actionable variants,[20,42,62,70] and the other 5 reported between 1% and 10%.[24,54,61,68,75]
- Most patients or parents of patients did not experience psychosocial harms from receiving negative or uncertain WES results; these findings come primarily from qualitative research studies.

We assessed the certainty of evidence related to the frequency of ACMG-defined medically actionable variants as *low* because of study designs and study limitations. We did not assess the certainty of other reported safety outcomes as they were too heterogenous or largely reported from qualitative research studies.

ES 3.6 Key Question 4: Costs

Seventeen studies (reported in 20 publications) reported cost-related outcomes.[13-28,77-80] Two of the 17 studies were conducted in the U.S.[24,25] Five studies were funded in part by industry funding;[13-17,22,27,78] the rest were government agency funded or the source of funding was not clear. Four studies used simulation or modeling to derive cost-related outcomes.[17,23,28,79] One study used a controlled cohort design[26] and the remaining 13 studies used a single-arm observational cohort design. We assessed 6 studies as having a high risk of bias,[17,18,24,25,77,78] and the rest we assessed as having some risk for bias.

Three studies were conducted among populations that included both children and adults;[18,21,78] the rest were conducted exclusively among infants or children. Nine studies were conducted among populations that included diverse phenotypes.[13-24] The other 8 studies enrolled populations with homogenous phenotypes including participants with autism,[79] congenital muscular dystrophy,[26] epilepsy,[27,28] IDD,[77,80] neurodevelopmental disorders,[25] and peripheral neuropathy.[78]

The key findings are:

- The cost of a WES test reported in studies varied between US$ 1,000 and US $15,000; trio WES costs more than singleton WES.
- In both single-phenotype and diverse phenotype populations, when compared to standard diagnostic pathways, testing pathways that used WES identified more diagnoses at a lower cost in some studies, or identified more diagnoses but at a somewhat higher cost in other studies (range US$ 1,775 to US$ 8,559 higher depending on where WES was used in the testing pathway).
- Pathways with earlier WES testing were more likely to be cost savings than pathways that used WES later in the testing pathway or as a last resort strategy.

We assessed the certainty of evidence related to all cost outcomes as *very low* because of study designs, study limitations, inconsistency, and imprecision.

ES 4. Discussion

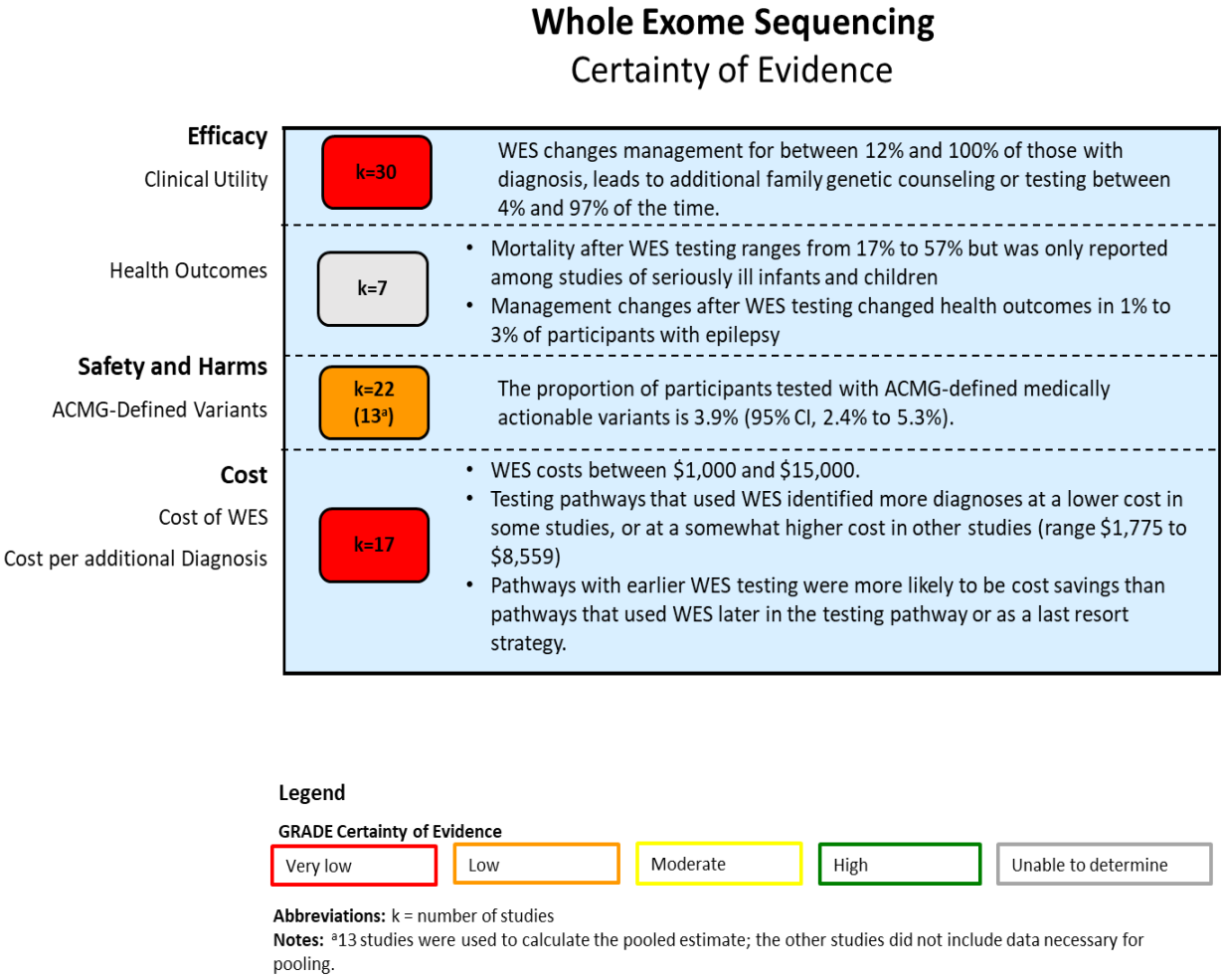
ES 4.1 Summary of the Evidence

WES has a higher diagnostic yield compared to standard testing pathways and phenotype-specific gene panels. Among all phenotypes, we calculated the pooled diagnostic yield for WES

as 38%, which is higher than the pooled diagnostic yield for traditional testing pathways (21%) and higher than the pooled diagnostic yield of gene panels (27%). Reanalysis of WES data using updated variant call algorithms and newly discovered pathogenicity information increases diagnostic yield on average by about 17%. Because this was a contextual question, we did not assess the certainty of the evidence.

The findings from the key questions and certainty of evidence is summarized in ***Figure ES-2***.

Figure ES-2. Summary of evidence from whole exome sequencing HTA



ES 4.2 Limitations of the Evidence Base

The body of evidence on WES has substantial limitations. Most studies were retrospective and collected data solely from medical records and few studies described protocols for data abstraction or approaches to ensure standardized, accurate, and replicable abstraction. Some studies explicitly excluded subjects for which they were unable to obtain outcomes data, which

introduces selection bias. Other studies did not report on how they handled subjects with missing records or data.

Few studies included a comparison group; therefore, we could only estimate the frequency of outcomes within a single group. Most studies are small, single-center studies with heterogenous study populations. As such, it is difficult to compare study outcomes among the studies, and likely that the results would have been different with a different patient mix. Studies that are not favorable to WES may not be published. We were unable to evaluate the extent of publication bias in the body of evidence because these studies are not typically registered in trial registries.

The complexity and rapid evolution of WES further complicates its evaluation. The technology continues to change rapidly, which hinders the ability to determine the applicability of studies from just a few years ago. It is also challenging to evaluate how sequencing platforms, bioinformatics approaches, or testing approaches may affect the findings of individual studies.

The nature of WES testing makes well-designed comparative effectiveness studies complicated. WES can diagnosis a wide range of conditions—many with very similar phenotypes but very different underlying genetic diagnoses with drastically different recommended management strategies and outcomes. Although randomized-controlled trials that use rigorous data collection and outcome measurement could be designed in order to produce results with a high degree of certainty under GRADE, they are likely not feasible to conduct in practice.

ES 4.3 Clinical Practice Guidelines and Related Health Technology Assessments

We did not identify any clinical practice guideline specific to diagnostic testing with WES. We identified 4 HTAs, 2 were not published in English and 2 were not publicly accessible.[81-84]

We identified 1 narrative review from the "Model Coverage Policies" page on the American Academy of Neurology's (AAN's) website.[85] This document includes suggested indications and contraindications for exome sequencing, which are detailed in ***Table 15*** of the full report.

We identified 6 documents produced by the ACMG including a policy statement published in 2012 entitled "Points to Consider in the Clinical Application of Genomic Sequencing"; these are listed in ***Table ES-1.***

Table ES-1. Indications for diagnostic testing from 2012 policy statement entitled "Points to Consider in the Clinical Application of Genomic Sequencing"[86]

WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

a. The phenotype of family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
b. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
c. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
d. A fetus with likely genetic disorder in which specific genetic tests, including targeted sequencing test, available for that phenotype have failed to arrive at a diagnosis.
    i. Prenatal diagnosis by genomic (i.e., next generation whole exome or whole genome) sequencing has significant limitations. The current technology does not support short-turn around times which are often expected in the prenatal setting. There are high false positive, false negative, and variants of unknown clinical significance rates.

bbreviations: WES = whole exome sequencing; WGS = whole genome sequencing

ES 4.4 Selected Payer Coverage Policies

An overview of selected payer coverage policies for WES is provided in ***Table ES-2***. CMS does not have a national coverage determination for WES. Five commercial payers cover WES when beneficiaries have met specific clinical criteria (detailed in ***Table 17*** of the full report).

Table ES-2. Overview of payer coverage policies for whole exome sequencing

Medicare	Medicaid	Aetna	Cigna	Humana	Kaiser Permanente	Premera Blue Cross	Regence BlueShield	Tri-care	UnitedHealth
—	—	✓	✓	x	✓	✓	x	—	✓

Notes: ✓ = covered when specific criteria have been met; ✕ = not covered; — = no policy identified.

ES 4.5 Limitations of this HTA

This HTA was limited to peer-reviewed studies published in English. Our search was limited to 3 bibliographic databases; however, we conducted extensive hand searches to identify potentially relevant articles. Because of practical constraints, our key questions focused on clinical utility outcomes, health outcomes, safety outcomes, and cost outcomes. We did not systematically review studies of diagnostic yield. However, we provided information about diagnostic yield based on 4 systematic reviews and 99 primary research studies that we identified as having relevant diagnostic yield information during full-text screening.

ES 4.6 Ongoing Research

We identified 15 recently completed or ongoing studies that may be relevant to this topic. Most are single arm observational cohorts. The only ongoing RCT that we identified is sponsored by the University of North Carolina at Chapel Hill in collaboration with the National Human Genome Research Institute and 2 other North Carolina-based health care systems.[87] In this RCT, children and adults with diverse phenotypes are randomized to 1 of 4 study arms 1) previsit preparation with usual care and exome sequencing, 2) previsit preparation with usual care, 3) no

previsit prep with exome sequencing, and 4) no previsit prep and usual care. This study plans to enroll 1,700 participants with an estimated study completion date of May 2021.

ES 5. Conclusion

WES increases diagnostic yield over standard diagnostic testing. A diagnosis from WES changes clinical management for some patients, but our certainty in the estimate of this frequency is very low. The evidence regarding the impact of WES testing on health and most safety outcomes is limited, though we have low certainty that the proportion of patients tested who receive a medically actionable secondary finding is about 4%. WES may be cost-effective in terms of diagnostic success, but our certainty is very low.

Full Technical Report

1. Background

We conducted this health technology assessment (HTA) to assist the State of Washington's independent Health Technology Clinical Committee with determining coverage for whole exome sequencing (WES).

1.1 Condition Description

WES may be indicated for testing for a wide range of genetic diseases. This test is most commonly used when a patient is suspected of having a genetic disorder, but the signs and symptoms are not recognizable as a specific genetic condition. This test is also used when the patient's phenotype could be consistent with multiple genetic disorders. Except for monozygotic twins, the genomes of all individuals are different in thousands of places. For convenience in genetic testing, one designated sequence serves as a reference sequence, and the sequences of patients who are tested are compared to the reference sequence. A single base pair may be different (called single nucleotide variant [SNV] or polymorphism [SNP]) or a whole section of a gene, chromosomal region, or chromosome may be different. These differences, collectively called genetic variants, make each individual unique. A variant in the sequence of a gene may or may not affect the gene's function or result in symptoms. Variants that cause malformation, dysfunction, or disorders are termed pathogenic variants.

Indications that a symptom or phenotype may be related to a pathogenic genetic variant include dysmorphic features, multiple anomalies, unexplained neurocognitive impairment, multifocal presentation, earlier or more severe onset of common symptoms, or a family history of similarly affected individuals.[88,89] Although genetic conditions are often thought of has having onset during infancy or childhood, many genetic disorders first become symptomatic in adulthood. Some conditions with pediatric onset may not be diagnosed until adulthood, when their presentation may be confusing.[90] Examples of clinical scenarios for which WES may result in a diagnosis, and the potential diagnoses are:

- Siblings with hypotonia, dystonia, oculogyric crises and developmental delay and onset at 2 months of age. No similarly affected patients in the family. Possible diagnosis: L-amino acid decarboxylase deficiency or other disease of neurotransmitter synthesis. These are rare autosomal recessive disorders, which means that both copies of the gene must include a pathogenic variant.

- Adolescent male presents with muscle weakness in his legs and arms that seems to be worsening. The extended family history is unknown. Possible diagnosis: any of over 20 muscular dystrophy types and subtypes, myopathy, or Pompe disease.

- Twenty-nine year-old woman presents with endometrial cancer. Family history includes multiple individuals diagnosed with different cancers, including multiple causes of colorectal cancer, before the age of 40. Possible diagnosis: Lynch syndrome, Li-Fraumeni syndrome, other inherited cancer syndromes.

- Two female siblings with congenital heart defect and neural tube defect, dysmorphic features, craniofacial abnormalities, cataracts and developmental retardation. Normal metabolic and chromosomal testing. Potential diagnoses: Meckel-Gruber syndrome, Roberts syndrome, Walker-Warburg syndrome. Testing for microdeletion of 22q11 was normal.

Because WES sequences the entire exome, it may also identify genetic disorders other than those that cause the patient's phenotype, some of which require specific medical management. For example, identification of a pathogenic mutation in the BRCA2 gene would prompt early, frequent screening for breast cancer or other preventive measures.[1] Initially, such mutations were referred to as incidental findings, until evidence emerged that such findings were common for WES or whole genome sequencing (WGS). They are now referred to as secondary findings. Depending on the patient's phenotype and resulting variant filtering, described in Section 1.3 below, such variants may not be identified unless they are specifically sought. In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended specifically looking for pathogenic and likely pathogenic variants in 56 genes for which medical management guidelines were available in order to standardize the reporting of secondary findings.[2] Three additional genes for which medical management guidelines had become available were added to the list in 2016.[91]

1.2 Disease Burden

There are more than 6,000 human genetic diseases.[3] Although genetic diseases are individually rare, they collectively affect approximately 1 in 17 individuals.[4] One study estimated that the range of total inpatient charges for U.S. pediatric patients related to suspected genetic diseases in 2012 was US$ 14 to US$ 57 billion—11% to 46% of all pediatric inpatient charges.[5]

1.3 Technology Description

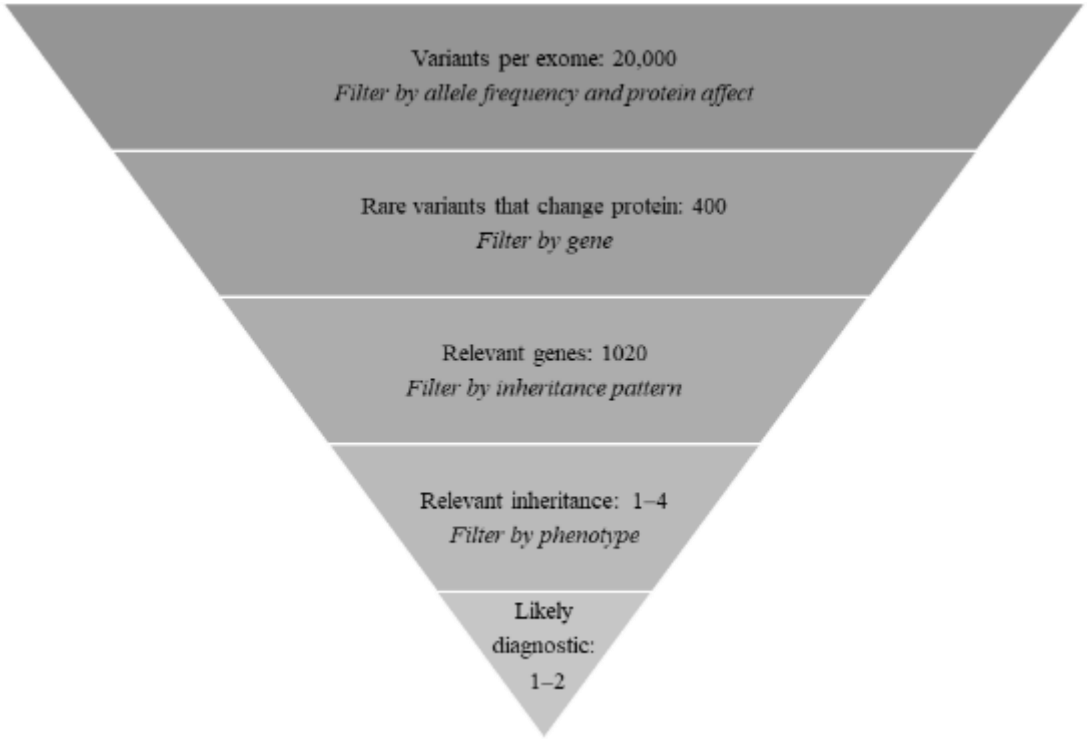
WES identifies the DNA base-pair sequence of the protein-coding regions of the genome, including proximal regulatory segments and splicing junctions.[6] WES is primarily used to identify small changes in base-pair sequences that disrupt protein function and cause disease; however, improved bioinformatics has increased the ability to identify chromosomal copy number variants (i.e., larger deletions or duplications involving larger stretches of DNA) from sequenced data and changes in the mitochondrial genome. WES may be performed for both clinical and research purposes. Diagnostic WES testing is ordered by a physician or other health care professional and is conducted in a clinical diagnostic laboratory to aid in the diagnosis of a patient. Parents' or siblings' genes may also be sequenced to help interpret identified variants (Trio WES). Research WES testing is used to identify novel gene variants, further characterize a common disease gene or genes among multiple families or patients with the same diagnosis, or evaluate alternative strategies for conducting WES testing.

WES uses next-generation sequencing (NGS) technologies; NGS makes many copies of the target genome, cuts them into random sequences, and simultaneously sequences the resulting fragments. After this sequencing step, WES requires a series of bioinformatics analyses to

interpret the sequencing. The stages of the bioinformatics analyses, often referred to as the analysis pipeline, are as follows:[92]

1. **Segment-sequence generation:** Bioinformatic algorithms that are provided by the manufacturer of the sequencer convert the raw data generated by the sequencing machine into strings of nucleotide bases (i.e., As, Cs, Ts, and Gs). In addition to the read sequences, these algorithms provide quality metrics for each base call that describe the likelihood that the call is correct.
2. **Genome-sequence generation:** In this step, bioinformatics software aligns the sequence segments to a reference genome. The Genome Reference Consortium produces the reference sequences,[93] which are periodically updated. The laboratory conducting the genome-sequence generation should specify the reference genome version it used in the laboratory report.
3. **Variant identification:** Statistical models identify the differences between a patient's exome and the reference genome. This process is complex and may require multiple algorithms to identify (i.e., call) different types of variants. The accuracy of calling variants differs by variant type, variant characteristics, and the details of the sequencing method. WES identifies single-nucleotide changes with high accuracy (> 99.5% sensitivity and specificity). Insertions and deletions are harder to call accurately, and—somewhat counterintuitively—the larger the insertion or deletion, the harder it is to identify. The details of the sequencing analysis determine if it is possible to identify large regions of homozygosity or the patient's genotype at a specific locus.
4. **Genome interpretation:** This analysis places the identified variants into the larger genomic and clinical context needed to interpret the variant. Information is extracted from bioinformatic databases to identify the gene in which the variant occurs and its function, the effect of the variant on the gene transcript, and the Human Genome Variation Society nomenclature of the variant. It would be impossible to manually review all the variants in an exome; therefore, bioinformatics algorithms filter and prioritize variants that are more likely to be pathogenic, which require a further, manually driven review. Algorithms filter out variants that are common in the population frequency or that do not change protein function, and gene variants that are either irrelevant to the phenotype or not expressed in the affected tissue (see ***Figure 1***). If parent or sibling exomes are available, algorithms filter out variants present in unaffected relatives and prioritize those shared with affected relatives.

Figure 1. Variant-filtering process



5. **Variant interpretation:** The final step of the analysis is to develop a full interpretation of the identified variants. This step is manually driven, although it uses multiple bioinformatic tools and databases. The laboratory may apply additional prioritization tools to make the number of variants interpreted feasible. Only variants that may be relevant to the patient's clinical condition or variants determined by the ACMG to be medically-actionable variants are included in the clinical report that is returned to the ordering clinician and patient. These variants are classified as pathogenic, likely pathogenic, variants of unknown significance, likely benign, or benign. Pathogenic variants may be confirmed by traditional Sanger sequencing, which uses enzymes to cut DNA into segments based on specific sequences then sequences the resulting segments.
6. **Reporting:** A clinical laboratory report for WES usually includes as primary findings all variants identified in genes associated with the clinical phenotype of the patient and their interpretation and ACMG-defined medically actionable variants as secondary findings. Some laboratories report additional secondary findings, including whether the patient is a carrier for any autosomal-recessive disorders and drug metabolism variants that affect the use of certain drugs.[94]

1.3.1 Use in Clinical Practice

The use of WES within clinical practice is still evolving in terms of how and where it is used within a diagnostic testing pathway for individual patients. Typically, WES is used when a monogenic disorder is suspected but when the patient's phenotype does not suggest a specific

disorder for testing. WES can replace most single and multi-gene panel testing, but up until recently could not replace chromosomal microarray analysis (CMA) for the detection of copy number variants.

1.4 Regulatory Status

The U.S. Food and Drug Administration (FDA) approves the sequencing platforms which are used to conduct clinical NGS, including WES. FDA approval is based on the demonstration of analytic validity, in other words that the sequencing machines correctly sequence DNA specimens. The FDA does not regulate WES as a diagnostic test, which involves both the sequencing component and the bioinformatics and variant interpretation component. WES is conducted by laboratories that are accredited by the Clinical and Laboratory Improvement Act (CLIA) to conduct high complexity testing. Because of the equipment and software involved (particularly for the bioinformatics platform), this test is generally only conducted in laboratories associated with large, tertiary medical centers or commercial genetics laboratories.

1.5 Policy Context

The State of Washington HCA selected this topic for review because of high concerns for safety and medium concerns for efficacy and cost.

1.6 Washington State Agency Utilization Data

The WES utilization analysis conducted by the State of Washington HCA combined member utilization and cost data from the following Washington agencies: Medicaid Managed Care (MCO) and Medicaid Fee-for-Service (FFS). The Department of Labor and Industries (LNI) Workers' Compensation Plan reported no WES utilization. The Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP) reported less than the minimum number of individuals necessary to safely release agency-by-agency findings and still protect patient confidentiality. Based on CPT codes for WES (i.e., 81415, 81416, and 81417), claims for 390 tests have been paid since 2015; nearly half were paid in 2018. The average cost per professional claim was $12,530 in 2015 and $888 in 2018. Additional details are provided in ***Appendix A***.

2. Methods

This section describes the methods we used to conduct this HTA.

2.1 Research Questions and Analytic Framework

We developed the following research questions to guide the systematic evidence review of primary research studies:

Key Question 1: Effectiveness (Clinical Utility)

1a. In what proportion of patients does testing with WES result in a clinically actionable finding (i.e., the diagnosis resulting from WES leads to something that can be treated, prevented, or mitigated)?

1b. In what proportion of patients does testing with WES result in an actual change to the patient's medical management (medication or therapies, follow-up testing, medical monitoring) or genetic counseling (reproductive risks or risks of other family members)?

1c. What is the effect of testing pathways that include WES on medical management or genetic risk counseling compared to testing pathways that do not include WES?

Key Question 2: Effectiveness (Health Outcomes)

2. What are the health outcomes, including mortality, among patients who have WES testing?

2b: What are the health outcomes, including mortality, of patients who receive testing pathways that include WES compared to alternative testing pathways with or without WES?

Key Question 3: Safety and Harms

3a: How many patients receive erroneous results after WES testing, either false positive or false negative results? What harms are caused by these test results and how many patients experience these harms?

3b: What harms are caused by uncertain WES results or a lack of diagnosis after WES testing?

3c: How many patients receive reports on ACMG-defined medically actionable variants after WES testing? What harms do they experience, and how many patients experience these harms?

3d: How frequently do WES results cause harm to family relationships?

Key Question 4: Cost

4a: What is the cost of WES testing?

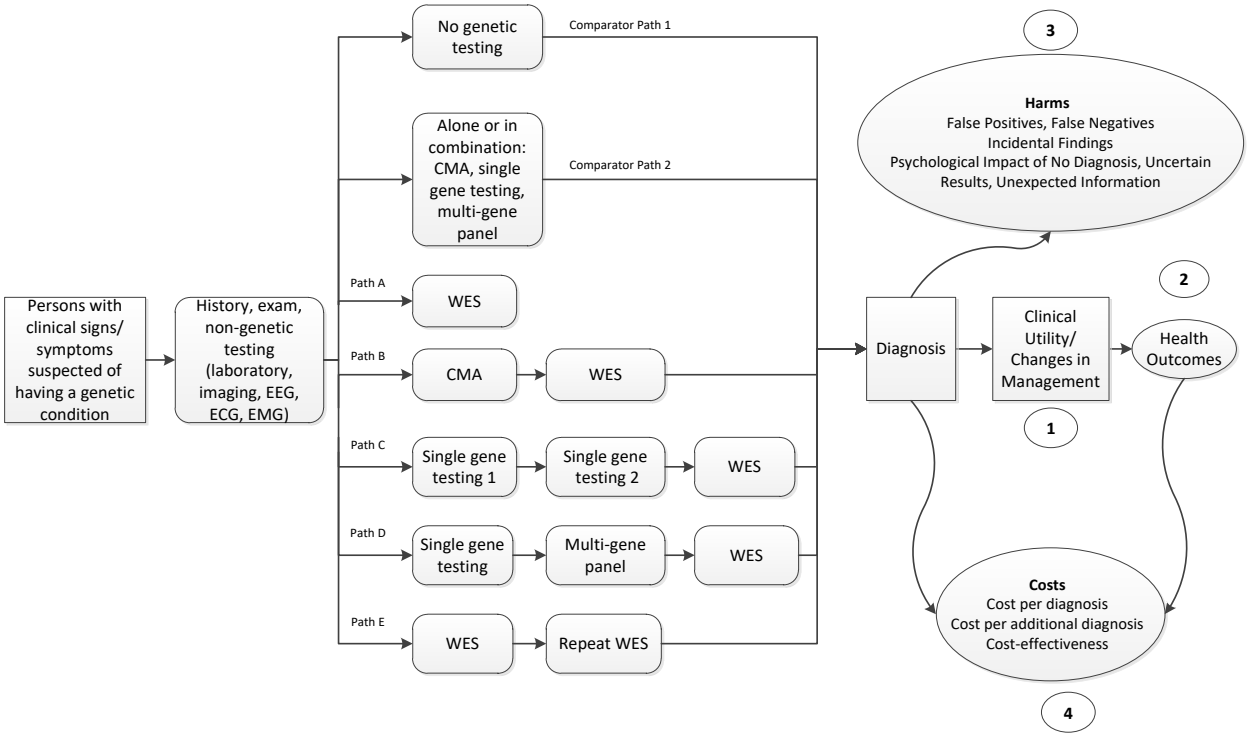
4b. What is the cost per diagnosis of pathways that include WES testing?

4c: What is the cost per additional diagnosis, comparing a pathway with WES to an alternative pathway with or without WES?

4d: What is the cost-effectiveness of testing with WES?

We also created the analytic framework, shown in ***Figure 2***, to guide our review.

Figure 2. Analytic framework for HTA on whole exome sequencing



Abbreviations: CMA=chromosomal microarray; ECG=electrocardiography; EEG=electroencephalography; EMG=electromyography; WES=whole exome sequencing

In addition, we addressed the following contextual questions, which were not systematically reviewed and therefore are not shown in the analytic framework.

Contextual Question 1: What is the diagnostic yield of WES either alone or as part of a testing pathway and what are the factors (e.g., phenotypes being tested, testing platforms and bioinformatics analysis used) that contribute to variation in diagnostic yields?

Contextual Question 2: How often does WES return variants of uncertain clinical significance and what impact does repeat bioinformatics analysis have on diagnostic yield?

The State of Washington HTA Program posted a draft of these research questions with study selection criteria for public comment from March 19, 2019 to March 28, 2019. The final key questions and response to public comments on the draft key questions were published on June 17, 2019 and are available at the Program's website.[95]

2.2 Data Sources and Searches

We searched MEDLINE® (via PubMed), Embase, and a clinical trials registry (www.clinicaltrials.gov) for relevant studies published in English from inception to March 14, 2019, and actively surveilled the published literature through August 31, 2019. In brief, we used

medical subject headings (MeSH terms) and text words associated with the WES. We limited the search by eliminating studies indexed using terms for bacteria, viruses, and animals. We used MeSH terms to remove editorials, letters, and publication types that did not represent primary research studies from the search yield. We conducted targeted searches of the Centers for Medicare & Medicaid Services (CMS) and FDA websites, selected payer and health care professional society websites, and websites of other organizations that conduct and disseminate HTAs or clinical practice guidelines. The detailed electronic search strategy is presented in ***Appendix B***. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on this topic to identify any relevant primary research studies that were not found through the electronic search.

2.3 Study Selection

Table 1 summarizes the study selection criteria related to the populations, interventions, comparators, outcomes, study time periods, study design, and settings that defined the scope of this HTA, which are further described in the sections that follow. Two review team members independently screened titles, abstracts, and full-text articles based on these study selection criteria. Discrepancies in study selection at the full-text level were adjudicated by the lead investigator, or in some cases, by team consensus.

Table 1. Population, intervention, comparator, outcomes, period, setting, and other study-selection criteria for HTA on WES

Domain	Included	Excluded
Population	Children or adults, with or without a clinical diagnosis, suspected of having a genetic disease	• Embryos and fetuses • Patients with nonsyndromic cancer or infections, where WES is being used to characterize the tumor or microbe • Deceased persons
Intervention	• Diagnostic WES alone (Path A in Figure 2) or as part of a sequential testing pathway after clinical, laboratory and imaging evaluation (Paths B, C, D in Figure 2) • Re-analysis of diagnostic WES findings at a later interval (Path E in Figure 2)	• Single gene sequencing (traditional Sanger sequencing or next generation sequencing) • Multi-gene panels (traditional Sanger sequencing or next generation sequencing) • Whole mitochondrial sequencing • WES to identify acquired mutations in tumors • WES of infectious agents • Genome-wide association studies • Research-based WES (i.e., studies focused on elucidating the biology or underlying genetics of a disorder) • WES when focused on evaluating alternative methods for sequencing or variant calling • WES when focused exclusively on identifying copy number variants • Whole genome sequencing
Comparator	• Clinical, laboratory, or imaging evaluation with no genetic testing (Comparator Path 1 ***in Figure 2***) • Testing pathways that use only CMA, single gene testing, or multigene panels (Comparator Path 2 in ***Figure 2***). Single	• Whole genome sequencing

Domain	Included	Excluded
	gene testing and multigene panels can be performed by traditional Sanger sequencing or with next generation sequencing. • Testing pathways that use WES in sequence with other testing, and including WES reanalysis (Paths B, C, D, and E in ***Figure 2***).	

Outcomes	• Clinical utility
	  ○ Results from WES could be or are used for medical management (e.g. therapy, further diagnostic testing, monitoring), reproductive counseling, or risk counseling for other family members
	• Health outcomes
	  ○ Mortality, length of survival
	  ○ Morbidity, cognitive ability, functional outcomes
	• Safety
	  ○ Misdiagnosis (false positives, false negatives)
	  ○ Proportion of patients with ACMG-defined medically actionable variants
	  ○ Psychosocial harms (e.g., anxiety, family stress, depression, distress, financial consequences) to proband and family from testing related to lack of diagnosis, uncertain findings, incidental findings, and unexpected information (e.g., carrier status, non-paternity)
	  ○ Employment or insurance discrimination
	• Costs
	  ○ Cost of testing (U.S. based studies from previous 2 years only)
	  ○ Cost per diagnosis
	  ○ Cost per additional diagnosis
	  ○ Cost-effectiveness
		• Outcome differences due only to different genetic defects
		• Clinical utility and health outcomes related to incidental findings
		• Cost of testing from studies performed in non-U.S. countries if this was the only cost outcome provided
		• Cost of testing from studies performed in the U.S. but that are older than 2 years if this was the only cost outcome provided

Setting	Any outpatient or inpatient clinical setting in countries categorized as 'very high' on the UN 2017 Human Development Index[a]	Non-clinical settings, countries categorized other than 'very high' on the 2017 UN Human Development Index[a]
Study Design and Risk of Bias Rating	Study designs[96] • Clinical trial (single group or controlled) • Cohort (single group of more than 10 participants or families or controlled) • Case-control • Cross-sectional	• Case reports (fewer than 5 participants) • Narrative reviews • Editorials and commentary • Letters to the editor • Systematic reviews were not included but were hand searched to identify relevant primary research studies

Domain	Included	Excluded
	• Case series (between 5 to 10 participants or families) • Cost analyses, cost-benefit analysis, cost utility analysis, cost-effectiveness analysis • Modeling studies (for clinical utility, health outcomes, and cost outcomes only) • Qualitative study designs (for safety outcomes only) Risk of Bias Rating • Any	
Language and Time Period	• English • 2010 or later	• Any language other than English • Studies published prior to 2010

Notes: [a] Countries categorized as "very high":[97] Andorra, Argentina, Australia, Austria, Bahrain, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States.

Abbreviations: ACMG =American College of Medical Genetics and Genomics; CMA = chromosomal microarray; HTA =Health Technology Assessment; NGS =next generation sequencing; U.N. = United Nations; U.S. =United States; WES = whole exome sequencing; WGS = whole genome sequencing

2.3.1 Population

Studies were selected if they enrolled children or adults suspected of having a genetic disease. We excluded studies focused primarily on suspected genetic disease in deceased persons, embryos, or fetuses.

2.3.2 Intervention and Comparator

We selected studies that used WES in a clinical diagnostic context, either alone or as part of a testing strategy that included other clinical laboratory, imaging, or other diagnostic evaluations. We excluded studies that used WES to (1) characterize tumors or infectious microbes, (2) sequence the whole mitochondrial genome, (3) conduct research for elucidating possible underlying genetics of a disorder or to identify novel variants, (4) assess different methodological approaches to conducting a WES analysis, and (5) exclusively characterize copy-number variants. We also did not select studies that only reported on WGS, genome-wide association studies, or were focused primarily on single-gene or multigene panel testing. Eligible comparator testing strategies included (1) standard clinical diagnostic testing without genetic testing; (2) usual testing with CMA or single- or multigene panel testing; or (3) usual care with CMA, single- or multigene testing, and WES but in different sequences, including WES reanalysis. However, we did not require studies to have a comparator testing strategy.

2.3.3 Outcomes

For the efficacy research question on clinical utility, we selected studies that reported on results from WES that either potentially could be used or had been used for medical management, further diagnostic testing or monitoring, or risk counseling for other family members, including reproductive risk counseling.

For the efficacy research question on health outcomes, we selected studies that reported on mortality, length of survival, morbidity, cognitive ability, and functional outcomes.

For the safety research question, we selected studies that reported misdiagnosis (i.e., false-positives, false-negatives), proportion of patients with ACMG-defined medically actionable variants (i.e., secondary or incidental findings), psychosocial harms, and employment or insurance discrimination.

For the cost research question, we selected studies that reported on the costs of the WES test, cost per patient of testing, cost per diagnosis of testing, and cost-effectiveness outcomes. We did not select studies in which the only eligible outcome was the cost of the WES test unless the study was conducted in the U.S. within the previous 2 years.

2.3.4 Settings

Studies conducted in any inpatient or outpatient clinical setting were eligible for selection. Studies that were conducted in countries with a development rating designated as *very high* by the United Nations Human Development Index in 2017 were eligible for selection because these countries (e.g., Canada, Europe, Australia, New Zealand, Japan, S. Korea, Singapore, Hong Kong) and others are like the U.S. with respect to standards of medical practice.[97] We excluded studies conducted in countries with a development rating designated as less than *very high*.

2.3.5 Study Design

We selected studies that used any of the following study designs: clinical trials, single or controlled cohorts (10 or more participants or families), case control studies, cross-sectional studies, case series studies (between 5 to 10 participants or families), cost analyses, cost-benefit analyses, cost-utility analyses, cost-effectiveness analyses, modeling studies, and qualitative research studies (for safety outcomes only). Case reports, editorials, comments, letters, and narrative reviews were not eligible for selection. We also did not include systematic reviews, but we did hand search them to identify relevant primary research studies that may have been missed by our search.

2.3.6 Time Period

We selected studies published in 2010 or later because WES had not been used for clinical purposes prior to this date.

2.3.7 What Is Excluded From This HTA

This review did not include studies published in languages other than English or conducted in countries that are not very highly developed based on the United Nations Human Development

Index.[97] For the key questions in this review, we did not include studies only reporting the diagnostic yield of WES.

2.4 Data Abstraction and Risk of Bias Assessment

One team member extracted relevant study data into a structured abstraction form, and a senior investigator checked those data for accuracy.

Two team members conducted independent risk of bias assessments on all included studies; discrepancies were resolved by discussion. Because most study designs were single-arm observational cohort studies and because existing instruments for diagnostic test accuracy studies were not well suited for the assessment of this body of literature (i.e., studies were not comparing an index test to a reference test), we developed a structured form to assess risk of bias for clinical utility, health outcomes, and safety outcomes. The form included signaling questions to assess the main domains of bias including selection, performance, missing data, and outcome measurement. Risk of bias was assessed as *high*, *some concerns*, or *low* for each separate outcome domain (clinical utility, health outcomes, and safety outcomes). We used the Quality of Health Economic Studies Instrument to assess the risk of bias of included cost analyses.[7] We considered studies with scores on this instrument of 90 or above to have low risk of bias, studies with scores between 60 and 89 to have some concerns for bias, and studies with scores below 60 to have high risk of bias.

2.5 Data Synthesis and Quality of Evidence Rating

We qualitatively synthesized study characteristics and results for each research question in tabular and narrative formats. We used Stata (version 15) to conduct quantitative pooling of the diagnostic yield estimate for contextual question 1. We were not able to conduct quantitative syntheses for any of the key questions because of the clinical and methodological heterogeneity in this evidence base.

We graded the certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8] With GRADE, the certainty of evidence can be graded as *very low*, *low*, *moderate*, or *high* based on imprecision, inconsistency, and study limitations. ***Table 2*** defines these levels.[98] Bodies of observational evidence begin with a *low* certainty rating and can be downgraded for imprecision, inconsistency and study limitations. Bodies of evidence can also be upgraded from *low* for other considerations (e.g., large effect, evidence of dose-response). We note here that the GRADE framework was initially developed for RCTs of interventions; it may not be well suited for assessing the strength of evidence for genetic testing.

Table 2. Certainty of evidence grades and definitions[98]

GRADE	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Very Low	**We have very limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has numerous major deficiencies. We believe that substantial additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

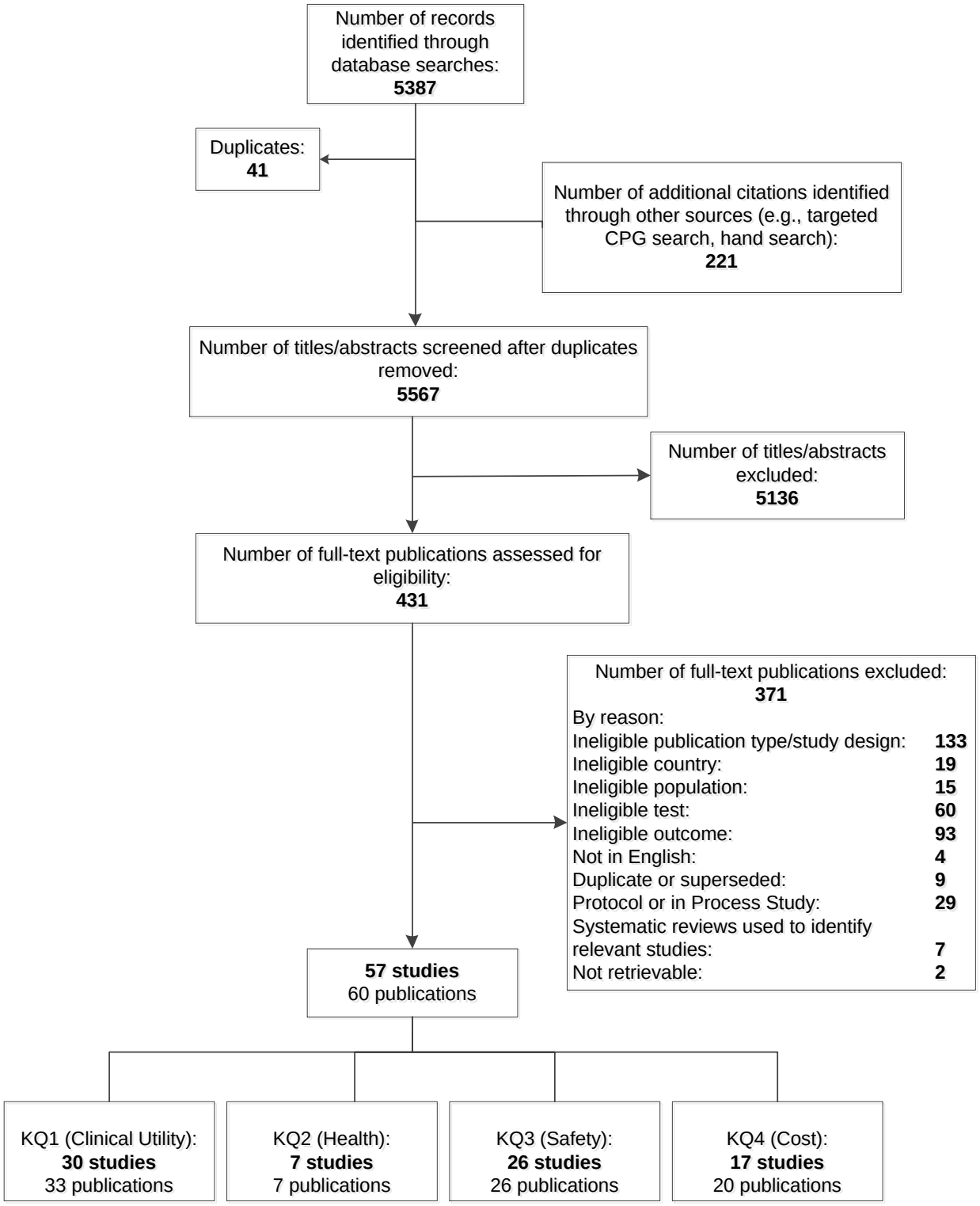
3. Results

3.1 Literature Search

Figure 3 depicts the study flow diagram. We screened 5,567 unique citations. We excluded 5,136 citations after title and abstract review. We dually reviewed 431 full-text articles and included a total of 57 studies reported in 60 articles published between 2014 and 2019. Thirty studies provided evidence on clinical utility (KQ1), 7 studies provided evidence on health outcomes (KQ2), 26 studies provided evidence on safety outcomes (KQ3), and 17 studies provided evidence on cost outcomes (KQ4). Individual study and population characteristics and findings are summarized in ***Appendix C***. The list of articles we screened at the full-text stage, but which we excluded, is provided in ***Appendix D***. Note that articles may have been excluded for more than one reason, but we report only one reason. We report our individual study risk of bias assessments for included studies in ***Appendix E***.

The rest of the results section is organized as follows. First, we describe findings related to the 2 contextual questions. Next we describe findings from key questions. This includes findings related to clinical utility (Section 3.3), health outcomes (Section 3.4), safety outcomes (Section 3.5), and cost outcomes (Section 3.6).

Figure 3. Study flow diagram for HTA on whole exome sequencing



Abbreviations: CPG = Clinical Practice Guidelines; KQ = key question

3.2 Contextual Questions

3.2.1 Contextual Question 1: Overall diagnostic yield

Four systematic reviews[9-12] and 99 individual studies (see ***Appendix F***) provided information on the diagnostic yield of WES. Three of the systematic reviews included articles on diverse phenotypes (**Table 3**).[9,11,12] The fourth review was limited to studies of epilepsy.[10] The degree of diagnostic testing prior to WES testing that was received by participants enrolled in these studies varied; most all had received some initial diagnostic evaluation (specialty consultation, laboratory, imaging). Many had also received some genetic testing (e.g., single or multi-gene panels, CMA).

Two reviews provided pooled estimates of diagnostic yield. Among children with any phenotype suspected to be of genetic origin, 36% were diagnosed by WES, 8% by CMA, and 41% by WGS.[11] Among patients of any age who presented with epilepsy, 45% were diagnosed by WES, 8% by CMA and 23% by epilepsy-specific gene panels. Two studies only reported the range across studies or individual study estimates. Schwarze et al. reported a range of 3% to 79%,[9] and Alam et al. reported a range of 16% to 79%.[12] The lowest estimate (3%) was for patients with colorectal cancer, of which approximately 5% of cases are due to a single gene disorder. [9] The highest estimate, 79%, was among patients with childhood-onset muscle disorders. [9]

Table 3. Systematic reviews of the diagnostic yield of WES

Author (Year)	Inclusion Criteria	Number of Studies; Total Patients	Diagnostic Yield
Schwarze (2018) [9]	• Published 2005 to2016 • WES or WGS • Any age group or phenotype • Studied cost (main focus), clinical utility, diagnostic yield or health outcomes	WES: 27; NR WGS: 3; NR	Range: 3% (colorectal cancer to 79% (childhood-onset muscle disorders)
Sanchez Fernández (2019)[10]	• Any publication date • WES, CMA, Epilepsy panel (EP) • Any age group • Phenotype of epilepsy	Any genetic test: 20, NR WES: 6; 1,193 CMA: 8; 2,341 EP: 9; 2,341	Pooled estimates: WES: 45% (95% CI, 33% to 57%) CMA: 8% (95% CI, 6% to 12%) EP: 23% (95% CI, 18% to 29%)
Clark (2018)[11]	• Published in 2011 to2017 • WES, WGS or CMA • Children • Any phenotype • Studied diagnostic yield	WES: 26; 9,014 CMA: 13; 1,1429 WGS: 7; 374	Pooled estimates (severe heterogeneity): WES:36% (95% CI, 33% to 40%) CMA: 10% (95% CI, 8% to 12%) WGS: 41% (95% CI, 34% to 48%)
Alam (2018) [12]	• Published in 2010 to2017 • WES • Children • Any phenotype • Studied cost	WES: 11, NR	Range: 16% to 79%

Abbreviations: CMA = chromosomal microarray analysis; WES = whole exome sequencing; WGS = whole genome sequencing; NR = not reported

We also analyzed diagnostic yield data from 99 individual studies (see ***Appendix F***), of which 19 were included in 1 or more of the above noted systematic reviews. Sixty-one of the studies were published in 2017 or later. Among these 99 studies, we calculated the pooled diagnostic yield for

WES as 38% (95% CI, 35.7% to 40.6%). In comparison, we calculated the pooled diagnostic yield of traditional testing pathways (4 studies[16,20,26,27]) as 21% (95% CI, 5.6% to 36.4%) and the diagnostic yield of gene panels (6 studies[26,28-32]) as 27% (95% CI, 13.7% to 40.5%).

One study conducted diagnostic WES in patients also undergoing traditional testing chosen by the patient's physician and compared diagnostic rates using the two testing strategies.[20] Thirty-six (24%) patients who received a diagnosis from WES did not receive a diagnosis from traditional testing.

Patient Characteristics That Affected Diagnostic Yield

The likelihood of a genetic cause and, therefore, the diagnostic yield of WES varied by patient age and phenotype. The diagnostic yield decreased as the age of participants increased: 42% among infants, 38% among children, and 20% among adults. There were 7 disorders or groups of related phenotypes for which there were more than 2 studies of diagnostic yield (see ***Table 4***). The diagnostic yield for these disorders ranged from 29% for participants with an intellectual or developmental disability to 48% for those with limb-girdle muscular dystrophy.

Table 4. Diagnostic yield for specific disorders

Phenotype	Number of Studies	Total Patients	Pooled Diagnostic Yield (%)
Epilepsy	8	598	40
Intellectual or Developmental Disability	7	2,737	29
Neurologic Disorders	7	434	33
Neurodevelopmental Disorders	5	709	28
Limb-girdle Muscular Dystrophy	4,	262	48
Peripheral Neuropathy	4	152	32
Undiagnosed After Standard Workup	4	809	31

3.2.2 Contextual Question 2: Reanalysis and Diagnostic Yield

Reanalysis of WES data using updated variant call algorithms and newly discovered pathogenicity information increases diagnostic yield. Among the 8 studies that examined the yield from reanalysis, on average 17% of previously undiagnosed patients were diagnosed by reanalysis of existing WES data.[13,21,33-38] One study compared reanalysis of existing WES data to performing WGS for patients with previous negative results.[36] This study found that 7 of 112 patients had a variant detected by WGS that was not detected by WES after reanalysis. Reanalysis may also reclassify variants previously thought to be pathogenic to benign, resulting in some previously diagnosed patients no longer having a genetic diagnosis. The single study that examined the frequency of such reclassification reported that 39 of 328 (12%) likely diagnoses of patients with developmental disorders had been retracted since their initial report in 2014.[99] However, 23 of the 39 (59%) would not have been considered as likely pathogenic under the laboratories 2018 guidelines for considering a variant pathogenic.

3.2.3 Analytic Validity

Although this HTA included the number of false-positives and false-negatives as eligible safety outcomes, studies defined by the scope of the key research questions for this HTA did not

generally report analytic validity. Thus, we provide additional contextual information to supplement the findings for those outcomes described in Section 3.4.

Analytic errors in next-generation sequencing can be due to sequencing quality or to the bioinformatics algorithms used to identify sequence variants. A 2014 study examined genotype discordance between multiple sequencing runs by sequencing platform (Illumina versus Complete Genomics), sequencing coverage, type of specimen (blood versus saliva), and WES vs. WGS.[100] Error rates were in the range of 1 per 200 to 1 per 500 single-nucleotide variants (SNVs) overall, and 4% to 6% for rare variants. False positive rates were much more common than false negative rates. The estimated error in rare variants is slightly higher than the reported discordance between WES and Sanger sequencing of 3%.[101] Of note, these studies were published in 2014 and 2015. It is likely that base calling algorithms have improved since these publications. Lower sequencing coverage resulted in lower discordance but fewer SNVs were called with high confidence. Specimen type did not affect error rates.

3.3 Key Question 1: Effectiveness (Clinical Utility)

Thirty studies (reported in 33 publications) reported on clinical utility outcomes.[13-16,18,19,22,24,25,27,28,32,34,39-58] Detailed information regarding study characteristics and outcomes are reported in ***Appendix C, Table C-1*** and ***C-2***. The key findings are:

- Among studies that enrolled patients with diverse phenotypes (18 studies):
  - A WES diagnosis changed clinical management for between 12% to 100%
  - A WES diagnosis changed medication for between 5% to 25%
  - A WES diagnosis resulted in counseling and genetic testing for family members for between 4% and 97%
- Among studies that enrolled patients with epilepsy (5 studies):
  - A WES diagnosis changed clinical management for between 0% to 31%
  - A WES diagnosis changed medication for between 0% to 20%
- Among studies that enrolled patients with a single phenotype (7 studies), all reported some changes in clinical management following a WES diagnosis, but the data was too heterogenous to synthesize into a single range.

We assessed the certainty of evidence related to all clinical utility outcomes as *very low* because of study designs, study limitations, inconsistency, and imprecision. Detailed certainty ratings are in ***Appendix G.***

3.3.1 Study and Population Characteristics

The included publications were published between 2014 and 2019. The WES testing was performed during the years 2011 to 2018 as reported in 20 studies. One study was a single-arm observational cohort with an economic modeling component,[28] 1 study was a case series,[53] and 1 study was a controlled observational cohort study[22]; all other studies were single-arm observational cohorts. The controlled observational cohort study compared a rapid WES protocol

to a standard WES protocol.[22] Fifteen studies were rated as having a high risk of bias, and 17 as having some risk of bias.

Sixteen of the included studies were conducted in the U.S.,[24,25,39-41,43,45-50,54,56-58] 6 were conducted in Australia,[13-16,19,22,27,28,34] and 2 each were conducted in Canada[44,55] and Germany.[51,52] One study was conducted in Argentina,[18] France,[42] Israel,[53] and The Netherlands,[32] respectively. One study was industry-sponsored,[39] 7 studies had some industry funding,[13-16,19,22,27,45,50,56] and 16 studies reported no industry funding.[18,24,25,28,32,34,40-44,47,52,54,55,57,58] Eight studies did not specifically list any study funders.[24,28,32,46,49,52,57,58] For the remaining 7 studies, it was unclear whether or not any industry funding was involved.[19,46,48,49,51,53,55]

The number of probands who underwent WES in each study ranged from 6 to 278 (32% to 68% were female among those reporting). One study was conducted among 62 health care providers who had referred patients for clinical WES.[39] The median age of patients ranged from 26 days to 66 years among those studies reporting. Enrollment in 29 studies was limited by age group: 3 studies[28,40,56] only included infants, 13 only included children, and 1[50] only included adults. The remaining 12 studies included both adults and children.[18,32,34,39,41-46,48,57] Seven studies reported on the ethnicity of participants, which ranged from 55% to 98% European.[32,43,44,46,49,52,54]

Eighteen of the included studies performed WES on patients with diverse phenotypes. The remaining studies enrolled single-phenotype participants. Five studies included patients with epilepsy,[27,28,32,34,58] and 7 studies included patients with another phenotype: familial hypercholesterolemia,[50] intellectual developmental disorder,[44] malignant infantile osteopetrosis,[53] kidney transplant,[48] young onset nephrolithiasis,[41] neurodevelopmental disorders,[25] and short stature.[51] Ten studies performed singleton WES,[13-16,19,22,28,34,48,50,53-55] and 5 performed trio WES.[25,27,45,47,56] Five studies reported using a combination of singleton, duo, or trio WES,[18,32,40,46,51] and an additional 6 studies included family members, either affected or unaffected, outside the parent-proband trio.[24,41,43,44,49,52] Four studies did not specify which family members were sequenced.[39,42,57,58]

3.3.2 Findings From Studies Among Diverse Populations

Characteristics and outcomes from the 20 studies that enrolled a diverse array of phenotypes are reported in ***Table 5***. All 20 reported on actual changes in management as a result of WES testing among their participants. The percent whose medical management changed after receiving a molecular genetic diagnosis from WES ranged from 12% to 100%. Of the 11 studies that specifically reported starting, stopping, or changing the dosage of a medication, the percentage ranged from 5% to 25% of those receiving a diagnosis from WES.[16,18,22,39,40,45-47,52,55,57] In 2 studies [40] [45] 13%[40] and 14% [45] of WES-diagnosed patients received a specific diet

Table 5. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling diverse populations

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Balridge (2017)[43]; U.S.	Some	155 adults and children with diverse phenotypes seen at a university exome clinic	Trio WES (n=128), parent, sibling proband WES (n=1), parent, sibling WES (n=6), or singleton WES (n=20)	43%	8 (12% of those with a diagnosis, 5% of those tested) had directly altered clinical care	18 (11% of those tested, 26% of those diagnosed)
Bourchany (2017)[42]; France	High	29 unrelated adults and children congenital anomalies and undiagnosed developmental disorder seen at a genetics center	WES	45%	2 (15.4%) of those with WES diagnosis had change in prognosis. 6 (46.2%) of those with WES diagnosis had change in inheritance pattern of presumed diagnosis 1 (7.7%) of those with WES diagnosis had investigation of systemic involvement	12/13 (92.3%) of those diagnosed using WES received prenatal counseling/testing
Cordoba (2018)[18]; Argentina	Some	40 adults and children with suspected neurogenetic conditions from a single tertiary genetics clinic	Singleton or trio WES	40%	7 (43.8% of those with a diagnosis, 17.5% of those tested)	NR
Evers (2017)[52]; Germany	Some	72 children from 60 families with undiagnosed, suspected genetic conditions and diverse phenotypes	Mostly trio WES with a few cases including affected or unaffected siblings	35%	8 (38%) had management changes;	20 (95%) said results were important for family planning 4 (19%) used results for prenatal diagnosis
Iglesias (2014)[46]; U.S.	Some	115 children and adults with diverse phenotypes evaluated at an academic health care center	Mostly trio WES	32%	8 (22%) screened for other manifestations of the disease 14 (38%) had changes in management	5 (14%) identified other family mutation carriers 6 (16%) had reproductive planning
Matias (2019)[49]; U.S.	Some	78 children with diverse phenotypes from a tertiary children's hospital	Mostly trio WES	48%	Change from pre-WES to post-WES 37 (100% of those with a diagnosis)	36 (97% of those with a diagnosis

(continued)

Table 5. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling diverse populations (continued)

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Meng (2017)[40]; U.S.	Some	278 infants less than 100 days old with diverse clinical phenotypes referred to a tertiary institution for WES	Majority singleton WES, some trio WES	38%	53 (52% of those with diagnosis)	90 (88% of those with diagnosis)
Niguidula (2018)[39]; U.S.	High	Survey of 62 health care providers receiving patient WES report from commercial laboratory for adult and pediatric patients with diverse phenotypes (2.2% of surveys returned)	WES not otherwise described	37%	Medication change: 11% of those tested, 17% of those with diagnosis Discontinued diagnostic studies: 58% of those tested, 96% of those with diagnosis Management change: 40% of those tested, 78% of those with diagnosis	45% of those tested, 87% of those with diagnosis
Nolan (2016)[24]; U.S.	Some	50 children from a single academic neurology clinic who were referred for diagnostic WES testing	Singleton or trio WES	NR	10 (19% of those tested, 42% of those with a diagnosis)	11 (22% of those tested, 46% of those with a diagnosis)
Sawyer (2016)[55]; Canada	High	105 families of patients with diverse phenotypes who had already received standard of care genetic evaluation and diagnostic testing	Singleton WES	NR	6 (26%) of 105 families 3 had adjustment of therapy and 3 had therapy initiated	NR
Srivastava (2014)[57]; U.S.	High	71 children and adults with neurodevelopmental disabilities and negative diagnostic workup prior to WES	WES	41%	32 (41% of those tested, 100% of those diagnosed)	27 (35%)
Stark (2016, 2017, 2019) [13-16]; Australia	Some	80 children age 0 to 2 years with diverse phenotypes suspected of having monogenic disorders and negative CMA result	Singleton WES in parallel with standard non-WES tests	Standard tests: 28% WES: 58%	16 (20% of those tested, 34% of those diagnosed)	14 (30%)
Stark (2018)[22]; Australia	High	40 acutely ill children and infants with suspected monogenic disorder, compared to 40 children from other published articles	Singleton WES	Rapid WES: 53% Standard WES: 58%	Reported for the Rapid WES Cohort Only 16 (20% of those tested, 34% of those diagnosed) 20% (16) of those tested	NR

(continued)

Table 5. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling diverse populations (continued)

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Tan (2017)[19]; Australia	Some	44 children age 2 to 18 years with diverse phenotypes suspected of having a monogenic condition from a single tertiary pediatric hospital. All had prior nondiagnostic CMA	Singleton WES with targeted analysis of only genes known to cause monogenic disorders, evaluated counterfactual strategies including WES at first presentation, at first genetic appointment, as final test, and without WES	52%	7 (30% of those diagnosed, 16% of those tested) had change in management (specific changes unspecified). 6 (26% of those diagnosed, 14% of those tested) had 1 (4% of those diagnosed, 2% of those tested) of those stopped planned investigations.	1 (4% of those diagnosed, 2% of those tested) had a prenatal implantation genetic diagnosis planned
Valencia (2015)[54]; U.S.	Some	40 pediatric patients with diverse clinical features referred by medical specialists for exome sequencing.	Singleton WES	30%	13% (5 of 40) had a potential change in management 2 (5%) had change in management 12 (30%) altered medical management including genetic counseling	NR
Waldrop (2019) [47]; U.S.	Some	31 pediatric patients belonging to 30 families seen in a neuromuscular clinic who had WES performed since 2013	Trio WES	37%	3 (25%) plan for disease surveillance 1 (8%) discontinued medication 1 (8%) with certainty of malignant hyperthermia risk 1 (8%) with diagnosis started palliative care	12 (100%)
Willing (2015)[56]; U.S.	High	35 children with diverse phenotypes at a children's hospital with an acute illness of suspected genetic cause	Rapid WGS of trios with whole exome analysis; Standard genetic testing based on clinical judgement	Rapid WES 57%, standard genetic testing: 9%	12 (60%) had a change in management	NR

(continued)

Table 5. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling diverse populations (continued)

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Zhu (2015)[45]; U.S.	High	113 trios reported for the first time and 6 previously unsolved trios from diverse clinical phenotypes of children and adults	Trio WES	24%	4 (3% of those tested, 14% of those diagnosed)	NR

Abbreviations: CMA = chromosomal microarray analysis; NR = not reported; WES = whole exome sequencing; WGS = whole genome sequencing;

recommendation. Between 5% and 54% of those diagnosed using WES were referred for additional surveillance or medical specialties in the 6 studies that reported this.[16,18,22,47,52,57] Among patients diagnosed with rapid WES, 5% of patients in one study[22] and 30% in a second study[56] were redirected to palliative care based on the diagnosis.

Two studies directly compared management changes in those who received a diagnosis to those who did not. Matias, et al., reported that 100% of probands with a diagnosis from WES experienced some change in management, compared with 95% of those without.[49] In the study by Niguidula, et al., 17% of those who received a molecular genetic diagnosis from WES experienced a medication change, compared with 29% of those who received uncertain results and 3% of those with negative results from WES.[39]

Twelve studies [13-16,19,39,42,43,46,47,49,52] reported on additional genetic counseling or testing in family members of sequenced probands. Three of these studies reported on cascade genetic testing in family members due to WES, ranging from 14% to 97% of those with a diagnosis.[16,46,49] Matias, et al., additionally reported that 0% of families who did not receive a molecular genetic diagnosis from WES went on to receive cascade genetic testing.[49] For the 8 studies that reported on reproductive counseling, testing, planning, or prenatal diagnosis, between 4% and 97% of families who received a diagnosis using WES used that information for the aforementioned purposes.[13-16,19,39,42,43,46,49,52] At the low end of this range, 2 studies both reported that 4% of families receiving a diagnosis from WES either planned to use or reported using that information for prenatal implantation genetic diagnosis.[19,43] At the high end of this range, Matias, et al.,[49] reported that 97% of families who received a diagnosis also received reproductive counseling, while Bourchany, et al.,[42] reported 92% of those who received a diagnosis using WES received either prenatal counseling or testing. Three of these studies also reported on the percentage of families who did not receive a diagnosis from WES, and found that between 0% and 6% sought out reproductive planning services after receiving their negative WES results.[13,39,49] In Waldrop et al, all 12 individuals who received a molecular genetic diagnosis from WES received genetic counseling regarding implications in family members.[47]

3.3.3 Findings From Studies Among Patients With Epilepsy

Characteristics and outcomes from the 5 studies that enrolled patients with epilepsy are reported in ***Table 6***. We rated all but 1 as having a high risk of bias.[58] All 5 studies reported on actual changes in management experienced by their patient population.[27,28,32,34,58] The percent with an actual change in management ranged from 0% to 31% of those who received a diagnosis from WES. Between 0% and 20% of those diagnosed by WES underwent a change in medication as a result of the WES results including one patient in a study for which the percentage was not calculable.[28] Palmer, et al., additionally reported that of 16 patients, 1 (6%) patient diagnosed by WES initiated palliative care, 1 (6%) patient had reduced number and expense of diagnostic interventions, and 1 (6%) patient had additional unspecified management changes.[27] For comparison, Ream et al. reported that of 23 patients diagnosed by other genetic testing strategies, and 3 (13%) changed medications and 1 (4%) was prescribed a special diet as a result of the molecular genetic diagnosis.[58]

Table 6. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling patients with epilepsy

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Howell (2018)[28]; Australia	High	49 infants with severe epilepsy	7 strategies evaluated that included different combinations of 3 tiers of testing (Tier 1: imaging, CMA, metabolic; Tier 2: mitochondrial mutations, advanced metabolic testing, CSF testing; Tier 3: skin biopsy, electron microscopy, histochemistry) with/without genetic testing that included singleton WES, but also included gene panel testing	Across the 7 strategies, range of 45% to 56%	Genetic diagnosis led to a management change in 1 participant (SCN2A mutation with sodium channel blocking AEDs used); unclear what % this represents since not calculable based on data reported in article.	100% of those with a genetic diagnosis; a significant recurrent risk was identified in 5 families.
Palmer (2018)[27]; Australia	High	30 children with infantile-onset epileptic encephalopathy who remained undiagnosed after "first-tier" testing at a single children's hospital	Pediatric neurology and clinical genetics consultation, first and second tier testing (blood, urine, and CSF chemistries and metabolic testing, imaging, single gene, gene panel, CMA, mitochondrial testing), trio WES	Without WES: 6%; With WES: 53%	5 (31.3%) of those diagnosed	44% (7) of those with diagnosed
Perucca (2017)[34]; Australia	High	40 adults and children with a diagnosis of focal epilepsy	Singleton WES of 27 focal and 35 non-focal epilepsy genes, then expanded to 29 focal epilepsy genes.	13%	1 (20%) of those with diagnosis had a change in medication	NR
Ream (2014)[58]; U.S.	Some	25 patients at tertiary care center diagnosed with pediatric drug resistance epilepsy	Patients underwent one of the following genetic tests - karyotype, chromosomal microarray, gene sequencing of specific single genes, gene sequencing using gene sequencing panels, and/or WES	WES: 17%; gene panel 46%; single gene 15%; microarray 17%; karyotype 14%; any genetic testing 35%	0 (0%) of patients diagnosed by WES 3 (13%) patients diagnosed by other genetic tests had a change in medication. 1 (4%) patients diagnosed by other genetic tests was prescribed a special diet	3 (50%)

(continued)

Table 6. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling patients with epilepsy (continued)

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Snoeijen-Schouwenaars (2019)[32]; The Netherlands	High	100 adults and children with epilepsy from outpatient specialty clinics	Targeted epilepsy/ID panel followed by WES if negative in mostly trios but some singletons	25%	1 (4%*) of those with diagnosis	NR

Abbreviations: CMA = chromosomal microarray analysis; CSF = cerebrospinal fluid; ID = intellectual and development disability; WES =whole exome sequencing

Of these 5 studies, 3 reported that families of probands had undergone either additional genetic counseling or reproductive planning as a result of their WES findings.[27,28,58] Howell, et al., identified 5 families with a significant risk of disease recurrence who received genetic counseling, though the number of eligible families was unclear from the study.[28] Although no patients received a molecular genetic diagnosis using WES in the study by Ream et al. the authors report that 50% of the families whose probands underwent WES received genetic counseling about heterozygous autosomal recessive mutations that the authors described as having "potential diagnostic significance."[58] Finally, Palmer et al., reported that 44% of the families whose probands were diagnosed using WES utilized reproductive planning services.[27]

Of the 5 studies, 2 reported on potential changes in management resulting from WES.[32,58] Ream et al. defined an *a priori* series of molecular genetic diagnoses that the authors felt would result in potential management changes and reported that none of the 6 patients who had received a diagnosis from WES would fall into that category, compared to 4 of 23 (17%) patients who had received a diagnosis from a non-WES genetic test.[58] Snoeijen-Schouwenaars et al.[32] reported that 10 of 25 patients (40%) with a pathogenic or likely pathogenic WES result had a potential change in management available to them.

3.3.4 Findings From Studies Among Patients With Other Single Phenotypes

Characteristics and outcomes from 7 studies that reported on the clinical utility of WES among patients with a specific phenotype other than epilepsy are reported in ***Table 7***.[25,41,44,48,50,51,53] Reported changes in clinical management of the primary phenotype included dietary changes, alterations to prescribed medications, or discontinuation of unnecessary treatment. Alternations to medication or diet occurred in 4 of 33 (12%) patients presenting with short stature,[51] 10 of 45 (22%) patients presenting with neurodevelopmental disorders,[25] 9 of 23 patients (39%) diagnosed with familial hypercholesterolemia,[50] and 15 of 28 (54%) patients presenting with neurometabolic disorders.[44] In 1 study,[25] unnecessary treatment was stopped for 3 of 45 (7%) patients diagnosed. In the study of infantile malignant osteopetrosis, 1 of 6 patients was redirected to palliative care because their specific genotype was untreatable.[53] Only Jones, et al., reported changes in genetic counseling as a result of WES findings.[50] They reported that 8 of 19 (42%) individuals discussed their WES results with a clinical genomics specialist. Mann, et al. reported that among 108 patients who had received a kidney transplant, their post-transplant WES results indicated that better pre-transplant management options were available for 5 of them.[48]

Table 7. Summary of characteristics and outcomes for studies evaluating clinical utility among studies enrolling other single phenotype populations

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Actual Changes in Management	Results Leading to Additional Genetic Counseling or Testing in Family
Daga (2018)[41]; U.S.	Some	65 children and adults from 15 families with nephrolithiasis or nephrocalcinosis before age 25	WES of multiple family members or trios	29%	3 (20%) of diagnosed families	NR
Hauer (2017)[51]; Germany	High	200 adults and children with short stature and extensive prior diagnostic work-up referred by their local medical specialists for evaluation of growth retardation/ short stature	Targeted WES of known short stature genes; singleton WES in 100, trio WES in 100.	17%	31 families (16%) led to preventive measures 23 families (12%) had orthopedic support and developmental evaluation 9 families (5%) had recommendations for symptomatic treatment or screening for associated malformations 4 families (2%) received new medications	NR
Jones (2018)[50]; U.S.	High	28 individuals with WES results from the MyCode initiative indicating a diagnosis of familial hypercholesterolemia	Singleton WES	NA	18 (78%) prescribed lipid-lowering therapy 8 (47%) changes to intensity of medication management 9 (39%) changes made to their treatment regimens 1 (11%) was initiated on new therapy	8 (42%)
Mann (2019)[48]; U.S.	Some	104 patients with chronic kidney disease who developed disease before 25 years of age and were transplanted	Targeted WES	32.70%	5 (4.8%) where diagnosis had clinical consequences	NR
Shamriz (2016)[53]; Israel	High	6 patients clinically diagnosed with malignant infantile osteopetrosis	Singleton WES	100%	1 (17%) decision to defer allogenic hematopoietic stem cell transplantation based on clinical and genetic findings	NR
Soden (2014)[25]; U.S.	High	119 children with diverse neurodevelopmental disorders	Trio WES	38.8%	49% (22 families with a diagnosis)	NR
Tarailo-Graovac (2016)[44]; Canada	Some	41 patients with intellectual developmental disorder and unexplained metabolic phenotypes	Trio WES with available affected siblings	68%	18 (44% of those tested, 64%* of those diagnosed)	NR

Abbreviations: WES =whole exome sequencing

3.4 Key Question 2: Effectiveness (Health Outcomes)

Seven studies reported on health outcomes.[22,32,34,40,53,56,58] Detailed information regarding study characteristics and outcomes are reported in ***Appendix C, Table C-1*** and ***Table C-3***. The key findings are:

- Mortality ranged from 17% to 57%, but the studies that reported mortality were conducted among infants in NICUs or hospitalized children with acute illness.
- Among patients with epilepsy, management changes resulting from WES diagnosis improved seizure control or behavior management in 0% to 3% of study participants.

We were unable to assess the certainty of evidence related to health outcomes because of very serious limitations in the study designs and reporting of outcomes. Further details are in ***Appendix G.***

3.4.1 Study and Population Characteristics

The included studies were published from 2014 to 2019 and had performed WES between 2011 and 2017. Two studies did not report when WES testing had taken place.[53,58] One study was a case series,[53] 1 study was a controlled observational cohort,[22] and the rest were single-arm observational cohort studies. Three studies were conducted in the U.S.,[40,56,58] 2 were conducted in Australia,[22,34] and 1 each were conducted in Israel[53] and The Netherlands.[32] Two studies had some industry funding,[22,56] and 4 studies had no industry funding.[32,34,40,58] Two studies did not specifically list any study funders.[32,58] For the remaining study it was unclear whether any industry funding was involved.[53] ***Table 8*** describes the characteristics of included studies that reported health outcomes.

The number of probands who underwent WES testing in each study ranged from 6 to 278 (40% to 52%; female). The median age of probands ranged from 26 days to 32.5 years. Three studies only included probands under the age of 18,[22,53,58] and 2 studies only included infants.[40,56] Two studies included both adults and children.[32,34]

Three of the included studies performed WES on probands with diverse phenotypes,[22,40,56] and 3 studies included probands with epilepsy.[32,34,58] The remaining study included only probands with a clinical diagnosis of malignant infantile osteopetrosis.[53] Two of the included studies performed singleton WES,[34,53] and 3 reported using a combination of singleton, duo, or trio WES.[32,40,56] Four studies were conducted at institutions that were described as either tertiary[22,34,58] or quaternary,[56] and the remaining 3 were described as academic medical institutions.[32,40,53]

3.4.2 Findings

Four publications reported mortality[22,40,53,56] and none reported length of survival. Four studies reported some other health outcome.[32,34,53,58] ***Table 8*** describes the characteristics and findings for studies that reported health outcomes.

Table 8. Summary of characteristics and findings for studies evaluating health outcomes

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Mortality	Other health outcomes (morbidity, cognitive ability, functional outcomes)
Meng (2017)[40]; U.S.	Some	278 infants less than 100 days old with diverse clinical phenotypes referred to a tertiary institution for WES	Majority singleton WES, some trio WES	5-yr death rate: Diagnosed, 39 of 102 (38%) Not diagnosed, 41 of 170 (24%) 120-day death rate: Diagnosed: 30 of 102 (29%) Not diagnosed: 28 of 170 (17%)	NR
Perucca (2017)[34]; Australia	High	40 adults and children with a diagnosis of focal epilepsy	Singleton WES of 27 focal and 35 non-focal epilepsy genes, then expanded to 29 focal epilepsy genes.	NR	1 experienced change from "uncontrolled monthly seizures" to seizure-free for 12 months since implementing change in management
Ream (2014)[58]; U.S.	High	25 patients at tertiary care center diagnosed with pediatric drug resistance epilepsy; 6 with WES	Patients underwent one of the following genetic tests: karyotype, chromosomal microarray, gene sequencing of specific single genes, gene sequencing using gene sequencing panels, and/or WES	NR	0 of WES patients had improved seizure control. 1 patient diagnosed with other genetic tests had improved seizure control based on medication change resulting from gene test
Shamriz (2016)[53]; Israel	High	6 patients clinically diagnosed with malignant infantile osteopetrosis	Singleton WES	1 (17%) with diagnosis from WES died 2 years after parent refusal of treatment,	1 with diagnosis experienced progressive neurological deterioration. 4 with diagnosis were alive and well
Snoeijen-Schouwenaars (2019)[32]; The Netherlands	High	100 adults and children with epilepsy previously received negative targeted gene testing and had a clinical indication for WES referred to outpatient specialty clinics	Targeted epilepsy/ID panel followed by whole exome analysis if negative in 66/100 trios and 34/100 singletons.	NR	1 patient had improved behavior and mood following medication change based on WES result
Stark (2018)[22]; Australia	Some	40 acutely ill children and infants with suspected monogenic disorder, compared to 40 children from other published articles	Singleton WES	Unclear length of follow-up: 9 (23%) of rapid WES cohort 9 (11%) of standard WES cohort	NR

(continued)

Table 8. Summary of characteristics and findings for studies evaluating health outcomes (continued)

Author (Year); Country	Risk of Bias	Study Population and Setting	Testing Strategies Used	Mortality	Other health outcomes (morbidity, cognitive ability, functional outcomes)
Willing (2015)[56]; U.S.	High	35 children with diverse phenotypes nominated for STATseq by treating physician at quaternary children's hospital with an acute illness of suspected genetic cause but without a genetic diagnosis	Rapid WGS of trios with whole exome analysis. Comparator: standard genetic testing based on clinical judgement	120-day mortality: 14 (40%) overall 12 (57%) with a diagnosis	NR

Abbreviations: ID = intellectual and developmental disability; WES =whole exome sequencing; WGS = whole genome sequencing

Health Outcomes Among Studies That Enrolled Diverse Phenotypes

Three studies reported outcomes among diverse phenotypes.[13-16,22,40,56] Two of these studies recruited critically ill children.[22,56] One recruited children aged 0 to 2 years with suspected monogenic disorders[22] and one recruited infants through 100 days old who had been referred for WES for a variety of medical concerns.[56]

Four studies reported mortality outcomes.[22,40,53,56] Stark, et al. reported that 9 of 40 (23%) infants who underwent rapid WES died, compared to 9 of 80 (11%) infants who underwent standard WES, though neither the length of follow-up time nor the percentage of those who died had received a molecular genetic diagnosis were reported.[22] Meng, et al. reported 120-day mortality for 30 of 102 (29%) participants with a diagnosis from WES, compared to 28 of 170 (17%) participants who remained undiagnosed.[40] At 5 years the mortality was 38% and 24% respectively. Willing, et al., reported a 120-day mortality in 12 of 21 (57%) critically ill infants with a diagnosis from rapid or standard testing.[56] Although they did not calculate a mortality rate exclusive to infants who received a diagnosis from WES, 2 of 14 (14%) infants who did not receive a genetic diagnosis by any method tested in this study died by 120 days.[56] The studies did not control for baseline differences, and in the three studies[15,22,40,56] of rapid WES, sicker infants were more likely to receive rapid WES.

Health Outcomes From Studies That Enrolled Participants With Epilepsy

Three studies included populations with epilepsy.[32,34,58] None reported mortality information; all reported on other health outcomes following medication changes due to WES results. Snoeijen-Schouwenaars et al. reported 1 of 25 (4%) patients who received a diagnosis from WES had improved behavior and mood symptoms after a medication changed that was based on the WES results.[32] Perucca, et al. reported 1 of 5 (20%) patients who received a diagnosis from WES and a corresponding change in epilepsy management improved from monthly seizures to having 12 months free from seizures.[34] Ream et al. reported that 0 of 6 (0%) probands diagnosed using WES had improved seizure control, compared with 1 of 23 (4%) probands who experienced a medication change based on the results of other genetic tests.[58]

Health Outcomes From Studies That Enrolled Other Single-Phenotype Participants

One study reported health outcomes for 6 probands diagnosed with malignant infantile osteopetrosis.[53] In this study, 1 of 6 (17%) probands who had received a molecular genetic diagnosis from WES died 2 years after receiving WES results and after parental refusal of further treatment. There was no minimum follow-up required by this study; length of follow-up ranged from 0.28 to 8.96 years. Of the other health outcomes reported, 4 of 6 (67%) probands were described as “alive and well” and 1 of 6 (17%) had experienced progressive neurological deterioration.

3.5 Key Question 3: Safety and Harms

Twenty-six studies provided evidence on the harms associated with WES.[20,24,40,42,43,50,54,58-76] Detailed information regarding study characteristics and outcomes are reported in ***Appendix C, Table C-1 and C-4***. The key findings are:

- Two percent of patients diagnosed using standard testing were not diagnosed by WES. The patients not diagnosed with WES had genetic variants that were not diagnosed well by WES technology at the time the study was done.
- We calculated the pooled percent of patients with an ACMG-defined medically actionable variant to be 4% (95% CI, 2.4% to 5.3%) across 13 studies that provided data suitable for use in pooling. Of the remaining studies, 4 reported 0% with actionable variants,[20,42,62,70] and the other 5 reported between 1% and 10%.[24,54,61,68,75]
- Most patients or parents of patients did not experience psychosocial harms from receiving negative or uncertain WES results; these findings come primarily from qualitative research studies.

We assessed the certainty of evidence related to the frequency of ACMG-defined medically actionable variants as *low* because of study designs and study limitations. We did not assess the certainty of other reported safety outcomes as they were too heterogenous or largely reported from qualitative research studies. Detailed certainty ratings are in ***Appendix G.***

3.4.1 Study and Population Characteristics

Twenty-six studies[20,24,40,42,43,50,54,58-76] published between 2014 and 2019 provided evidence on the harms associated with WES. The studies were conducted between 1998 and 2017. Twenty-one quantitative studies[20,24,40,42,43,54,58,60,61,63-66,69-76] were single-arm observational cohort studies. Twelve had a low risk of bias,[42,54,60,63,64,66,69-74] 7 had some risk of bias,[20,24,40,43,61,65,75] and 2 had a high risk of bias.[58,76] The single-modeling study[75] was rated as having some risk of bias. We did not assess the risk of bias for the 4 qualitative research studies.[59,62,67,68] Twelve studies received no industry funding,[15,20,42,43,54,59,65,68-70,72,73, #9124] 4 studies received some industry funding[40,60,63,66] and 4 studies were completely funded by industry.[50,61,64,71] Funding source was not reported for the remaining 6 studies.[24,58,62,67,74,75]

Two studies[71,75] were conducted in Australia and one each in Canada,[72] France,[42] Japan,[70] The Netherlands,[20] and Saudi Arabia.[61] The remainder of the studies were conducted in the U.S. One study[40] limited enrollment to infants, 6 to children,[20,24,54,58,62,72] and 4 to adults.[50,63,67,76] Three studies[65,70,75] did not report the age range of their participants, and the remainder included both children and adults. Twenty studies[20,24,40,42,43,54,59-69,74-76] included patients with diverse phenotypes, and 6 studies included patients with a single phenotype.[50,58,70-73]

3.4.2 Findings

The harms potentially resulting from WES include false positive or false negative test results and downstream adverse health outcomes or distress, distress resulting from receipt of undesired information on other genetic conditions or family relationships, and other sources of

psychosocial harm. We found evidence regarding each of these potential harms. None of the studies reported other types of harms.

Misdiagnosis

We report the frequency of sequencing errors and overdiagnosis in ***section 3.2.3***, the contextual questions on diagnostic yield. One study[20] compared the proportion of patients with missed diagnoses with WES and with standard testing (***Table 9***). The authors found that 3 of 150 (2%) patients diagnosed by standard testing were not diagnosed by WES. These 3 patients had genetic diseases caused by copy number variants or trinucleotide repeat expansions, variants that are less likely to be detected by WES.

Table 9. Study and population characteristics of the one controlled cohort studies evaluating missed diagnoses in WES compared to standard genetic testing

Author (Year); Country	Study Design; Risk of Bias	Population Characteristics	Intervention (N Missed; N Analyzed)	Comparator (N Missed; N Analyzed)
Vissers (2017), Netherlands	Single-arm observational cohort, Some	Children with nonacute neurological symptoms of suspected but undiagnosed genetic origin.	WES: 3; 150	Standard testing pathway: 36; 150

Abbreviations: WES = whole exome sequencing

Reported Secondary Findings (ACMG-defined medically actionable variants)

Twenty-two studies reported on the proportion of participants who received results on genetic variants that had health implications for diseases other than the one for which they were evaluated (***Table 10***).[20,24,40,42,43,54,58,60-66,68,70-76] We rated 11 of the studies as having a low risk of bias,[42,54,60,63,64,66,70-74] 7 as having some risk of bias,[20,24,40,43,61,65,75] and 2 as having a high risk of bias.[58,76] The remaining 2 studies had qualitative study designs that were nested within larger studies.[62,68] Four studies reported on the proportion of patients who chose to receive information on secondary findings.[43,60,64,74] Three[60,64,74] of these studies had a low risk of bias, and 1 had some risk of bias.[43]

Among the studies that reported on the proportion of patients who chose to receive secondary findings, 90% (2,781 of 3,089 patients) opted to receive such findings. In a survey of participants who chose not to receive nonmedically actionable results, 5 of 36 respondents said they feared the information would be an emotional burden.[76]

We calculated that the pooled percent of patients with an ACMG-defined medically actionable variant to be 4% (95% CI, 2.4% to 5.3%) across 13 studies (6,653 participants) that provided data suitable for use in pooling. Of the remaining studies, 4 reported 0% with actionable variants,[20,42,62,70] and the other 5 reported between 1% and 10%.[24,54,61,68,75]

Table 10. Study and population characteristics of the 22 studies that reported on the frequency of ACMG-defined medically actionable variants and participants' choice to receive them

Author (Year); Country	Study Design; Risk of Bias	Population Characteristics	Patients With ACMG-Defined Medically Actionable Variants		Proportion of Patients Who Chose to Receive Reports of ACMG-Defined Medically Actionable Variants	
			N, With Variants	N, Analyzed for ACMG Variants	N	Total With WES
Baldridge (2017); U.S.	Single-arm observational; Some	Patients with diverse phenotypes who were referred by exome clinic; mixed children and adults	14	141	141	146
Bourchany (2017); France	Single-arm observational; Low	Patients who had been seen at genetics centers for congenital anomalies or undiagnosed DD; Mixed children and adults	0	29	NR	29
Ding (2014); Australia	Modeling Study; Some	24 autosomal-dominant, highly penetrant conditions characterized by long asymptomatic periods and response to preventive measures or treatment. Modeling only, no participants.	NR (2% to 7%)	NA	NA	NA
Jurgens (2015); U.S.	Single-arm observational; Some	Families with diverse apparent Mendelian conditions that had undergone WES at academic medical center. Characteristics of sequenced individuals not described.	2	232	NR	232
Lee (2015); U.S.	Single-arm observational; Low	Children who had been seen at ophthalmic genetics clinic for diverse ophthalmic conditions.	1	26	NR	26
Meng (2017); U.S.	Single-arm observational; Some	Infants < 100 days old with diverse phenotypes who had been referred for exome sequencing	21	267	NR	267
Monies (2017); Saudi Arabia	Single-arm observational; Some	Families (affected children and parents) that had been referred for multigene panels or WES; diverse phenotypes	NR (1%)	NR	NR	NR
Muramatsu (2017); Japan	Single-arm observational; Low	Patients with inherited bone marrow failure syndromes. Patient characteristics not described.	0	250	NR	250
Nolan (2016); U.S.	Single-arm observational; Some	Pediatric neurology patients with diverse neurologic phenotypes	NR (10%)	NR	NR	NR
Posey (2015); U.S.	Single-arm observational; Low	Unrelated adults with diverse phenotypes who had received clinical WES	6	482	NR	482
Ream (2014); U.S.	Single-arm observational; High	Children with drug-resistant epilepsy	4	6	NR	6
Retterer (2016); U.S.	Single-arm observational; Low	Children who had been tested at commercial laboratory with diverse phenotypes	129	2091	2091	2382
Roche (2019); U.S.	Single-arm observational; High	Adults who had received WES and education on nonmedically actionable secondary findings	13	622	NR	622

(continued)

Table 10. Study and population characteristics of the 22 studies that reported on the frequency of ACMG-defined medically actionable variants and participants' choice to receive them (continued)

Author (Year); Country	Study Design; Risk of Bias	Population Characteristics	Patients With ACMG Medically Actionable Variants		Proportion of Patients Choosing to Receive Reports of ACMG Medically Actionable Variants	
			N, With Variants	N, Analyzed for ACMG Variants	N	Total With WES
Rosell (2016); U.S.	Qualitative	Parents whose children had undergone WES	0	19	NR	19
Shashi (2016); U.S.	Single-arm observational; Low	Children and adults who received clinical WES for diverse phenotypes	2	59	59	59
Strauss (2017); U.S.	Single-arm observational; Low	Old Order Amish and Mennonite children with diverse phenotypes	21	490	490	502
Tammimies (2015); Canada	Single-arm observational; Low	Children with autism who were referred by developmental pediatric clinics	6	95	NR	95
Valencia (2015); U.S.	Single-arm observational; Low	Children who had received physician-ordered WES with diverse phenotypes	NR (8%)	NR	NR	NR
Vanderver (2016); Australia	Single-arm observational; Low	Children and adults with suspected diagnosis of leukodystrophy or genetic leukoencephalopathy	3	142	NR	142
Vissers (2017); Netherlands	Single-arm observational; Some	Children with nonacute neurological symptoms of suspected but undiagnosed genetic origin	0	150	NR	150
Werner-Lin (2018); U.S.	Qualitative research design	Adolescents and parents who were from disease-specific clinics with diverse phenotypes	NR (10%)	NR	NR	NR
Yang (2014); U.S.	Single-arm observational; Low	Children and adults who had received physician-ordered WES with diverse phenotypes	59	2,000	NR	2000

Abbreviations: ACMG = American College of Medical Genetics and Genomics; NR = Not Reported; U.S. = United States; WES = Whole Exome Sequencing

Psychosocial Harms

Eight studies (2 quantitative[66,69] and 6 qualitative[50,59,62,67,68,76]) provided evidence on the psychosocial harms or other reactions experienced by patients who underwent WES or their parents (***Table 11***).

The studies provided little indication of significant psychosocial harms from receiving nondiagnostic or uncertain WES results. Anxiety and depression was higher among parents of undiagnosed children than normative populations, but did not differ between parents whose children had a nondiagnostic WES and those whose child had not.[69] The initial reaction of parents and patients who received uncertain WES results included frustration, disappointment, stress, anger and fear,[62,67,68] but 1 study[68] found these feeling had resolved within 3 months. Parents reported that the uncertain result did not affect their ability to take care of their child or alter their perception of their child's condition.[67] Some families felt a need for more follow-up counseling or outreach or a need to help families manage expectations.[62]

A third study of reactions to variants of unknown significance (VUS) found that almost all participants understood the VUS was not a definitive diagnosis.[59] One participant in this study experienced distress from the VUS result, but no participants regretted getting the result or the test. Most felt the information would be useful in the future.

No studies directly examined the impact of WES results on family dynamics or relationships. In 1 case, a participant experienced shock after discovering nonpaternity during a family discussions of the WES result and the family's history of heart disease.[50] One study reported on the uptake of cascade testing among family members.[66] Among the families of 92 patients with a medically actionable secondary finding, 33 relatives from 19 families requested testing for the variant found in the proband.

Table 11. Study and population characteristics of the 8 studies reporting on psychosocial harms and reactions among patients and parents of patients who underwent WES

Author (Year); Country	Study Design; Risk of Bias	Population Characteristics	Sample Size	Study Findings			
McConkie-Rosell (2018); U.S.	Single-arm observational; Low	Parents of children with suspected genetic disorder	50	Instrument	All	Nondiagnostic WES	Norm
				GAD-7	4.9 ± 4.38	5.36 ± 4.96	3.57 ± 3.38
				PHQ-9	4.8 ± 4.76	5.45 ± 5.99	2.91 ± 3.52
				CSE	186 ± 44	188 ± 38	137 ± 46
				HCEI subscales			
				ICCE	18.0 ± 2.2	18.5 ± 1.8	15.9 ± 2.6
				TU	16.3 ± 2.7	16.2 ± 2.7	17.4 ± 2.3
Yang (2014); U.S.	Single-arm observational; Low	Patients with physician-ordered WES	2,000	Of 92 patients with a medically actionable secondary finding, 33 relatives from 19 families requested testing for the variant found in the proband			
Jones (2018); U.S.	Qualitative; NA	Apparently healthy clinic patients who received WES for routine care and were found to carry familial hypercholesterolemia	23	Shock from discovery of nonpaternity discovered in family discussion of family history of heart disease			
Li (2019); U.S.	Qualitative; NA	Parents of children whose WES results included a VUS	14	Range of emotions from VUS result, including confusion, anger, stress, fear., relief, and disappointment. Majority of participants reported VUS result did not affect their ability to take care of their child or alter their perception of their child's condition.			
Roche (2019); U.S.	Single-arm observational; High	Patients who received WES and education about nonmedically actionable secondary findings	155	5 of 36 respondents stated their reason for not requesting nonmedically actionable secondary findings were concern that the information would be an emotional burden.			

Table 11. Study and population characteristics of the 8 studies reporting on psychosocial harms and reactions among patients and parents of patients who underwent WES (continued)

Author (Year); Country	Study Design; Risk of Bias	Population Characteristics	Sample Size	Study Findings
Rosell (2016); U.S.	Qualitative; NA	Parents whose child had undergone WES	19	All parents hoped for diagnosis. 21% had high expectations of diagnosis; 68% had tempered expectations; 11% had low expectations. Some parents voiced frustration and disappointment with long waiting and not getting complete answers. Some families felt need for more follow-up counseling or outreach and some expressed need to help families manage expectations.
Skinner (2018); U.S.	Qualitative: NA	Patient with VUS	32	1 (3%) misinterpreted an uncertain result as a definitive answer. Some adult participants for whom family testing was recommended did not pursue it because they did not want to pressure family members. Patients pursuing testing did not worry while waiting on results. Some commented that uncertainty was not new. One participant reported experiencing distress related to the uncertain result. No participants expressed regret at learning the uncertain result. No participants reacted to the uncertain result in ways that could cause harm. Most regarded the information as potentially valuable in the future.
Werner-Lin (2018); U.S.	Qualitative; NA	Adolescents and parents from disease specific clinics	10	Initially disappointed with uncertain results; Experienced frustration, disappointment, and fear. Feelings evolved over time; and moved toward acceptance and satisfaction, generally within the ensuing 3 months.

Abbreviations: CSE = Coping Self-Efficacy Scale; GAD-7 = Generalized Anxiety Disorder; HCEI = Health Care Empowerment Inventory; ICCE = Informed, Committed, Collaborative, Engaged score from HCEI; PHQ-9 = Patient Health Questionnaire; NA = not applicable; TU = Tolerance of Uncertainty from HCEI; VUS = variants of uncertain significance; WES = whole exome sequencing

3.6 Key Question 4: Costs

Seventeen studies (reported in 20 publications) reported cost-related outcomes.[13-28,77-80] Detailed information regarding study characteristics and outcomes are reported in ***Appendix C, Table C-1, Table C-5*** and ***Table C-6.*** The key findings are:

- The cost of a WES test reported in studies varied between US$ 1,000 and US $15,000; trio WES costs more than singleton WES.
- In both single-phenotype and diverse phenotype populations, when compared to standard diagnostic pathways, testing pathways that used WES identified more diagnoses at a lower cost in some studies, or identified more diagnoses but at a somewhat higher cost in other studies (range US$ 1,775 to US$ 8,559 higher depending on where WES was used in the testing pathway).

- Pathways with earlier WES testing were more likely to be cost savings than pathways that used WES later in the testing pathway or as a last resort strategy.

We assessed the certainty of evidence related to all cost outcomes as *very low* because of study designs, study limitations, inconsistency, and imprecision. Detailed certainty ratings are in ***Appendix G.***

3.6.1 Study and Population Characteristics

Study characteristics are briefly summarized in ***Table 12***. Two of the 17 studies were conducted in the U.S.;[24,25] the rest were conducted in Australia (10), The Netherlands (3), Canada (2), and Argentina (1). One study was conducted using data from the years 1998 to 2013,[26] and most were conducted from 2011 to 2017. Five studies were funded in part by industry funding;[13-17,22,27,78] the rest were government agency funded (9) or the source of funding was not clear (3). We assessed 6 studies as having a high risk of bias,[17,18,24,25,77,78] and the rest we assessed as having some risk for bias. Sources of bias were generally related to inadequate information about costing methodology and model assumptions, lack of incremental analysis, and selective outcome reporting.

Sample size ranged from 14 to 370 participants across these studies. Three studies were conducted among populations that included both children and adults;[18,21,78] the rest were conducted exclusively among infants or children. Ten studies were conducted among populations that included diverse phenotypes.[13-25] The other 7 studies enrolled populations with homogenous phenotypes including participants with autism,[79] congenital muscular dystrophy,[26] epilepsy,[27,28] IDD,[77,80] and peripheral neuropathy.[78]

The testing strategies evaluated across the studies were highly varied and no single testing strategy was evaluated by more than one study. Only 3 studies were explicitly reported as being conducted prospectively.[13-16,19,78] Four studies used simulation or modeling to derive cost-related outcomes.[17,23,28,79] One study used a controlled cohort design[26] and the remaining 13 studies used a single-arm observational cohort design. The most commonly reported outcomes in this body of evidence were cost per patient for the testing strategy involving WES. Eight studies also reported cost per additional diagnosis because an actual or counterfactual comparison was available.[13-16,19,21,26-28,78,79] Only 1 study reported cost per quality life year (QALY) gained.[13-16]

Table 12. Summary of characteristics for studies evaluating cost outcomes related to whole exome sequencing

Author (Year); Country; Perspective	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Costs Included	Outcomes reported
Single-phenotype Populations						
Howell (2018)[28] Australia; Payer	Some	49 infants with severe epilepsy	7 strategies evaluated that included different combinations of 3 tiers of testing (Tier 1: imaging, CMA, metabolic; Tier 2: mitochondrial mutations, advanced metabolic testing, CSF testing; Tier 3: skin biopsy, electron microscopy, histochemistry, others) with/without genetic testing that included singleton WES with targeted analysis, but also included gene-panel testing	Across the 7 strategies, range of 45% to 56%	All costs related to diagnostic testing, including office visits, costs associated with sedation or operating rooms for diagnostic procedures	Cost of WES gene panel Cost per patient Cost per diagnosis Cost per additional diagnosis
Monroe (2016)[80] Netherlands; Payer	Some	17 children with IDD from a tertiary specialty clinic	Trio WES; traditional diagnostic evaluation including lab testing, imaging, and genetic tests other than WES	Trio WES: 30%	Costs of inpatient and outpatient medical interventions, imaging, and diagnostics, health professional visits. In the comparative analyses, WES costs replace all other genetic testing costs except CMA	Cost of WES Cost per patient
Palmer (2018)[27] Australia; Payer	Some	30 children with infantile-onset epileptic encephalopathy who remained undiagnosed after "first-tier" testing at a single children's hospital	Pediatric neurology and clinical genetics consultation, first and second tier testing (blood, urine, and CSF chemistries and metabolic testing, imaging, single gene, gene panel, CMA, mitochondrial testing), trio WES	Without WES: 6% With WES: 53%	Actual costs of diagnostic test	Cost of WES? Cost per patient Cost per diagnosis Cost per additional diagnosis

(continued)

Table 12. Summary of characteristics for studies evaluating cost outcomes related to whole exome sequencing (continued)

Author (Year); Country; Perspective	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Costs Included	Outcomes reported
Schofield (2017)[26] Australia; Payer	Some	56 children seen at a single tertiary neuromuscular center for congenital muscular dystrophy or nemaline myopathy	Traditional diagnostic pathway (metabolic testing, nerve conduction testing, imagine, muscle biopsy, candidate gene testing, CMA); Traditional pathway plus neuromuscular gene panel (464 genes); traditional pathway followed by singleton WES then trio WES if remained undiagnosed	Traditional pathway: 46% Neuromuscular gene panel: 75% WES: 79%	Cost of all diagnostic investigations and procedures, including neuromuscular gene panel and WES	Cost of WES Cost per patient Cost per diagnosis Cost per additional diagnosis
Tsiplova (2017)[79] Canada; Payer	Some	Synthetic modeling population for children with autism using a microcosting approach from a single tertiary pediatric hospital	CMA alone; CMA plus singleton WES	NR	Labor and material costs for CMA and WES; costs of confirmatory follow-up testing	Cost of WES Cost per patient Cost per additional diagnosis
Vrijenhoek (2018)[77] Netherlands; Payer	High	370 children with intellectual disabilities who had diagnostic WES at a single tertiary pediatric hospital	Trio WES	35%	Costs of all health care activities starting with the first visit to the medical center	Cost of WES Cost per patient

(continued)

Table 12. Summary of characteristics for studies evaluating cost outcomes related to whole exome sequencing (continued)

Author (Year); Country; Perspective	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Costs Included	Outcomes reported
Walsh (2017)[78] Australia; Payer	High	50 adults and children with neurophysiologically confirmed peripheral neuropathy suspected of having a monogenic cause	Singleton WES with initial analysis targeted to 55 genes, expanded to 88 genes plus SNP array if initial test nondiagnostic, then expanded to whole exome analysis if still nondiagnostic.	Initial WES 55 gene panel: 24% Expanded analysis and SNP array: additional 2 cases, cumulative yield 28% Whole exome analysis: additional 8 cases, cumulative yield 40%	Cost for all investigations, diagnostic procedures, first three neurology appointments for children, first neurology appointment for adults	Cost of WES Cost per patient Cost per diagnosis Cost per additional diagnosis
Diverse Phenotype						
Cordoba (2018)[18] Argentina; Payer	High	40 adults and children with diverse phenotypes and suspected neurogenetic conditions seen at a single tertiary genetics clinic, mean age 23 years	Singleton or trio WES	40%	Costs of tests, procedures, and visits	Cost of expendable diagnostic workup
Dillon (2018)[17] Australia; Payer	High	Simulation based study using data from 145 children with diverse phenotypes who had undergone diagnostic WES testing	WES with analysis limited to genes known to cause monogenic disorders; comparator strategies were simulated by applying up to 3 commercial gene panels to each child diagnosed with WES	54%	Cost of WES, costs of comparison gene panels	Cost of WES Other cost-related outcome

(continued)

Table 12. Summary of characteristics for studies evaluating cost outcomes related to whole exome sequencing (continued)

Author (Year); Country; Perspective	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Costs Included	Outcomes reported
Dragojlovic (2018)[23] Canada; Payer	Some	Data from 167 families used in a model evaluating pediatric diagnostic exome sequencing, no further study population information provided	Singleton and trio WES with targeted analysis focused on genes known to cause disease; reanalysis of nondiagnostic results every 6 to 12 months	Singleton WES: 28%; trio WES (after genomics consultation): 34%; Trio WES without consultation: 34%	Labor costs of clinical and laboratory staff, WES infrastructure, laboratory, and bioinformatics costs	Cost of WES Cost per patient Cost per diagnosis
Ewans (2018)[21] Australia; Payer	Some	14 adults and children with diverse phenotypes thought to have a monogenic etiology from a single clinical genetics unit	Singleton and trio WES, with whole exome analysis; reanalysis after 12 months for participants who were undiagnosed after initial testing	Initial WES: 30% (46% trio; 22% singleton) After reanalysis: 41%	Cost for diagnostic encounters and procedures	Cost of WES Cost per patient Cost per diagnosis Cost per additional diagnosis
Nolan (2016)[24] U.S.; Payer	High	50 children from a single academic neurology clinic who were referred for diagnostic WES testing	Singleton or trio WES with whole exome analysis	48%	Costs for initial and secondary genetic and metabolic tests, including karyotype, CMA, methylation PCR, single-gene and gene-panel testing	Cost of WES Cost per patient
Soden (2014)[25] U.S.; Payer	High	119 children with diverse neurodevelopmental disorders	Trio WES	39%	Costs of prior negative diagnostic testing for children who received a diagnosis, including lab, imaging, electromyograms, NCV studies. Not considered: physician visits, tests for patient management (e.g. EEG)	Cost of WES Cost per diagnosis

(continued)

Table 12. Summary of characteristics for studies evaluating cost outcomes related to whole exome sequencing (continued)

Author (Year); Country; Perspective	Risk of Bias	Study Population and Setting	Testing Strategies Used	Diagnostic Yield	Costs Included	Outcomes reported
Stark (2016, 2017, 2019)[13-16] Australia; Payer	High	80 children age 0 to 2 years with diverse phenotypes suspected of having monogenic disorders and negative CMA result	Singleton WES in parallel with standard non-WES tests	Standard care: 28% WES: 58%	All investigations, procedures, and assessments that occurred for diagnostic purposes; for cost-effectiveness also considered costs of future care after diagnosis	Cost of WES Cost per patient Cost per diagnosis Cost per additional diagnosis Cost per QALY gained
Stark (2018)[22] Australia; Payer	Some	40 acutely ill children and infants with suspected monogenic disorder, compared to 40 children from other published articles.[13-16]	Singleton WES, with likely whole exome analysis	Rapid WES: 53% Standard WES: 58%	Costs for all diagnostic investigations, procedures, and assessments	Cost of WES Cost per patient Cost per diagnosis
Tan (2017)[19] Australia; Payer	Some	44 children age 2 to 18 years with diverse phenotypes suspected of having a monogenic condition from a single tertiary pediatric hospital. All had prior nondiagnostic CMA	Singleton WES with targeted analysis, evaluated counterfactual strategies including WES at first presentation, at first genetic appointment, as final test, and without WES	52%	All diagnostic costs (inpatient and outpatient) from initial presentation to tertiary services for diagnostic assessment, including travel from home	Cost of WES Cost per patient Cost per diagnosis Cost per additional diagnosis
Vissers (2017)[20] Netherlands; Payer	Some	150 children through age 18 with nonacute neurological symptoms of suspected genetic origin from a single tertiary referral center	Singleton or trio WES, initial targeted analysis based on phenotype with expansion of analysis if no diagnosis; non-WES pathway was determined by providers and may have included CMA, single gene tests	Standard pathway: 7% WES: 29%	Actual costs of diagnostic tests both prior to and after inclusion in the study	Cost of WES Cost per patient

Abbreviations: CMA = chromosomal microarray analysis; WES =whole exome sequencing

3.6.2 Findings

Cost of WES Testing

The cost of WES testing varied by whether singleton or trio testing was used; the lowest reported cost was US$ 1,000 and the highest reported cost was US $15,000. In general, trio WES cost more than singleton WES.

Findings Among Diverse Phenotype Populations

Cost-related outcomes from the 10 studies enrolling diverse phenotype populations are reported in ***Table 13***. These studies evaluated various diagnostic pathways that included one or more of the following strategies: a standard diagnostic pathway without WES testing, WES as a last resort strategy, early WES (such as at initial tertiary presentation or initial clinical genetics presentation), rapid WES, and WES reanalysis.

Five studies reported cost per patient comparing a standard diagnostic pathway to one or more pathways that included WES testing.[13-16,19-22] The cost per patient for the standard diagnostic pathway ranged from AU$ 4,734 to €10,685. The cost per patient for diagnostic pathways that included WES testing ranged from CA$ 5,263 to AU$ 8,384. Across the studies that evaluated multiple WES testing strategies, pathways that involved earlier WES testing cost less than pathways that used WES later in the pathway.[13-16,19-21,23]

The cost per diagnosis was reported in 4 studies and ranged from AU$ 10,843 to US$ 24,215.[13-16,19,21-23] Similarly, pathways that involved earlier WES testing cost less per diagnosis than pathways that used WES later in the pathway. Furthermore, the 2 studies that involved reanalysis of WES after an interval of 12 to 18 months cost less per diagnosis then pathways without reanalysis.[21] For example, Ewans et al. (conducted in Australia but reported in US$) reported a cost per diagnosis of $23,010 (95% CI, $10,135 to $102,147) for WES at initial symptom presentation, a cost per diagnosis of $24,215 (95% CI, $11,195 to $103,173) for WES at the time of the clinical genetics review (a later stage in the diagnostic pathway), and a cost per diagnosis of $15,653 (95 %CI, $7,619 to $49,752) for WES at initial presentation with reanalysis at 12 months. A similar pattern was observed in the Stark et al. study with respect to the cost per diagnosis with reanalysis.[13-16]

Three studies reported the cost per additional diagnosis with WES testing when compared to a standard diagnostic pathway.[13-16,19,21] Test strategies that involved early WES testing generally cost less and identified more diagnoses when compared to the standard pathway (range of estimates US$ -586 to AU$ -6,482). The reported cost per additional diagnosis for WES when used after some initial tertiary evaluations, but not as a last resort, ranged from US$-3,709 to AU$ 2,622 when compared to the standard diagnostic pathway. Two studies reported the cost per additional diagnosis for WES as a last resort strategy and estimates of the cost per additional diagnosis were US$ 4,804 and AU$ 8,112.[13-16,19] With one exception,[19] estimates were imprecise and confidence intervals did not exclude $0.

Table 13. Summary of cost-related outcomes from studies enrolling diverse phenotype populations

Author (Year); Country	Study Population and Setting	Currency; Year	Cost of WES	Cost Per Patient; Mean (95% CI)	Cost Per Diagnosis; Mean (95% CI)	Cost Per Additional Diagnosis; Mean (95% CI)	Other Cost Outcomes
Cordoba (2018)[18] Argentina	40 adults and children suspected neurogenetic conditions	US$; NR	Singleton or trio; $1,000	NR	NR	NR	Cost of expendable diagnostic workup: $1,646 (95% CI, $1,439 to $1,835)
Dillon (2018)[17] Australia	Simulation using data from 145 children who had undergone diagnostic WES testing	AU$; 2016	$2,000	NR	NR	NR	In 26% of WES-diagnosed children for whom a comparator panel would have been diagnostic, the least costly panel had a higher price than the price of WES in this study
Dragojlovic (2018)[23] Canada	Data from 167 families used in a model evaluating pediatric diagnostic exome sequencing	CA$;2016	Singleton; $2,576 Trio $6,437	Last resort singleton WES: $5,125 Last resort trio WES after consultation: $6,138 Last resort trio WES without consultation: $5,263	Singleton WES: $18,223 Trio WES after consultation: $14,405 Trio WES without consultation: $15,495	NR	NR
Ewans (2018)[21] Australia	14 adults and children monogenic etiology from a clinical genetics unit	US$; 2016	Singleton; $1,200 Trio; $3,150	Traditional path: $6,742 ($5,262 to $8,432) WES at initial presentation: $6,574 ($4,831 to $8,524) WES at clinical genetics review: $6,918 ($5,358 to $8,763) WES at initial presentation and reanalysis at 12 months: $6,709 ($4,937 to $8,688) WES at clinical genetics review and reanalysis at 12 months: $7,053 ($5,458 to $8,929)	Traditional path: $0 (no diagnoses made) WES at initial presentation: $23,010 ($10,135 to $102,147) WES at clinical genetics review: $24,215 ($11,195 to $103,173) WES at initial symptoms presentation and reanalysis at 12 months: $15,653 ($7,619 to $49,752) WES at clinical genetics review and reanalysis at 12 months: $16,457) $8,521 to $50,531)	Compared to traditional path: WES at initial symptoms presentation: $-586 (95% CI, $-3,769 to $16,144) WES at clinical genetics review: $618 (95% CI, $-2,431 to $17,439) WES at initial symptoms presentation and reanalysis at 12 months: $-77 (95%CI, $-2,990 to $7,334) WES at clinical genetics review and reanalysis at 12 months: $726 ($-1,873 to $8,060)	NR

(continued)

Table 13. Summary of cost-related outcomes from studies enrolling diverse phenotype populations (continued)

Author (Year); Country	Study Population and Setting	Currency; Year	Cost of WES	Cost Per Patient; Mean (95% CI)	Cost Per Diagnosis; Mean (95% CI)	Cost Per Additional Diagnosis; Mean (95% CI)	Other Cost Outcomes
Nolan (2016)[24] U.S.	50 children from a neurology clinic referred for diagnostic WES testing	US$; NR	Range $2,000 to $15,000	NR	NR	NR	Average cost of initial and secondary genetic and metabolic testing prior to WES: $4,853 If WES was performed after initial but prior to secondary testing, estimated average savings of $2,968
Soden (2014)[25] U.S.	119 children with neurodevelopmental disorders	NR; NR	NR	NR	NR	NR	At an average cost of prior testing of $19,100 per family, WES would be cost-effective at $2,996 per individual
Stark (2016, 2017, 2019)[13-16] Australia	80 children age 0 to 2 years suspected of having monogenic disorders	AU$;2015	Singleton; $1,500 to $3,100	Standard path: $ 4,734 ($3,693 to $ 5,895) WES after basic and complex investigations: $ 8,384 ($ 7,079 to $ 9,619) WES after basic investigations: $ 5,914 ($ 5,243 to $ 6,641) WES as first-tier test: $3,752 ($ 3,752 to $ 3,752) For those with noninformative initial testing: Reanalysis at 18 months: $ 391 ($ 360 to $ 433)	Standard path: $ 27,050 ($ 15,366 to $ 68,530) WES after basic and complex investigations: $13,415 ($ 10,165 to $ 18,351) WES after basic investigations: $ 9,462 ($ 7,497 to $ 12,619) WES as first-tier test: $ 6,003 ($4,841 to $ 7,899) For those with noninformative initial testing: Reanalysis at 18 months: $ 2,838 ($1,569 to $10,450)	Compared to standard path: WES after basic and complex investigations: $ 8,112 ($ 5,851 to $ 11,967) WES after basic investigations: $ 2,622 ($ 847 to $ 4,459) WES as first-tier test: $ -2,182 ($-5,855 to $ 130) In 97% of simulations, WES as first-tier test was dominant (less cost with more diagnoses compared to standard care).	Results from 2017 publication:[13] Compared to standard path after median 473 days: Cost per QALY gained AU$ -1,578 (95% CI, AU$ -205,450 to AU$19,780). [resulting changes in management for proband only]. Cost per QALY gained AU$ 8,119 (95% CI, AU$ 1,962 to AU$ 38,944) [Changes in proband management, cascade

(continued)

Table 13. Summary of cost-related outcomes from studies enrolling diverse phenotype populations (continued)

Author (Year); Country	Study Population and Setting	Currency; Year	Cost of WES	Cost Per Patient; Mean (95% CI)	Cost Per Diagnosis; Mean (95% CI)	Cost Per Additional Diagnosis; Mean (95% CI)	Other Cost Outcomes
Stark (2016, 2017, 2019)[13-16] Australia (continued)				Reanalysis every 6 months: $ 1,031 ($ 988 to $ 1,071) No reanalysis: $ 537 ($ 159 to $ 1,051)	Reanalysis every 6 months: $ 7,475 ($3,625 to $30,400) No reanalysis: NA (no diagnoses)	Compared to no reanalysis: Reanalysis at 18 months: $ -1,059 ($ -10,502 to $ 1,937) Reanalysis every 6 months:$3,578 ($ -232 to $17,003)	testing, and reproductive planning in first-degree relatives]. Results from 2019 publication projecting health outcomes over 20 years compared to standard care:[15] WES after basic investigations: cost per QALY gained $ 31,144 (probands only); $ 20,840 (probands plus cascade outcomes in 1st degree relatives); $ 14,235 (probands, cascade outcomes in 1st degree relatives, reproductive outcomes)
Stark (2018)[22] Australia	40 acutely ill children and infants with suspected monogenic disorder, compared to 40 children from other published articles.[13-16]	AU$; NR	NR	Usual care + conventional sequencing costs: $ 4,734 Standard WES: $ 6,777 Rapid WES: $ 7,029	Usual care + conventional sequencing: $27,050 ($15,366 to $68,530) Standard WES: $10,843 ($7,488 to $14,090) Rapid WES: $13,388 (95% CI, $9,269 to $17,507)	NR	NR

(continued)

Table 13. Summary of cost-related outcomes from studies enrolling diverse phenotype populations (continued)

Author (Year); Country	Study Population and Setting	Currency; Year	Cost of WES	Cost Per Patient; Mean (95% CI)	Cost Per Diagnosis; Mean (95% CI)	Cost Per Additional Diagnosis; Mean (95% CI)	Other Cost Outcomes
Tan (2017)[19] Australia	44 children age 2 to 18 years suspected of having a monogenic condition	US$; 2015	Singleton; <AU$2,300	Standard path: $7,515 ($5,743 to $9,486) Standard path with WES: $9,800 ($8,033 to $11,758) WES at first genetics appointment: $5,349 ($4,583 to $6,295) WES at first tertiary presentation: $3,927 ($3,520 to $4,413)	Standard path: NA (study design assumed no diagnoses made) Standard path with WES: $18,762 ($13,640 to $26,628) WES at first genetics appointment: $10,239 ($7,667 to $14,614) WES at first tertiary presentation: $7,534 ($5,832 to $10,494)	Compared to standard path: Standard path with WES: $4,804 ($3,904 to $6,523) WES at first genetics appointment: $-3,709 ($-7,491 to $ -694) WES at first tertiary presentation: $-6,412 ($-11,192 to $-2,887)	NR
Vissers (2017)[20] Netherlands	150 children through age 18 with nonacute neurological symptoms of suspected genetic origin	€; 2016	€3,240	Standard path: €10,685 (€9,544 to €11,909) WES pathway: €9,941* WES-first pathway: €8,356 (€7,591 to €9,247)	NR	NR	NR

Abbreviations: AU$ = Australian Dollar; CI = confidence interval; € = Eurodollar; NA = not applicable; NR = not reported; WES = whole exome sequencing

Only 1 study reported cost-effectiveness after a median follow-up of 473 days.[13-16] In a 2017 publication from this study, authors reported a cost per QALY gained of AU$ -1,578 (95% CI, AU$ -205,450 to AU$ 19,780) when only considering the changes in management that would have occurred because of diagnosis for the proband. When considering changes in management to the proband, cascade testing for first-degree relatives, and reproductive planning in relatives, the cost per QALY gained was AU$ 8,119 (95% CI, AU$ 1,062 to AU$ 38,944). In a follow-up publication to this same study, the authors modeled health outcomes over 20 years and reported cost per QALY gained of AU$ 31,144 for management changes to probands only and AU$ 14,235 when also considering cascade testing and reproductive outcomes in first-degree relatives.

The other 4 studies reported heterogenous outcomes. Cordoba et al. reported the cost of expendable diagnostic workup (i.e., workup that could be replaced by WES) was US$ 1,646.[18] Dillon et al. reported that in 26% of the WES-diagnosed children for whom an available commercial gene panel would have been diagnostic, the least costly panel had a higher price than the price of WES.[17] Nolan et al. reported that the average cost of initial and secondary testing prior to WES was US$ 4,853 and if WES was performed after initial but prior to secondary testing, an estimated savings of US$ 2,968 would have been observed.[24] Lastly, Soden et al. reported that for an average cost of prior testing of US$ 19,100 per family, WES would be cost-effective at a price of US$ 2,996 per individual.[25]

Findings Among Single-Phenotype Populations

Cost-related outcomes from the 8 studies enrolling single-phenotype populations are reported in ***Table 14***. For most of the phenotypes evaluated in this evidence base, only 1 study was available precluding definitive conclusions about cost for specific phenotypes. Because of differences in currency and year reported across studies, we focus our synthesis on qualitative differences among testing strategies. Overall, when compared to standard diagnostic pathways, testing pathways that used WES identified more diagnoses at a lower cost in some studies, identified more diagnoses but at a higher cost in other studies (range US$ 1,775 to US$ 8,559 higher depending on where WES was used in the testing pathway). And, testing with WES earlier in the diagnostic pathway appeared to be associated with more cost savings or lower costs per additional diagnosis compared to WES as a last resort strategy. The rest of this section provides detailed findings.

Five studies compared a standard diagnostic pathway to one or more pathways that included WES for Australian infants and children with epilepsy.[27,28] Dutch children with intellectual and developmental disability (IDD),[80] Australian children with muscular dystrophy or nemaline myopathy,[26] and Australian adults and children with peripheral neuropathy. In 3 of these studies, the cost per patient was less in the WES pathways compared to the standard pathways.[26,27,80] In the fourth study, the cost per patient was only less in the pathways that used WES early in the diagnostic pathway, but not later in the pathway.[28] In the fifth study, the cost per patient in the standard diagnostic pathway was lower than in the pathways that used WES as a last resort and slightly lower in the pathway that used WES early in the pathway.[78]

Table 14. Summary of cost-related outcomes from studies enrolling single-phenotype populations

Author (Year); Country	Study Population and Setting	Currency; Year	Cost of WES	Cost Per Patient; Mean (95% CI)	Cost Per Diagnosis; Mean (95% CI)	Cost Per Additional Diagnosis; Mean (95% CI)	Other Cost Outcomes
Howell (2018)[28] Australia	86 Infants with severe epilepsy	US$; 2016	Singleton, targeted analysis: $1,639	Path 1 (Tier 1, Tier 2, Repeat MRI, Tier 3): $7,687 Path 2 (Tier 1, Tier 2, Repeat MRI, Tier 3, WES): $8,538 Path 3 (Tier 1, Tier 2, Repeat MRI, WES, Tier 3): $8,027 Path 4 (Tier 1, Tier 2, WES, Repeat MRI, Tier 3): $8,069 Path 5 (Tier 1, WES, Tier 2, Repeat MRI, Tier 3): $7,873 Path 6 (Tier 1, WES, Repeat MRI, Tier 2): $6,453 Path 7 (Tier 1, WES, Repeat MRI): $5,298	Path 1: $16,951 Path 2: $15,378 Path 3: $14,382 Path 4: $14,457 Path 5: $14,106 Path 6: $11,530 Path 7: $9,904	Compared to Path 1: Path 2: $8,559 Path 3: $3,250 Path 4: $3,650 Path 5: $1,775 Path 6: Dominates (i.e., identified more diagnoses at lower cost) Path 7: Dominates	NR
Monroe (2016)[80] Netherlands	17 children with IDD from a tertiary specialty clinic	US$; 2014	Trio: $3,972	Median (range) Traditional path: $14,153 ($6,343 to $47,841) Median (range) cost savings from early WES: Diagnosed participants: $5,342 ($0 to $10,684) Undiagnosed participants: $4,854 ($890 to $18,696)	NR	NR	NR
Palmer (2018)[27] Australia	30 children with infantile-onset epileptic encephalopathy	AU$; NR	Trio: $4,036 to $12,362 (varied by commercial lab)	Standard path: $11,827 ($10,677 to $13,027) WES path: $9,536 ($9,412 to $9,683)	Mean (95% CI) Standard path: $182,243 ($72,703 to $406,142) WES path: $19,074 ($14,421 to $27,969)	Compared to standard path: WES path: $-5,236 ($-2,483 to $-9,784)	NR
Schofield (2017)[26] Australia	56 children with congenital muscular dystrophy or nemaline myopathy	AU$; 2016	Singleton: $1,718	Mean (95% CI) Traditional path: $10,491 ($9,115 to $11,848) Neuromuscular gene path: $3,808 ($3,293 to $4,373) WES path: $6,077 ($5,284 to $6,846)	Mean (95% CI) Traditional path: $22,596 ($17,004 to $31,498) Neuromuscular gene path: $5,077 ($4,228 to $6,100) WES path: $7,734 ($6,166 to $9,696)	Compared to the traditional pathway Neuromuscular gene pathway: $-23,390 ($-14,595 to $-41,184) WES path: $-13,732 ($-7,938 to $-473)	NR

(continued)

Table 14. Summary of cost-related outcomes from studies enrolling single-phenotype populations (continued)

Author (Year); Country	Study Population and Setting	Currency; Year	Cost of WES	Cost Per Patient; Mean (95% CI)	Cost Per Diagnosis; Mean (95% CI)	Cost Per Additional Diagnosis; Mean (95% CI)	Other Cost Outcomes
Tsiplova (2017)[79] Canada	Synthetic modeling population for children with autism	CA$; 2015	Singleton; $1,655	Per sample CMA: $744 ($714 to $773) CMA + WES: $1,655 ($1,611 to $1,699)	NR	Compared to CMA alone: CMA + WES: $25,458	NR
Vrijenhoek (2018)[77] Netherlands	370 children with intellectual disabilities	€; NR	Trio; €3,600	NR	NR	NR	Costs after WES as last test in diagnostic trajectory: 82% lower than before testing Costs after WES as first-tier test: 58% lower than before testing
Walsh (2017)[78] Australia	50 adults and children with peripheral neuropathy	AU$; NR	Singleton; $2,000	Standard investigations: $4,013 (SD $2,761) Standard investigations and WES as last resort: $6,344 Early WES: $4,914	Standard investigations and WES as last resort strategy: $16,027 Early WES: $12,413	Compared to standard investigations alone: WES as last resort strategy: $5,889 Early WES: $2,276	NR

Abbreviations: AU$ = Australian Dollar; CI = confidence interval; CMA = chromosomal microarray analysis; NR = not reported; WES = whole exome sequencing

In the 4 studies that reported cost per diagnosis, costs were all less in the WES pathways compared to the standard diagnostic pathways.[26-28] or in the early WES pathways compared to WES as a last resort.[78] In 2 studies reporting cost per additional diagnosis, authors reported a cost savings in the WES path compared to the standard diagnostic pathway.[26,27] In other words, the WES pathway identified more diagnoses than the standard pathway at a lower cost. In the third study reporting cost per additional diagnosis, the pathways evaluating WES early in the diagnostic pathway also demonstrated cost savings.[28] In that same study, the cost per additional diagnosis for pathways involving WES later in the diagnostic pathway ranged from US$ 1,775 to US$ 8,559 when compared to the standard pathway. In the fourth study, the cost per additional diagnosis ranged from US$ 2,276 (early WES) to US$ 5,889 (last resort WES).[78]

In the study conducted among children with muscular dystrophy or myopathy, a third diagnostic pathway involved a neuromuscular gene panel (464 genes) was also evaluated.[26] This pathway had a lower cost per patient and cost per diagnosis compared to both the standard diagnostic pathway and the WES pathway. In addition, compared to the standard pathway, the neuromuscular gene panel pathway demonstrated higher cost savings than the WES pathway.

The other 2 studies reported heterogenous outcomes. Tsiplova et al., a modeling study of Canadian children with autism, estimated that the cost per additional diagnosis for a strategy of CMA plus WES compared to CMA alone was CA$ 25,458.[79] Vrijenhoek et al., a study among Dutch children with IDD, estimated that health care costs after WES as a last resort strategy were 82% lower than before WES testing, and were 58% lower than before testing if used as a first-tier test.[77]

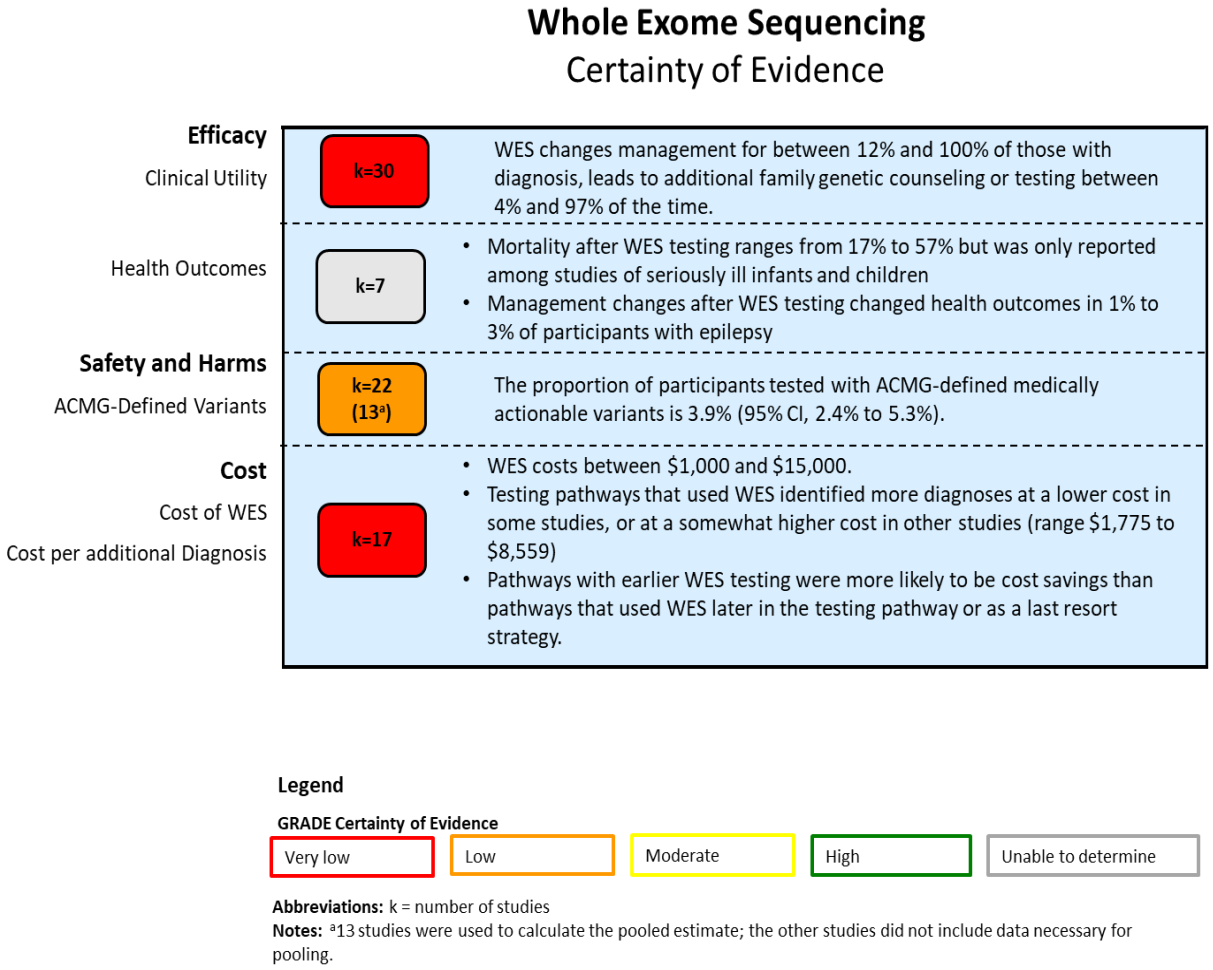
4. Discussion

4.1 Summary of the Evidence

Our assessment of the evidence from the contextual questions confirmed that WES has a higher diagnosis yield compared to standard testing pathways and phenotype-specific gene panels. Among all phenotypes, we calculated the pooled diagnostic yield for WES as 38%, which is higher than the pooled diagnostic yield for traditional testing pathways and gene panels. Reanalysis of WES data using updated variant call algorithms and newly discovered pathogenicity information increases diagnostic yield on average by about 17%. Because this was a contextual question, we did not assess the certainty of the evidence.

The findings from the key questions and certainty of evidence is summarized in ***Figure 4***.

Figure 4. Summary of evidence from whole exome sequencing HTA



A molecular diagnosis with WES changed medical management for 12% to 100% of diagnosed patients among diverse populations and for 0% to 31% of diagnosed patients with epilepsy. Medication was changed for 5% to 25% of patients who received a diagnosis from WES. Additional counseling or testing of family members occurred in between 4% and 97% of families who received a diagnosis with WES. The certainty of the evidence was *very low*.

Patients who received a diagnosis from WES had higher mortality than those who remained undiagnosed, and infants that received rapid WES had higher mortality than those who received standard WES. Differences in the time period of reported mortality rates precluded our calculation of pooled estimates. No study controlled for baseline differences and, in some studies of rapid WES, rapid WES was performed on the sickest infants. Among patients with epilepsy, management changes resulting from WES diagnosis improved behavior or seizure control in 1% and 3% of participants, respectively. Due to differences in study design and reported outcomes, we were unable to evaluate the certainty of the evidence regarding health outcomes.

We found little evidence of safety issues related to WES testing. We calculated the pooled percent of patients with an ACMG-defined medically actionable variant as 3.9%. We rated the certainty of evidence on the frequency of ACMG-defined medically actionable variants as *low*.

In the 1 reported case in which WES results led to discovery of unexpected family relationships, the participant experienced only mild shock. Very few patients or parents of patients who received negative or uncertain WES results experienced psychosocial harms from the test results. We did not rate the certainty of these findings because this evidence was primarily qualitative.

In both single-phenotype and diverse-phenotype populations, testing pathways that included WES identified more diagnoses and ranged from either costing less or costing somewhat more (the highest reported estimate was US$ 8,559 per additional diagnosis) compared to a standard diagnostic pathway. Pathways with earlier WES testing were more likely to have cost savings than pathways that used WES later in the testing pathway or as a last-resort strategy. WES test costs reported in studies ranged from $1,000 to $15,000; we found that costs reported for trio WES are higher than those for singleton WES. The certainty of the evidence on the cost and cost-effectiveness of WES was *very low*.

4.2 Limitations of the Evidence Base

The body of evidence on WES has substantial limitations. There are few prospective studies that have collected standardized data on clinical-utility or health outcomes. Most studies were retrospective and collected data solely from medical records. Few studies described protocols for data abstraction or approaches to ensure standardized, accurate, and replicable abstraction. Some studies explicitly excluded subjects for which they were unable to obtain outcomes data, which introduced selection bias. Other studies did not report on how they handled subjects with missing records or data.

Few studies included a comparison group; therefore, we could only estimate the frequency of outcomes within a single group. We were unable to compare the clinical utility or health impact of WES to that of other genetic testing methods. Most studies are small, single-center studies with heterogenous study populations. As such, it is difficult to compare study outcomes among the studies, and likely that the results would have been different with a different patient mix. The clinical trials focused only on diagnostic yield between rapid WES and standard WES. Studies that are not favorable to WES may not be published. We were unable to evaluate the extent of publication bias in the body of evidence because these studies are not typically registered in trial registries.

The complexity and rapid evolution of WES further complicates its evaluation. The technology continues to change rapidly, which hinders the ability to determine the applicability of studies from just a few years ago. It is also challenging to evaluate how sequencing platforms, bioinformatics approaches, or testing approaches may affect the findings of individual studies.

The nature of WES testing makes well-designed comparative effectiveness studies complicated. WES can diagnosis a wide range of conditions—many with very similar phenotypes but very different underlying genetic diagnoses with drastically different recommended management

strategies and outcomes. It is difficult to determine the most appropriate comparison group, and given the interpatient variability, very large sample sizes would be required to ensure precise measurement. Although randomized-controlled trials that use rigorous data collection and outcome measurement could be designed in order to produce results with a high degree of certainty under GRADE, they are likely not feasible to conduct in practice. Such trials would require large, multisite networks to be able to include enough patients with similar phenotypes and would need to follow up participants over years.

4.3 Clinical Practice Guidelines and Related Health Technology Assessments

We did not identify any clinical practice guideline specific to diagnostic testing with WES. We identified 4 HTAs cataloged in the University of York's Centre for Reviews and Dissemination of the National Institute for Health Research in the United Kingdom. Two of these assessments (i.e., Hayes, Inc. and Blue Cross/Blue Shield) require a subscription to access.[81,82] The other 2 HTAs were produced in the Netherlands and Argentina and are not available in English.[83,84]

We identified 1 narrative review from the "Model Coverage Policies" page on the American Academy of Neurology's (AAN's) website.[85] This document includes suggested indications and contraindications for exome sequencing, which are detailed in ***Table 15***.

Table 15. Indications and contraindications for clinical exome sequencing from the American Academy of Neurology's Model Coverage Policies[85]

Indications
• Undiagnosed neurologic disorder with nonspecific or clinically heterogenous phenotype • Expert evaluation with detailed clinical history, comprehensive neurologic examination, and complete family history • Complete evaluation for common causes that do not require genetic testing • Negative initial genetic testing (e.g., high-yield, single-gene, or multigene testing; chromosomal microarray) based on clinical evaluation, as appropriate
Contraindications
• Exome sequencing is not to be considered as a primary or first-line test for establishing a diagnosis in a patient when a genetic disorder is suspected unless the indications criteria are met. • Testing is not to be carried out without prior clinical evaluation and confirmation of need by appropriately trained professional health care providers with experience in the diagnostic evaluation of genetic disease. • Testing is not to be carried out without careful consideration, appropriate genetic counseling (including discussion of the possibility of secondary or incidental findings), and the availability of clinical expertise to interpret the findings, render advice, and provide appropriate care and management decisions based on the results of the testing.

We identified 6 documents produced by the ACMG. Two of these documents, published in 2013 and 2016, specify recommendations for reporting on incidental findings.[2,91] One document published in 2015 specifies standards and guidelines for the interpretation of sequence variants.[102] A policy statement published in 2012, "Points to Consider in the Clinical Application of Genomic Sequencing,"[86] describes indications for testing, which are listed in ***Table 16***.

Table 16. Indications for diagnostic testing from 2012 policy statement entitled "Points to Consider in the Clinical Application of Genomic Sequencing"[86]

WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when: e. The phenotype of family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis. f. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach. g. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis. h. A fetus with likely genetic disorder in which specific genetic tests, including targeted sequencing test, available for that phenotype have failed to arrive at a diagnosis. j. Prenatal diagnosis by genomic (i.e., next generation whole exome or whole genome) sequencing has significant limitations. The current technology does not support short-turn around times which are often expected in the prenatal setting. There are high false positive, false negative, and variants of unknown clinical significance rates.

Abbreviations: WES = whole exome sequencing; WGS = whole genome sequencing

The last ACMG document we identified provides guidance about the reevaluation and reanalysis of genomic test results.[103] This document describes considerations for variant-level reevaluation, case-level reanalysis, and retesting. It describes general considerations but does not provide a specific timeframe for considering reanalysis.

4.4 Selected Payer Coverage Policies

Specific payor coverage policies for WES are detailed in ***Table 17***. CMS does not have a national coverage determination for WES. Five commercial payers cover WES when beneficiaries have met specific clinical criteria.

Table 17. Payer coverage policies for whole exome sequencing

Payer; Effective Date	Policy
Aetna[104] May 16, 2019	Whole exome sequencing (WES) is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorder in children </= 21 years of age when all of the following criteria are met: A. A genetic etiology is considered the most likely explanation for the phenotype, based on either of the following: 1. Multiple congenital abnormalities affecting unrelated organ systems; *or* 2. *Two* of the following criteria are met: i. Abnormality affecting at minimum a single organ system (e.g., brain), ii. Significant developmental delay, intellectual disability (e.g., characterized by significant limitations in both intellectual functioning and in adaptive behavior), symptoms of a complex neurodevelopmental disorder (e.g., self-injurious behavior, reverse sleep-wake cycles, dystonia, hemiplegia, spasticity, epilepsy, muscular dystrophy), and/or severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome), iii. Family history strongly suggestive of a genetic etiology, including consanguinity, iv. Period of unexplained developmental regression, v. Biochemical findings suggestive of an inborn error of metabolism, *and* B. The member and family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, *and* C. Member receives pre- and post-test counseling by an appropriate independent provider (not an employee of the genetics testing laboratory), such as an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), *and* D. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), *and* E. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available, *and* F. WES is more efficient than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity), *and* G. A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy, *and* H. WES is predicted to have an impact on health outcomes, including: 1. Guiding prognosis and improving clinical decision-making, which can improve clinical outcome by: i. application of specific treatments as well as withholding of contraindicated treatments for certain rare genetic conditions, ii. surveillance for later-onset comorbidities, iii. initiation of palliative care, iv. withdrawal of care; *or* 2. Reducing diagnostic uncertainty (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved); *or* 3. For persons planning a pregnancy, informing genetic counseling related to recurrence risk and prenatal diagnosis options; *and* I. Family trio testing (whole exome sequencing of the biologic parents or sibling of the affected child) is considered medically necessary when criteria for whole exome sequencing of the child are met.

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Table 17. Payer coverage policies for whole exome sequencing for any indication (continued)

Payer; Effective Date	Policy
Cigna[105] December 15, 2018	Whole exome sequencing is considered medically necessary when disease specific criteria* listed below are met and when a recommendation for testing is confirmed by ONE of the following: ➢ An independent Board-Certified or Board-Eligible Medical Geneticist ➢ An American board of Medical Genetics or American Board of Genetic Counseling- certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself). ➢ A genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurse Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory. (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself). WHO: ➢ Has evaluated the individual ➢ Completed a three generation pedigree ➢ Intends to engage in post-test follow-up counseling *Disease Specific Criteria Whole exome sequencing (CPT code 81415) is considered medically necessary for a phenotypically-affected individual when ALL of the following criteria are met: ➢ Individual has been evaluated by a board-certified medical geneticist or other board certified specialist physician specialist with specific expertise in the conditions and relevant genes for which testing is being considered ➢ WES results will directly impact clinical decision-making and clinical outcome for the individual being tested ➢ A genetic etiology is the most likely explanation for the phenotype as demonstrated by ANY of the following: o Multiple abnormalities affecting unrelated organ systems o Known or suspected early infantile epileptic encephalopathy (onset before three years of age) o TWO of the following criteria are met ▪ Abnormality affecting a single organ system ▪ Significant intellectual disability, symptoms of a complex neurodevelopmental disorder (e.g. self-injurious behavior, reverse sleep-wake cycles), or severe neuropsychiatric condition (e.g. schizophrenia, bipolar disorder, Tourette syndrome) ▪ Family history strongly implicating a genetic etiology ▪ Period of unexplained developmental regression (unrelated to autism or epilepsy) ➢ No other causative circumstances (e.g. environmental exposures, injury, infection) can explain symptoms ➢ Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing (e.g., comparative genomic hybridization (CGH)/chromosomal microarray analysis [CMA], is available

(continued)

Table 17. Payer coverage policies for whole exome sequencing for any indication (continued)

Payer; Effective Date	Policy
Cigna December 15, 2018 (continued)	➢ The differential diagnosis list and/or phenotype warrant testing of multiple genes and ONE of the following: o WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis o WES results may preclude the need for multiple and/or invasive procedures, follow=up, or screening that would be recommended in the absence of testing Comparator exome sequence analysis (CPT code 81416) is considered medically necessary when the above criteria for WES (CPT code 81415) have been met and WES is being performed concurrently or has been previously performed. Experimental/Investigational/Unproven Prenatal diagnosis or preimplantation testing of an embryo using WES is considered experimental, investigational, and unproven. WES in the general population is considered not medically necessary.
Humana[106] July1, 2019	Any state mandates for WGS, exome sequencing or GWAS take precedence over this clinical policy. Genetic testing may be excluded by contract. Please consult the member's individual contract, regarding Plan coverage. Humana members many NOT be eligible under the Plan for the following: • Exome sequencing including the following: o Custom exome panels (e.g., XomeDXSlice, XomeDx Slice Xpanded) for single gene or multigene panels; OR o EXaCT-1 Whole Exome Testing; OR o Trio whole exome sequencing; OR • Genome wide association studies (GWAS); OR • Mate-pair sequencing (i.e., MatePair, Targeted Rearrangements, Oncology; MatePair, Targeted Rearrangements; Hematologic); OR • Testing an at-risk (unaffected) individual or affected individual when a family member has been tested for mutations and received a result of VUS (also known as unclassified variant or variant of uncertain significance); OR • Whole genome sequencing (WGS) including RCIGM Rapid WGS These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

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Table 17. Payer coverage policies for whole exome sequencing for any indication (continued)

Payer; Effective Date	Policy
Humana July 1, 2019 (continued)	Medical Alternatives to WGS, exome sequencing or GWAS include, but may not be limited to, the following: • Chromosomal microarray analysis • Fluorescent situ hybridization (FISH) • Standard cytogenetic testing (e.g., karyotype) • Targeted mutation analysis consistent with personal and family histories Physician consultation is advised to make an informed decision based on an individual's health needs.
Kaiser Permanente (Washington)[107] NR	Whole exome sequencing (WES) is considered medically necessary for a phenotypically-affected individual when ALL of the following criteria are met: 1. Individual has been evaluated by a board-certified medical geneticist (MD) or other board-certified physician specialist with specific expertise in the conditions and relevant genes for which testing is being considered 2. Results have the potential to directly impact clinical decision-making and clinical outcomes for the patient 3. A genetic etiology is the most likely explanation for the phenotype as demonstrated by EITHER of the following: A. multiple abnormalities affecting unrelated organ systems OR B. TWO of the following criteria are met: a. abnormality affecting a single organ system b. significant intellectual disability, symptoms of a complex neurodevelopmental disorder (e.g. self-injurious behavior, reverse sleep-wake cycles) or severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome) c. family history strongly implicating a genetic etiology d. period of unexplained developmental regression (unrelated to autism or epilepsy) e. dysmorphic facial features f. abnormal growth not otherwise explained 4. No other causative circumstances (e.g. environmental exposures, injury, infections) can explain symptoms 5. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available 6. The differential diagnosis list and/or phenotype warrant testing of multiple genes and ONE of the following: A. WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis B. WES results may precede the need for multiple and/or invasive procedures, follow-up , or screening that would be recommended in the absence of testing All requests must be approved by a KP geneticist, regardless of whether they have seen the patient.

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Table 17. Payer coverage policies for whole exome sequencing for any indication (continued)

Payer; Effective Date	Policy
Premera (Blue Cross)[108] January 4, 2019	This payor defers to the clinical appropriateness guidelines entitled "Whole Exome and Whole Genome Sequencing" published by AIM Specialty Health (version dated March 31, 2019). Whole exome sequencing (WES) is medically necessary for a phenotypically affected individual when all of the following criteria are met: • Individual has been evaluated by a board-certified medical geneticist or other board-certified specialist physician with specific expertise in the conditions being tested for and relevant genes • WES results will directly impact clinical decision-making and/or clinical outcome • A genetic etiology is the most likely explanation for the phenotype as demonstrated by one of the following: ➢ Multiple abnormalities affecting unrelated organ systems ➢ Known or suspected infantile or early-onset epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy (e.g. environmental exposures; brain injury secondary to complications of extreme prematurity, infection trauma) have been excluded Or two of the following four criteria: • Abnormality affecting a single organ system • Significant intellectual disability or severe psychological/ psychiatric disturbance (e.g. self-injurious behavior, reversed sleep-wake cycles) • Family history strongly implicating a genetic etiology • Period of unexplained developmental regression (unrelated to autism or epilepsy) • No other causative circumstances (e.g. environmental exposures, injury, infection) can explain symptoms • Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available • The differential diagnosis list and/or phenotype warrant testing of multiple genes, and at least one of the following: ➢ WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis ➢ WES results may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing Prenatal diagnosis or preimplantation testing of an embryo using WES is not medically necessary. WES for the purpose of genetic carrier screening is not medically necessary Whole Exome Reanalysis • Reanalysis of previously obtained uninformative whole exome sequencing is medically necessary when one of the following criteria is met: ➢ There has been onset of additional symptoms that broadens the phenotype assessed during the original exome evaluation ➢ There has been the birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture.
Regence (Blue Shield)[109] July 1, 2019	WES and whole genome sequencing is considered investigational for all indications, including but not limited to, diagnosis in patients with suspected genetic disorders, preimplantation or prenatal (fetal) testing, and general screening.

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Table 17. Payer coverage policies for whole exome sequencing for any indication (continued)

Payer; Effective Date	Policy
United HealthCare Commercial[110] July 1, 2019	Genetic counseling is strongly recommended prior to these tests in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person. WES is proven and medically necessary for diagnosing or evaluating a genetic disorder when the results are expected to directly influence medical management and clinical outcomes and ALL of the following are met: • Clinical presentation is nonspecific and does not fit a well-defined syndrome for which a specific or targeted gene test is available. If a specific genetic syndrome is suspected, a single gene or targeted gene panel should be performed prior to determining if WES is necessary; and WES is ordered by a board-certified medical geneticist, neonatologist, neurologist, or developmental and behavioral pediatrician; and one of the following: • The clinical presentation or clinical and family history strongly suggest a genetic cause for which a specific clinical diagnosis cannot be made with any clinically available targeted genetic tests; or • There is a clinical diagnosis of a genetic condition where there is significant genetic heterogeneity and WES is a more practical approach to identifying the underlying genetic cause than are individual tests of multiple genes; or • There is likely a genetic disorder and multiple targeted gene tests that have failed to identify the underlying cause Comparator (e.g., parents or siblings) WES is proven and medically necessary for evaluating a genetic disorder when the above criteria have been met and WES is performed concurrently or has been previously performed on the individual. WES is unproven and not medically necessary for all other indications, including but not limited to the following: • Screening and evaluating disorders in individuals when the above criteria are not met • Prenatal genetic diagnosis or screening • Evaluation of fetal demise • Preimplantation Genetic Testing (PGT) in embryos • Molecular profiling of tumors for the diagnosis, prognosis or management of cancer Further studies are needed to evaluate the clinical utility of whole exome sequencing for other indications.

Abbreviations: PGT = preimplantation genetic testing; WES = whole exome sequencing

4.5 Limitations of This HTA

This HTA was limited to peer-reviewed studies published in English. Our search was limited to 3 bibliographic databases; however, we conducted extensive hand searches to identify potentially relevant articles. Because of practical constraints, our key questions focused on clinical utility outcomes, health outcomes, safety outcomes, and cost outcomes. We did not systematically review studies of diagnostic yield. However, we provided information about diagnostic yield based on 4 systematic reviews and 99 primary research studies that we identified as having relevant diagnostic yield information during full-text screening.

4.6 Ongoing Research

We identified 15 recently completed or ongoing studies that may be relevant to this topic (***Table 18***). Most are single arm observational cohorts. The only ongoing RCT that we identified is sponsored by the University of North Carolina at Chapel Hill in collaboration with the National Human Genome Research Institute and 2 other North Carolina-based health care systems.[87] In this RCT, children and adults with diverse phenotypes are randomized to 1 of 4 study arms 1) previsit preparation with usual care and exome sequencing, 2) previsit preparation with usual care, 3) no previsit prep with exome sequencing, and 4) no previsit prep and usual care. This study plans to enroll 1,700 participants with an estimated study completion date of May 2021. The trial registry record lists 22 primary care outcome measures including various measures of health care utilization, patient and caregiver quality of life.

Table 18. Summary of ongoing whole exome sequencing studies

Registration Number	Sponsor	Study Designed	Title	Number of Participants	Status	Estimated Completion Date
NCT02862808[111]	Centre Hospitalier Universitaire de Besancon	Retrospective observational cohort	Molecular Diagnosis of Syndromic or Isolated Severe Intellectual Disability Using Whole Exome Sequencing: a Pilot Study.	17	Recruiting	9/2019
NCT03721458[112]	Milton S. Hershey Medical Center	Retrospective observational cohort	Whole Genome Sequencing in the Neonatal Intensive Care Unit	150	Recruiting	6/2021
NCT03890679[113]	Tufts Medical Center	Single arm trial	Genomic Medicine for Ill Neonates and Infants (The GEMINI Study) (GEMINI)	400	Recruiting	8/2023
NCT02380729[114]	Charite University, Berlin, Germany	Prospective observational cohort	Mutation Exploration in Non-acquired, Genetic Disorders and Its Impact on Health Economy and Life Quality (MENDEL)	200	Completed	12/2017
NCT03287193[115]	Centre Hospitalier Universitaire Dijon	Prospective observational cohort	Identification of the Molecular and/or Pathophysiological Bases of Developmental Diseases (DISCOVERY)	500	Recruiting	12/2022
NCT03287206[116]	Centre Hospitalier Universitaire Dijon	Prospective observational cohort	Medico-economic Evaluation of Different High-throughput Sequencing Strategies in the Diagnosis of Patients With Intellectual Deficiency (DISSEQ)	330	Recruiting	12/2020

(continued)

Table 18. Summary of ongoing whole exome sequencing studies (continued)

Registration Number	Sponsor	Study Designed	Title	Number of Participants	Status	Estimated Completion Date
NCT03288727[117]	Centre Hospitalier Universitaire Dijon	Non-randomized clinical trial	Secondary Findings From High-throughput Sequencing: How to Announce Them With Respect to the Patient's Needs (FIND)	250	Recruiting	2/2021
NCT02769975[118]	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	Observational cohort	Evaluation of Children With Endocrine and Metabolic-Related Conditions	15,000	Recruiting	12/2030
NCT03175692[119]	National Taiwan University Hospital	Cross-sectional observational cohort	Rapid Genetic Diagnosis Employing Next Generation Sequencing for Critical Illness in Infants and Children	150	Recruiting	5/2020
NCT02077894[120]	National Eye Institute (NEI)	Prospective observational cohort	Whole Exome and Whole Genome Sequencing for Genotyping of Inherited and Congenital Eye Conditions	810	Recruiting	9/2019
NCT03605004[121]	National Human Genome Research Institute (NHGRI)	Retrospective observational cohort	Adult Patients With Undiagnosed Conditions and Their Responses to Clinically Uncertain Results From Exome Sequencing	250	Recruiting	2/2025
NCT02699190[122]	Children's Hospital of Philadelphia	Observational cohort	LeukoSEQ: Whole Genome Sequencing as a First-Line Diagnostic Tool for Leukodystrophies	450	Recruiting	8/2019
NCT02995538[123]	University of Pittsburgh	Patient registry	Neurogenetics Patient Registry	1,000	Recruiting	1/2028
NCT03525431[124]	University of California, San Francisco	Single arm trial	Clinical Utility of Pediatric Whole Exome Sequencing	800	Recruiting	3/2021
NCT03548779[87]	University of North Carolina, Chapel Hill	Randomized controlled trial	North Carolina Genomic Evaluation by Next-generation Exome Sequencing, 2 (NCGENES2)	1,700	Recruiting	5/2021

5. Conclusion

WES increases diagnostic yield over standard diagnostic testing. A diagnosis from WES changes clinical management for some patients, but our certainty in the estimate of this frequency is very low. The evidence regarding the impact of WES testing on health and most safety outcomes is limited, though we have low certainty that the proportion of patients tested who receive a medically actionable secondary finding is about 4%. WES may be cost-effective in terms of diagnostic success, but our certainty is very low. Testing pathways that included WES identified more diagnoses and either cost less or cost somewhat more than a standard diagnostic pathway. Pathways with earlier WES testing were more likely to have cost savings than pathways that used WES later in the testing pathway or as a last-resort strategy.

6. References

1. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Clinical Practice Guidelines in Oncology* https://www2.tri-kobe.org/nccn/guideline/gynecological/english/genetic_familial.pdf. Published 2018. Accessed August 18, 2019.
2. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med.* 2013;15(7):565-574. PMID: 23788249. doi: 10.1038/gim.2013.73
3. Wei X, Ju X, Yi X, et al. Identification of sequence variants in genetic disease-causing genes using targeted next-generation sequencing. *PLoS One.* 2011;6(12):e29500-e29500. PMID: 22216297. doi: 10.1371/journal.pone.0029500
4. Jackson M, Marks L, May GHW. The genetic basis of disease. 2018;62(5):643-723. PMID: 30509934. doi: 10.1042/ebc20170053
5. Gonzaludo N, Belmont JW, Gainullin VG, Taft RJ. Estimating the burden and economic impact of pediatric genetic disease. *Genet Med.* 2019;21(8):1781-1789. PMID: 30568310. doi: 10.1038/s41436-018-0398-5
6. Adams DR, Eng CM. Next-Generation Sequencing to Diagnose Suspected Genetic Disorders. *N Engl J Med.* 2019;380(2):201. PMID: 30625069. doi: 10.1056/NEJMc1814955
7. Chiou CF, Hay JW, Wallace JF, et al. Development and validation of a grading system for the quality of cost-effectiveness studies. *Med Care.* 2003;41(1):32-44. PMID: 12544542. doi: 10.1097/01.Mlr.0000039824.73620.E5
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926. PMID: 18436948. doi: 10.1136/bmj.39489.470347.AD
9. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med.* 2018;20(10):1122-1130. PMID: 29446766. doi: 10.1038/gim.2017.247
10. Sanchez Fernandez I, Loddenkemper T, Gainza-Lein M, Sheidley BR, Poduri A. Diagnostic yield of genetic tests in epilepsy: a meta-analysis and cost-effectiveness study. *Neurology*. 2019. PMID: 30610098. doi: 10.1212/wnl.0000000000006850
11. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med.* 2018;3:16. PMID: 30002876. doi: 10.1038/s41525-018-0053-8
12. Alam K, Schofield D. Economic evaluation of genomic sequencing in the paediatric population: a critical review. *Eur J Hum Genet.* 2018;26(9):1241-1247. doi: 10.1038/s41431-018-0175-6
13. Stark Z, Schofield D, Martyn M, et al. Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. *Genet Med.* 2019;21(1):173-180. PMID: 29765138. doi: 10.1038/s41436-018-0006-8
14. Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet Med.* 2016;18(11):1090-1096. PMID: 26938784. doi: 10.1038/gim.2016.1

15. Schofield D, Rynehart L. Long-term economic impacts of exome sequencing for suspected monogenic disorders: diagnosis, management, and reproductive outcomes. 2019. PMID: 31110331. doi: 10.1038/s41436-019-0534-x
16. Stark Z, Schofield D, Alam K, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. *Genet Med.* 2017;19(8):867-874. PMID: 28125081. doi: 10.1038/gim.2016.221
17. Dillon OJ, Lunke S, Stark Z, et al. Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. *Eur J Hum Genet.* 2018;26(5):644-651. PMID: 29453417. doi: 10.1038/s41431-018-0099-1
18. Cordoba M, Rodriguez-Quiroga SA, Vega PA, et al. Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. *PLoS One.* 2018;13(2):e0191228. PMID: 29389947. doi: 10.1371/journal.pone.0191228
19. Tan TY, Dillon OJ, Stark Z, et al. Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. *JAMA Pediatr.* 2017;171(9):855-862. PMID: 28759686. doi: 10.1001/jamapediatrics.2017.1755
20. Vissers L, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med.* 2017;19(9):1055-1063. PMID: 28333917. doi: 10.1038/gim.2017.1
21. Ewans LJ, Schofield D, Shrestha R, et al. Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. *Genet Med.* 2018;20(12):1564-1574. PMID: 29595814. doi: 10.1038/gim.2018.39
22. Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. *Genet Med.* 2018;20(12):1554-1563. PMID: 29543227. doi: 10.1038/gim.2018.37
23. Dragojlovic N, Elliott AM, Adam S, et al. The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: a benchmarking study. *Genet Med.* 2018;20(9):1013-1021. PMID: 29300375. doi: 10.1038/gim.2017.226
24. Nolan D, Carlson M. Whole Exome Sequencing in Pediatric Neurology Patients: Clinical Implications and Estimated Cost Analysis. *J Child Neurol.* 2016;31(7):887-894. PMID: 26863999. doi: 10.1177/0883073815627880
25. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med.* 2014;6(265):265ra168. PMID: 25473036. doi: 10.1126/scitranslmed.3010076
26. Schofield D, Alam K, Douglas L, et al. Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases. *NPJ Genom Med.* 2017;2. PMID: 29152331. doi: 10.1038/s41525-017-0006-7
27. Palmer EE, Schofield D, Shrestha R, et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness. *Mol Genet Genomic Med.* 2018;6(2):186-199. PMID: 29314763. doi: 10.1002/mgg3.355
28. Howell KB, Eggers S, Dalziel K, et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. *Epilepsia.* 2018;59(6):1177-1187. PMID: 29750358. doi: 10.1111/epi.14087

29. Seidelmann SB, Smith E, Subrahmanyan L, et al. Application of whole exome sequencing in the clinical diagnosis and management of inherited cardiovascular diseases in adults. *Circ Cardiovasc Genet.* 2017;10(1). PMID: 28087566. doi: 10.1161/circgenetics.116.001573
30. Angione K, Eschbach K, Smith G, Joshi C, Demarest S. Genetic testing in a cohort of patients with potential epilepsy with myoclonic-atonic seizures. *Epilepsy Res.* 2019;150:70-77. PMID: 30660939. doi: 10.1016/j.eplepsyres.2019.01.008
31. Charbit-Henrion F, Parlato M, Hanein S, et al. Diagnostic yield of next-generation sequencing in very early-onset inflammatory bowel diseases: a multicenter study. *J Crohns Colitis.* 2018. PMID: 29788237. doi: 10.1093/ecco-jcc/jjy068
32. Snoeijen-Schouwenaars FM, van Ool JS, Verhoeven JS, et al. Diagnostic exome sequencing in 100 consecutive patients with both epilepsy and intellectual disability. *Epilepsia.* 2019;60(1):155-164. PMID: 30525188. doi: 10.1111/epi.14618
33. Need AC, Shashi V, Schoch K, Petrovski S, Goldstein DB. The importance of dynamic re-analysis in diagnostic whole exome sequencing. *J Med Genet.* 2017;54(3):155-156. PMID: 27899421. doi: 10.1136/jmedgenet-2016-104306
34. Perucca P, Scheffer IE, Harvey AS, et al. Real-world utility of whole exome sequencing with targeted gene analysis for focal epilepsy. *Epilepsy Res.* 2017;131:1-8. PMID: 28199897. doi: 10.1016/j.eplepsyres.2017.02.001
35. Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. *Genet Med.* 2017;19(2):209-214. PMID: 27441994. doi: 10.1038/gim.2016.88
36. Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med.* 2018;20(11):1328-1333. PMID: 29565419. doi: 10.1038/gim.2018.41
37. Nambot S, Thevenon J, Kuentz P, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: substantial interest of prospective annual reanalysis. *Genet Med.* 2018;20(6):645-654. PMID: 29095811. doi: 10.1038/gim.2017.162
38. Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. *Genet Med.* 2018;20(10):1216-1223. PMID: 29323667. doi: 10.1038/gim.2017.246
39. Niguidula N, Alamillo C, Shahmirzadi Mowlavi L, Powis Z, Cohen JS, Farwell Hagman KD. Clinical whole-exome sequencing results impact medical management. *Mol Genet Genomic Med.* 2018;6(6):1068-1078. PMID: 30318729. doi: 10.1002/mgg3.484
40. Meng L, Pammi M, Saronwala A, et al. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. *JAMA Pediatr.* 2017;171(12):e173438. PMID: 28973083. doi: 10.1001/jamapediatrics.2017.3438
41. Daga A, Majmundar AJ, Braun DA, et al. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. *Kidney Int.* 2018;93(1):204-213. PMID: 28893421. doi: 10.1016/j.kint.2017.06.025
42. Bourchany A, Thauvin-Robinet C, Lehalle D, et al. Reducing diagnostic turnaround times of exome sequencing for families requiring timely diagnoses. *Eur J Med Genet.* 2017;60(11):595-604. PMID: 28807864. doi: 10.1016/j.ejmg.2017.08.011

43. Baldridge D, Heeley J, Vineyard M, et al. The Exome Clinic and the role of medical genetics expertise in the interpretation of exome sequencing results. *Genet Med.* 2017;19(9):1040-1048. PMID: 28252636. doi: 10.1038/gim.2016.224
44. Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome Sequencing and the Management of Neurometabolic Disorders. *N Engl J Med.* 2016;374(23):2246-2255. PMID: 27276562. doi: 10.1056/NEJMoa1515792
45. Zhu X, Petrovski S, Xie P, et al. Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. *Genet Med.* 2015;17(10):774-781. PMID: 25590979. doi: 10.1038/gim.2014.191
46. Iglesias A, Anyane-Yeboa K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* 2014;16(12):922-931. PMID: 24901346. doi: 10.1038/gim.2014.58
47. Waldrop MA, Pastore M, Schrader R, et al. Diagnostic Utility of Whole Exome Sequencing in the Neuromuscular Clinic. *Neuropediatrics.* 2019. PMID: 30665247. doi: 10.1055/s-0039-1677734
48. Mann N, Braun DA, Amann K, et al. Whole-Exome Sequencing Enables a Precision Medicine Approach for Kidney Transplant Recipients. *J Am Soc Nephrol.* 2019;30(2):201-215. PMID: 30655312. doi: 10.1681/asn.2018060575
49. Matias M, Wusik K, Neilson D, Zhang X, Valencia CA, Collins K. Comparison of medical management and genetic counseling options pre- and post-whole exome sequencing for patients with positive and negative results. *J Genet Couns.* 2019. PMID: 30648779. doi: 10.1002/jgc4.1054
50. Jones LK, Kulchak Rahm A, Manickam K, et al. Healthcare Utilization and Patients' Perspectives After Receiving a Positive Genetic Test for Familial Hypercholesterolemia. *Circ Genom Precis Med.* 2018;11(8):e002146. PMID: 30354341. doi: 10.1161/circgen.118.002146
51. Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. *Genet Med.* 2018;20(6):630-638. PMID: 29758562. doi: 10.1038/gim.2017.159
52. Evers C, Staufner C, Granzow M, et al. Impact of clinical exomes in neurodevelopmental and neurometabolic disorders. *Mol Genet Metab.* 2017;121(4):297-307. PMID: 28688840. doi: 10.1016/j.ymgme.2017.06.014
53. Shamriz O, Shaag A, Yaacov B, et al. The use of whole exome sequencing for the diagnosis of autosomal recessive malignant infantile osteopetrosis. *Clin Genet.* 2017;92(1):80-85. PMID: 27187610. doi: 10.1111/cge.12804
54. Valencia CA, Husami A, Holle J, et al. Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. *Front Pediatr.* 2015;3:67. PMID: 26284228. doi: 10.3389/fped.2015.00067
55. Sawyer SL, Hartley T, Dyment DA, et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. *Clin Genet.* 2016;89(3):275-284. PMID: 26283276. doi: 10.1111/cge.12654
56. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med.* 2015;3(5):377-387. PMID: 25937001. doi: 10.1016/s2213-2600(15)00139-3

57. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol.* 2014;76(4):473-483. PMID: 25131622. doi: 10.1002/ana.24251
58. Ream MA, Mikati MA. Clinical utility of genetic testing in pediatric drug-resistant epilepsy: a pilot study. *Epilepsy Behav.* 2014;37:241-248. PMID: 25108116. doi: 10.1016/j.yebeh.2014.06.018
59. Skinner D, Roche MI, Weck KE, et al. "Possibly positive or certainly uncertain?": participants' responses to uncertain diagnostic results from exome sequencing. *Genet Med.* 2018;20(3):313-319. PMID: 29593351. doi: 10.1038/gim.2017.135
60. Strauss KA, Gonzaga-Jauregui C, Brigatti KW, et al. Genomic diagnostics within a medically underserved population: efficacy and implications. *Genet Med.* 2018;20(1):31-41. PMID: 28726809. doi: 10.1038/gim.2017.76
61. Monies D, Abouelhoda M, AlSayed M, et al. The landscape of genetic diseases in Saudi Arabia based on the first 1000 diagnostic panels and exomes. *Hum Genet.* 2017;136(8):921-939. PMID: 28600779. doi: 10.1007/s00439-017-1821-8
62. Rosell AM, Pena LD, Schoch K, et al. Not the End of the Odyssey: Parental Perceptions of Whole Exome Sequencing (WES) in Pediatric Undiagnosed Disorders. *J Genet Couns.* 2016;25(5):1019-1031. PMID: 26868367. doi: 10.1007/s10897-016-9933-1
63. Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. *Genet Med.* 2016;18(7):678-685. PMID: 26633545. doi: 10.1038/gim.2015.142
64. Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med.* 2016;18(7):696-704. PMID: 26633542. doi: 10.1038/gim.2015.148
65. Jurgens J, Ling H, Hetrick K, et al. Assessment of incidental findings in 232 whole-exome sequences from the Baylor-Hopkins Center for Mendelian Genomics. *Genet Med.* 2015;17(10):782-788. PMID: 25569433. doi: 10.1038/gim.2014.196
66. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA.* 2014;312(18):1870-1879. PMID: 25326635. doi: 10.1001/jama.2014.14601
67. Li X, Nusbaum R, Smith-Hicks C, Jamal L, Dixon S, Mahida S. Caregivers' perception of and experience with variants of uncertain significance from whole exome sequencing for children with undiagnosed conditions. *J Genet Couns.* 2019. PMID: 30680845. doi: 10.1002/jgc4.1093
68. Werner-Lin A, Zaspel L, Carlson M, et al. Gratitude, protective buffering, and cognitive dissonance: How families respond to pediatric whole exome sequencing in the absence of actionable results. *Am J Med Genet A.* 2018;176(3):578-588. PMID: 29446570. doi: 10.1002/ajmg.a.38613
69. McConkie-Rosell A, Hooper SR, Pena LDM, et al. Psychosocial Profiles of Parents of Children with Undiagnosed Diseases: Managing Well or Just Managing? *J Genet Couns.* 2018;27(4):935-946. PMID: 29297108. doi: 10.1007/s10897-017-0193-5
70. Muramatsu H, Okuno Y, Yoshida K, et al. Clinical utility of next-generation sequencing for inherited bone marrow failure syndromes. *Genet Med.* 2017;19(7):796-802. PMID: 28102861. doi: 10.1038/gim.2016.197

71. Vanderver A, Simons C, Helman G, et al. Whole exome sequencing in patients with white matter abnormalities. *Ann Neurol.* 2016;79(6):1031-1037. PMID: 27159321. doi: 10.1002/ana.24650
72. Tammimies K, Marshall CR, Walker S, et al. Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder. *JAMA.* 2015;314(9):895-903. PMID: 26325558. doi: 10.1001/jama.2015.10078
73. Lee K, Berg JS, Milko L, et al. High Diagnostic Yield of Whole Exome Sequencing in Participants With Retinal Dystrophies in a Clinical Ophthalmology Setting. *Am J Ophthalmol.* 2015;160(2):354-363.e359. PMID: 25910913. doi: 10.1016/j.ajo.2015.04.026
74. Shashi V, McConkie-Rosell A, Schoch K, et al. Practical considerations in the clinical application of whole-exome sequencing. *Clin Genet.* 2016;89(2):173-181. PMID: 25678066. doi: 10.1111/cge.12569
75. Ding LE, Burnett L, Chesher D. The impact of reporting incidental findings from exome and whole-genome sequencing: predicted frequencies based on modeling. *Genet Med.* 2015;17(3):197-204. PMID: 25077650. doi: 10.1038/gim.2014.94
76. Roche MI, Griesemer I, Khan CM, et al. Factors influencing NCGENES research participants' requests for non–medically actionable secondary findings. *Genet Med.* 2018. PMID: CN-01645540. doi: 10.1038/s41436-018-0294-z
77. Vrijenhoek T, Middelburg EM, Monroe GR, et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. *Eur J Hum Genet.* 2018;26(11):1566-1571. PMID: 29959382. doi: 10.1038/s41431-018-0203-6
78. Walsh M, Bell KM, Chong B, et al. Diagnostic and cost utility of whole exome sequencing in peripheral neuropathy. *Ann Clin Transl Neurol.* 2017;4(5):318-325. PMID: 28491899. doi: 10.1002/acn3.409
79. Tsiplova K, Zur RM, Marshall CR, et al. A microcosting and cost-consequence analysis of clinical genomic testing strategies in autism spectrum disorder. *Genet Med.* 2017;19(11):1268-1275. PMID: 28471434. doi: 10.1038/gim.2017.47
80. Monroe GR, Frederix GW, Savelberg SM, et al. Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. *Genet Med.* 2016;18(9):949-956. PMID: 26845106. doi: 10.1038/gim.2015.200
81. Whole exome sequencing for noncancer indications. *Genetic Testing Publication.* https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32013000831&UserID=0. Published 2013. Accessed August 18, 2019.
82. BlueCross BlueShield Association. Special Report: exome sequencing for clinical diagnosis of patients with suspected genetic disorders. *TEC Assessment 28(3).* https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32013000682&UserID=0. Published 2013. Accessed August 18, 2019.
83. Health Council of the Netherlands. Next generation sequencing in diagnosis. https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32015000612&UserID=0. Published 2015/01, 2015. Accessed August 18, 2019.
84. Larrea Bonavento N BA, Pichon-Riviere A, Augustovski F, García Martí S, Alcaraz A, Ciapponi A. [Whole exome sequencing in patients with undiagnosed neurological diseases]. *Documentos de Evaluación de Tecnologías Sanitarias, Informe de Respuesta*

Rapida No 529. https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32017000294&UserID=0. Published 2017. Accessed August 18, 2019.
85. Fogel BL, Satya-Murti S, Cohen BH. Clinical exome sequencing in neurologic disease. *Neurol Clin Pract.* 2016;6(2):164-176. PMID: 27104068. doi: 10.1212/cpj.0000000000000239
86. American College of Medical Genetics and Genomics (ACMG). Policy Statement. Points to Consider in the Clinical Applications of Genomic Sequencing. https://www.acmg.net/PDFLibrary/Genomic-Sequencing-Clinical-Application.pdf. Published 2012. Accessed August 18, 2019.
87. University of North Carolina at Chapel Hill. North Carolina genomic evaluation by next-generation exome sequencing, 2. Published 2018. Updated September 28.
88. Solomon BD, Muenke M. When to Suspect a Genetic Syndrome. *Am Fam Physician.* 2012;86(9):826-833. PMID: WOS:000310824200008.
89. Gilchrist DM. Medical genetics: 3. An approach to the adult with a genetic disorder. *Can Med Assoc J.* 2002;167(9):1021-1029. PMID: WOS:000179276900017.
90. Church JA. A pediatric genetic disorder diagnosed in adulthood. *PLoS Med.* 2006;3(1):46-47. PMID: WOS:000236342700012.
91. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2017;19(2):249-255. PMID: 27854360. doi: 10.1038/gim.2016.190
92. Oliver GR, Hart SN, Klee EW. Bioinformatics for clinical next generation sequencing. *Clin Chem.* 2015;61(1):124-135. PMID: 25451870. doi: 10.1373/clinchem.2014.224360
93. The Genome Reference Consortium. https://www.ncbi.nlm.nih.gov/grc. Published 2019. Accessed August 18, 2019.
94. Swaminathan R, Huang Y, Astbury C, et al. Clinical exome sequencing reports: current informatics practice and future opportunities. *J Am Med Inform Assoc.* 2017;24(6):1184-1191. PMID: 28535206. doi: 10.1093/jamia/ocx048
95. Washington State Health Care Authority. Whole Exome Sequencing: Final key questions: public comment and response. https://www.hca.wa.gov/assets/program/WES-final-key-questions-20190612.pdf. Published 2019. Updated June 12, 2019. Accessed August 15, 2019.
96. Abu-Zidan FM, Abbas AK, Hefny AF. Clinical "case series": a concept analysis. *Afr Health Sci.* 2012;12(4):557-562. PMID: 23515566.
97. United Nations Development Programme. Human Development Index. Website. http://hdr.undp.org/en/composite/HDI. Published 2017. Accessed August 16, 2019.
98. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: An EPC update. *J Clin Epidemiol.* 2014;68(11):1312-1324. PMID: 25721570. doi: 10.1016/j.jclinepi.2014.11.023
99. Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. *The Lancet.* 2015;385(9975):1305-1314.
100. Wall JD, Tang LF, Zerbe B, et al. Estimating genotype error rates from high-coverage next-generation sequence data. *Genome Res.* 2014;24(11):1734-1739. PMID: 25304867. doi: 10.1101/gr.168393.113

101. Hamilton A, Tetreault M, Dyment DA, et al. Concordance between whole-exome sequencing and clinical Sanger sequencing: implications for patient care. *Mol Genet Genomic Med.* 2016;4(5):504-512. PMID: 27652278. doi: 10.1002/mgg3.223
102. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2015;17(5):405-424. PMID: 25741868. doi: 10.1038/gim.2015.30
103. Deignan JL, Chung WK, Kearney HM, Monaghan KG, Rehder CW, Chao EC. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2019;21(6):1267-1270. PMID: 31015575. doi: 10.1038/s41436-019-0478-1
104. Aetna. Clinical Policy Bulletins, Genetic Testing Number 0140. http://www.aetna.com/cpb/medical/data/100_199/0140.html. Published 2018. Updated May 16, 2019. Accessed August 26, 2019.
105. Cigna. Medical coverage policy. Whole Exome and Whole Genome Sequencing. No. 0519. https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0519_coveragepositioncriteria_exome_genome_sequence.pdf. Published 2019. Updated December 15, 2018. Accessed August 26, 2019.
106. Humana. Medical and pharmacy coverage policies. Whole Genome/Exome Sequencing and Genome-wide Association Studies. http://apps.humana.com/tad/Tad_New/Search.aspx?criteria=whole+exome+sequencing&searchtype=freetext&policyType=both. Published 2019. Updated July 1, 2019. Accessed August 26, 2019.
107. Kaiser Foundation Health Plan of Washington. Clinical review criteria-Genetic screening and testing. https://wa-provider.kaiserpermanente.org/static/pdf/hosting/clinical/criteria/pdf/genetic_screening.pdf. Published 2016. Updated Last update date not reported. Accessed August 26, 2019.
108. Premera Blue Cross. Administrative Guideline 10.01.526 Molecular Genetic Testing: Services Reviewed by AIM. http://www.aimspecialtyhealth.com/PDF/Guidelines/2019/Mar31/WholeExomeandWholeGenomeSequencing.pdf. Published 2019. Updated January 4, 2019. Accessed August 26, 2019.
109. Regence Blue Shield. Medical policy manual. Whole Exome and Whole Genome Sequncing, Policy No. 76. http://blue.regence.com/trgmedpol/geneticTesting/gt76.pdf. Published 2019. Updated July 1, 2019. Accessed August 26, 2019.
110. UnitedHealthCare. Medical Policy CS150.F Whole Exome and Whole Genome Sequencing. https://www.uhcprovider.com/content/dam/provider/docs/public/policies/medicaid-comm-plan/whole-exome-whole-genome-sequencing-cs.pdf. Published 2019. Updated July 1, 2019. Accessed August 26, 2019.
111. Centre Hospitalier Universitaire de Besancon. Molecular diagnosis of syndromic or isolated severe intellectual disability using whole exome sequencing : a pilot study. https://ClinicalTrials.gov/show/NCT02862808. Published 2017. Updated September 20.

112. Milton S. Hershey Medical Center. Whole genome sequencing in the neonatal intensive care unit. https://ClinicalTrials.gov/show/NCT03721458. Published 2019. Updated May 1.
113. Tufts Medical Center. Genomic medicine for ill neonates and infants (The GEMINI Study). https://ClinicalTrials.gov/show/NCT03890679. Published 2019. Updated March 21.
114. Charite University; German Federal Ministry of Education Research. Mutation exploration in non-acquired, genetic disorders and its impact on health economy and life quality. https://ClinicalTrials.gov/show/NCT02380729. Published 2015. Updated January 31.
115. Centre Hospitalier Universitaire Dijon. Identification of the molecular and/or pathophysiological bases of developmental diseases. https://ClinicalTrials.gov/show/NCT03287193. Published 2017. Updated March 13.
116. Centre Hospitalier Universitaire Dijon. Medico-economic evaluation of different high-throughput sequencing strategies in the diagnosis of patients with intellectual deficiency. https://ClinicalTrials.gov/show/NCT03287206. Published 2017. Updated June 28.
117. Centre Hospitalier Universitaire Dijon. Secondary findings from high-throughput sequencing: how to announce them with respect to the patient's needs. https://ClinicalTrials.gov/show/NCT03288727. Published 2017. Updated November 4.
118. Eunice Kennedy Shriver National Institute of Child Health. Evaluation of children with endocrine and metabolic-related conditions. https://ClinicalTrials.gov/show/NCT02769975. Published 2016. Updated May 11.
119. National Taiwan University Hospital. Rapid genetic diagnosis employing next generation sequencing for critical illness in infants and children. https://ClinicalTrials.gov/show/NCT03175692. Published 2017. Updated June 14.
120. National Eye Institute. Whole exome and whole genome sequencing for genotyping of inherited and congenital eye conditions. https://ClinicalTrials.gov/show/NCT02077894. Published 2014. Updated February 28.
121. National Human Genome Research Institute. Adult patients with undiagnosed conditions and their responses to clinically uncertain results from exome sequencing. https://ClinicalTrials.gov/show/NCT03605004. Published 2019. Updated April 12.
122. Children's Hospital of Philadelphia. LeukoSEQ: whole genome sequencing as a first-line diagnostic tool for leukodystrophies. https://ClinicalTrials.gov/show/NCT02699190. Published 2017. Updated January 6.
123. University of Pittsburgh. Neurogenetics patient registry. https://ClinicalTrials.gov/show/NCT02995538. Published 2017. Updated January 30.
124. University of California, San Francisco. Clinical utility of pediatric whole exome sequencing. https://ClinicalTrials.gov/show/NCT03525431. Published 2017. Updated August 1.

Appendix A. State of Washington Health Care Authority Utilization Data

Populations

The Whole Exome Sequencing (WES) analysis combined member utilization and cost data from the following Washington agencies: Medicaid Managed Care (MCO) and Medicaid Fee-for-Service (FFS).

The Department of Labor and Industries (LNI) Workers' Compensation Plan reported no WES utilization. The Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP) reported less than the minimum number of individuals necessary to safely release agency-by-agency findings and still protect patient confidentiality.

Population inclusion criteria specified incurring at least one CPT 81415-claim line, with or without a concurrent 81416 CPT(s) or having a standalone 81417 CPT (see Table I). The data process involved extracting all WES claims; however, denied claims received a separate analysis and were not included in utilization counts. The analysis period contained 4 calendar years of claims data from 2015 through 2018. All chart and graph analyses is by calendar year.

Methods

Initial criteria identified all WES CPTs (see Appendix A-Table 1). Next, we obtained patient claims containing the targeted WES CPTs along with a WES date of service. Next, we sorted claims into 2 groupings: paid claims or denied claims. The paid claims grouping required extraction of all paid claims incurred on a patient's WES date of service. Data evaluation involved examining utilization by member; analysis of individual and aggregate CPT codes by age and calendar year; and by total claims' costs incurred by a member on the date of their service. Denied claims received a separate analysis for volume of denials.

Appendix A-Table 1. Targeted CPT - Whole Exome Sequencing

CPT	Procedure Code Description
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	Test conducted on the individual under study (IUS).
81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	Tests conducted on the parents, siblings, etc. of the IUS. Codes attributed to the IUS.
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/ syndrome)
	Re-read of a test previously conducted on the IUS.

Findings

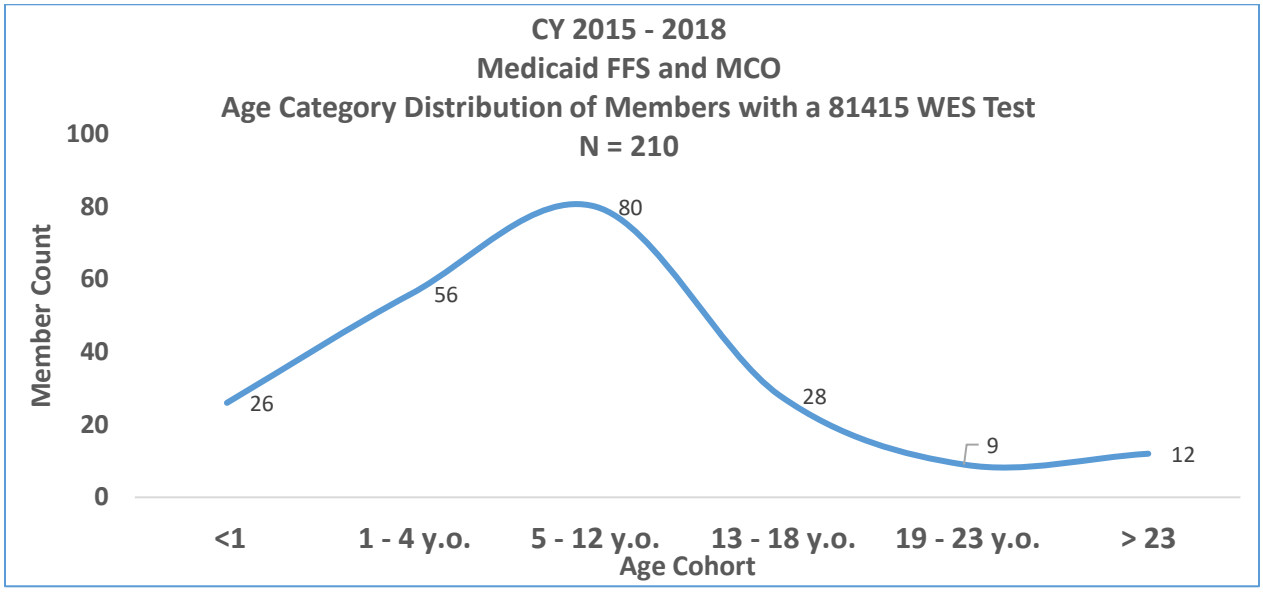
Table A-2 provides the results of the WES analysis for calendar years 2015 through 2018.

Table A-2. Calendar Years 2015 to 2018 Medicaid FFS and MCO Whole Exome Sequencing Summary Utilization and Costs, CPTs 81415, 81416, 81417

	2015	2016	2017	2018
Unique Individuals Under Study	21	41	58	91
Total WES Tests conducted	23	75	108	184
Total Paid for all Tests	$72,191	$46,510	$78,995	$163,346
Paid as a Professional Claim	$62,650	$45,600	$76,886	$159,295
Average Paid - Professional Claim	$12,530	$5,700	$4,055	$888
Paid as an Outpatient Claim	$9,541	$910	$2,109	$4,051
Average Paid - Outpatient Claim	$20	$16	$25	$32

Appendix A-Figure 1 depicts the age category distribution of members who received WES testing.

Appendix A-Figure 1



Appendix A-Figure 2 depicts the age distribution of tests by year.

Appendix A-Figure 2

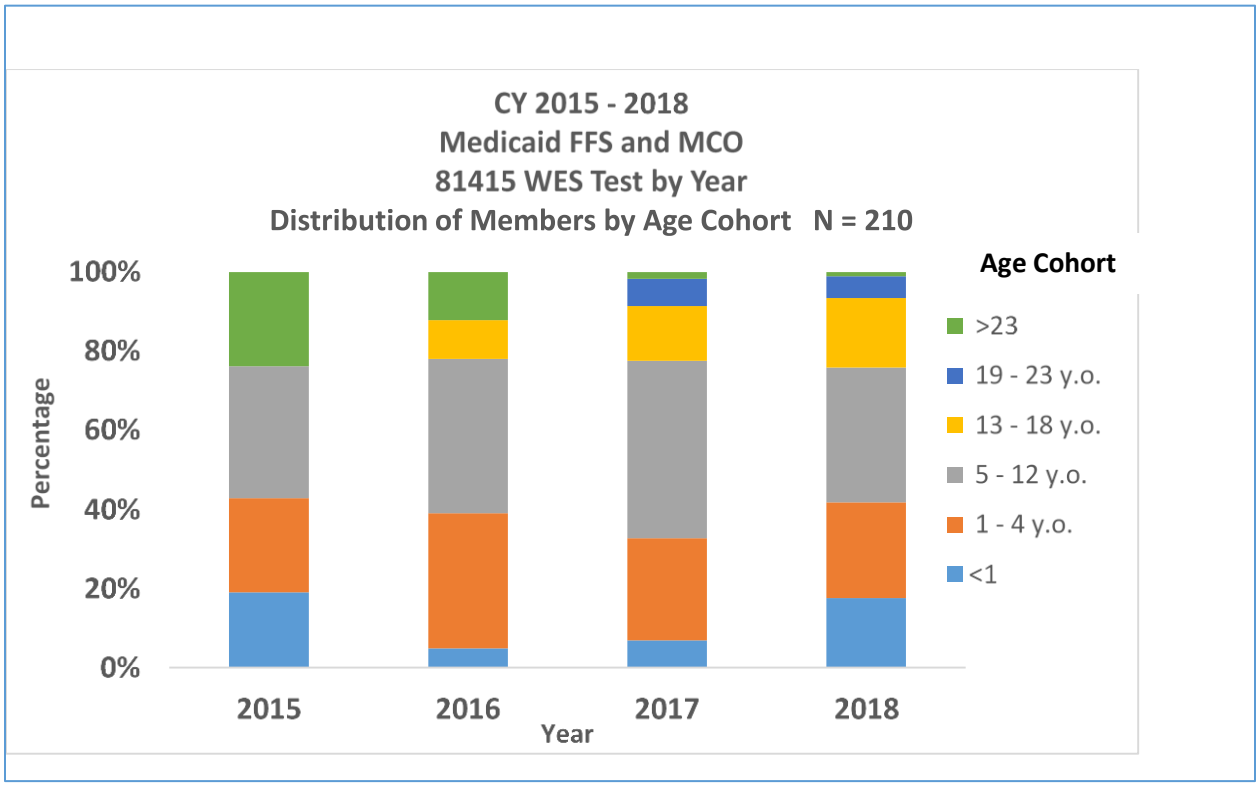
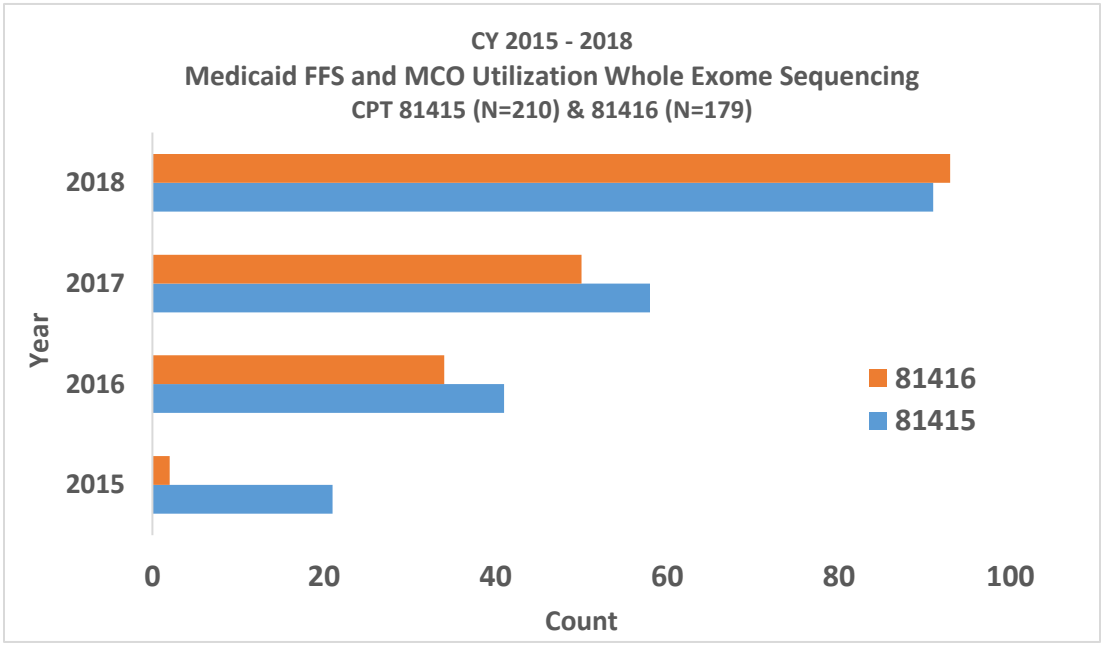


Figure A-3 depicts the distribution of WES testing by CPT code and year.

Appendix A Figure A-3.



Appendix B. Search Strategy

PubMed Search, 2010 Through March 14, 2019

Search	Query	Items found
#1	Search (“Whole Exome Sequencing”[Mesh] OR “Whole Genome Sequencing”[Mesh] OR "whole exome"[All Fields] OR "whole exome"[All Fields] OR "whole genome"[All Fields] OR "whole-genome"[All Fields])	41129
#2	Search (“Cost-Benefit Analysis”[Mesh] OR “Genetic Diseases, Inborn”[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Patient Care Management"[Mesh] OR “Precision Medicine”[Mesh] OR "Prospective Payment System"[Mesh] OR “Reproducibility of Results”[Mesh] OR “Sensitivity and Specificity”[Mesh] OR “diagnostic utility”[tiab] OR “Mendelian diagnostics”[tiab])	2997695
#3	Search (#1 and #2)	4248
#4	Search (#1 and #2) Filters: English	4163
#5	Search (#1 and #2) Filters: Publication date from 2010/01/01 to 2019/12/31; English	3610
#6	Search (#5 NOT ("Bacteria/genetics"[Mesh] OR “DNA, Plant”[Mesh] OR “DNA, Bacterial”[Mesh] OR "Fungi"[Mesh] OR "Genetic Predisposition to Disease"[Mesh] OR “Genome, Bacterial”[Mesh] OR "HIV"[Mesh] OR "Infection"[Mesh] OR "Neoplasms"[Mesh] OR Pregnancy[Mesh] "Viruses"[Mesh] OR "Virology"[Mesh] OR “bacterial DNA”[tiab] OR “bacterial typing”[tiab] OR “bacterial genetics”[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR “CRISPR-Cas”[All Fields] OR fungal[tiab] OR “gene editing”[tiab] OR HIV*[tiab] OR infection*[tiab] or infectious[tiab] OR neoplasm*[tiab] OR “plant DNA”[All Fields] OR pregnancy[tiab] OR pregnant[tiab] OR sarcoma*[tiab] or viral[tiab] OR virus*[tiab]))	2771
#7	Search ("Systematic Review" [Publication Type] OR “systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “cochrane database syst rev”[ta] OR "Umbrella Review"[tiab] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab])	235171
#8	Search (#6 and #7)	19
#9	Search (#6 NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type] OR Review[Publication Type]))	1699
#10	Search (“Whole Exome Sequencing”[All Fields] OR “Whole Genome Sequencing”[All Fields] OR “whole exome”[tiab] OR “whole exome”[tiab] OR “whole-genome”[tiab] OR “whole genome”[tiab] OR WES[tiab] OR WGS[tiab] or rWGS[tiab])	41960
#11	Search (“clinical benefit”[tiab] OR “clinical utility”[tiab] OR ClinSeq[tiab] OR “Cost-Benefit”[tiab] OR “cost effectiveness”[tiab] OR costs[ti] OR “diagnostic”[tiab] OR “disease management”[tiab] OR (health*[tiab] AND outcome*[tiab]) OR “inborn genetic diseases”[tiab] OR hospitalization*[tiab] OR (insurance*[tiab] AND reimburse*[tiab]) OR “medical management”[tiab] OR “Mendelian diagnostics”[tiab] OR “monogenic disease risk”[tiab] OR MDR[tiab] OR "Patient Care Management"[tw] OR “Precision Medicine”[tw] OR "Prospective Payment System"[tw] OR reimburse*[ti] OR “Reproducibility of Results”[tw] OR “Sensitivity and Specificity”[tw])	1750571
#12	Search (#10 and #11)	4372
#13	Search (“bacterial DNA”[tiab] OR “bacterial typing”[tiab] OR “bacterial genetics”[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR “CRISPR-Cas”[All Fields] OR fungal[tiab] OR “gene editing”[tiab] OR HIV*[tiab] OR infection*[tiab] or infectious[tiab] OR neoplasm*[tiab] OR “plant DNA”[All Fields] OR pregnancy[tiab] OR pregnant[tiab] OR sarcoma*[tiab] OR viral[tiab] OR virus*[tiab])	4516768
#14	Search (#12 not #13)	2948
#15	Search (#14 and ("2010/01/01"[edat]:"2019/12/31"[edat]))	2552
#16	Search (#15 and (#7 or "systematic review"[tiab]))	38
#17	Search (#16 not (#8 or #9))	25
#18	Search (#15 not (#8 or #9 or #17))	1812

PubMed Yield: 3,541

Embase Search, 2010 to March 14, 2019

Search	Search History	Results
#1	'Whole Exome Sequencing'/exp OR 'whole genome sequencing'/exp OR "whole exome" OR "whole exome" OR "whole genome" OR "whole-genome"	64,618
#2	'cost benefit analysis'/exp OR 'genetic disorder'/exp OR 'reimbursement'/exp OR 'outcome assessment'/exp OR 'patient care'/exp OR 'personalized medicine'/exp OR "precision medicine" OR 'prospective payment'/exp OR 'reproducibility'/exp OR 'sensitivity and specificity'/exp OR 'diagnostic value'/exp OR "diagnostic utility" OR "Mendelian diagnostics"	3,099,850
#3	#1 and #2	14,235
#4	#3 and [English]/lim	14,062
#5	#4 and [2010-2019]/py	13,099
#6	#5 not ('bacteria genetics'/exp OR 'plant DNA'/exp OR 'bacterial DNA'/exp OR 'fungus'/exp OR 'genetic predisposition'/exp OR 'bacterial genome'/exp OR 'Human immunodeficiency virus'/exp OR 'infection'/exp OR 'neoplasm'/exp OR 'pregnancy'/exp OR 'virus'/exp OR 'virology'/exp OR 'bacterial DNA':ab,ti OR 'bacterial typing':ab,ti OR 'bacterial genetics':ab,ti OR cancer*:ab,ti OR carcinoma*:ab,ti OR 'CRISPR-Cas' OR fungal:ab,ti OR 'gene editing':ab,ti OR HIV*:ab,ti OR infection*:ab,ti or infectious:ab,ti OR neoplasm*:ab,ti OR 'plant DNA' OR pregnancy:ab,ti OR pregnant:ab,ti OR sarcoma*:ab,ti or viral:ab,ti OR virus*:ab,ti)	6,650
#7	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta-analysis'/exp OR 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'systematic literature review':ti OR 'this systematic review' OR ('systematic review':ti,ab AND 'review'/exp) OR 'meta synthesis':ti OR 'cochrane database syst rev' OR 'Umbrella Review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab	385,491
#8	#6 and #7	88
#9	#6 not (('animal'/exp NOT 'human'/exp) OR 'editorial'/exp OR 'case report'/exp OR 'review'/exp)	4,199
#10	'Whole Exome Sequencing' OR 'Whole Genome Sequencing' OR 'whole exome':ti,ab OR 'whole exome':ti,ab OR 'whole-genome':ti,ab OR 'whole genome':ti,ab OR WES:ti,ab OR WGS:ti,ab or rWGS:ti,ab	65,278
#11	'clinical benefit':ti,ab OR 'clinical utility':ti,ab OR ClinSeq:ti,ab OR 'Cost-Benefit':ti,ab OR 'cost effectiveness':ti,ab OR costs:ti OR 'diagnostic':ti,ab OR 'disease management':ti,ab OR (health*:ti,ab AND outcome*:ti,ab) OR 'inborn genetic diseases':ti,ab OR hospitalization*:ti,ab OR (insurance*:ti,ab AND reimburse*:ti,ab) OR 'medical management':ti,ab OR 'Mendelian diagnostics':ti,ab OR 'monogenic disease risk':ti,ab OR MDR:ti,ab OR 'Patient Care Management' OR 'Precision Medicine':ti,ab OR 'Prospective Payment System' OR reimburse*:ti OR 'Reproducibility of Results' OR 'Sensitivity and Specificity'	2,005,600
#12	#10 and #11	6,892
#13	'bacterial DNA':ti,ab OR 'bacterial typing':ti,ab OR 'bacterial genetics':ti,ab OR cancer*:ti,ab OR carcinoma*:ti,ab OR 'CRISPR-Cas' OR fungal:ti,ab OR 'gene editing':ti,ab OR HIV*:ti,ab OR infection*:ti,ab or infectious:ti,ab OR neoplasm*:ti,ab OR 'plant DNA' OR pregnancy:ti,ab OR pregnant:ti,ab OR sarcoma*:ti,ab OR viral:ti,ab OR virus*:ti,ab	5,740,507
#14	#12 not #13	4,171
#15	#14 and ('2010/01/01'[edat]:'2019/12/31'[edat])	3,940
#16	#15 and (#7 or 'systematic review':ti,ab)	92
#17	(#16 not (#8 or #9)	55
#18	#15 not (#8 or #9 or #17)	2,771
#19	#8 or #17	143

Embase Yield: 2,914 (1,610 after deduplication)

Cochrane Library Search, 2010 to March 14, 2019

ID	Search	Hits
#1	"whole exome":ti,ab,kw OR "whole exome":ti,ab,kw OR "whole genome":ti,ab,kw OR "whole-genome":ti,ab,kw OR rWGS:ti,ab,kw OR WES:ti,ab,kw OR WGS:ti,ab,kw	621
#2	"bacterial DNA":ti,ab,kw OR "bacterial typing":ti,ab,kw OR "bacterial genetics":ti,ab,kw OR cancer*:ti,ab,kw OR carcinoma*:ti,ab,kw OR "CRISPR-Cas":ti,ab,kw OR fungal:ti,ab,kw OR "gene editing":ti,ab,kw OR HIV*:ti,ab,kw OR infection*:ti,ab,kw or infectious:ti,ab,kw OR neoplasm*:ti,ab,kw OR "plant DNA":ti,ab,kw OR pregnancy:ti,ab,kw OR pregnant:ti,ab,kw OR sarcoma*:ti,ab,kw OR viral:ti,ab,kw OR virus*:ti,ab,kw	332111
#3	#1 not #2	293
#4	#3 with Cochrane Library publication date Between Jan 2010 and Dec 2019	285

Cochrane Yield: 285 (236 after deduplication)

Total Bibliographic Database Yield: 5,387

ClinicalTrials.Gov Search, 2010 to April 9, 2019

("whole exome" OR "whole exome" OR "whole genome" OR "whole-genome" OR rWGS OR WES OR WGS) AND NOT ("bacterial DNA" OR "bacterial typing" OR "bacterial genetics" OR cancer* OR carcinoma* OR "CRISPR-Cas" OR drug* OR fungal OR "gene editing" OR glioma* OR healthy OR HIV* OR infection* or infectious OR leukemia* OR neoplasm* OR "plant DNA" OR predisposition* OR pregnancy OR pregnant OR radiation* OR sarcoma* OR tumor* OR viral OR virus*) AND INFLECT ("01/01/2010" : "04/09/2019") [LAST-UPDATE-POSTED]

CT.gov Yield: 145 (after deduplication)

Other Data

We searched websites of the organizations listed in Table B-1 to identify related health technology assessment, clinical practice guidelines, position or policy statements, payor coverage policies, or other clinical guidance.

Appendix B-Table 1. Websites Searched for Documents Relevant to Whole Exome Sequencing

Organization	Potentially Relevant Documents
American Academy of Pediatrics	0
American Academy of Neurology	1
Society for Developmental and Behavioral Pediatrics	0
American College of Medical Genetics and Genomics	5
National Institute for Clinical Excellence	0
Institute for Clinical and Economic Review	0
University of York Centre for Reviews and Dissemination/National Institutes for Health Research	4
U.S. Food and Drug Administration	0
U.S. Agency for Healthcare Research and Quality	0
Centers for Medicare and Medicaid Services	0
Aetna	1
Cigna	1
Humana	1
BlueCross BlueShield (Premera and Regence)	1
Kaiser Permanente	1
United Health	1
Tricare	0

Abbreviations: U.S. = United States

Appendix C. Evidence Tables

Table C-1. Characteristics of Included Studies

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
Balridge (2017)[43]	Single-arm observational cohort	U.S.	2012-2015	NIH, Washington University	155	155 patients seen at Washington University Exome clinic; phenotypes were 66% (103) neurological, 10% (15) multiple congenital anomalies, 10% (15) mixed and 14% (21) another phenotype; mean age 6 years (range: 3 days to 33 years); 44% (68) female, 84%; (130) White	Trio WES (n=128), parent, sibling proband WES (n=1), parent/ sibling WES (n=6), or singleton WES (n=20) performed at three commercial laboratories Variants initially classified by the laboratory, then reassessed and reclassified by clinical geneticist. Diagnostic yield: 67 (43%) definitive diagnosis
Bourchany (2017)[42]	Single-arm observational cohort	France	NR	Regional Council of Burgundy	29 patients enrolled, 23 pediatric patients, 4 fetuses after pregnancy termination, and 2 adults	29 unrelated patients at five French genetics centers. Patients had expert consultation with clinical geneticist from a reference center for congenital anomalies. Inclusion criteria were association of undiagnosed developmental disorder and on-going pregnancy of at-risk relatives requesting genetic counseling; hospitalization in an intensive care unit with a diagnostic request for guiding care Female = 48.3%* (14/29) Ethnicity = NR Mean age = 5.8 years (range: 0 months to 37 years)	Trio WES, variants annotated with SeattleSeq SNP Annotation 138; looks for MAF <0.01 in dbSNP and ExAC, filtered based on local database of 69 healthy individuals using MAF >0.05%, OMIM genes, phenotypic concordance considered Sanger sequencing to confirm, 21/29 patients had multiple genetic and metabolic tests before WES All patients had array CGH before or during inclusion. WES was first-line test in 8/29. Diagnostic yield: 13/29 = 44.8% For non-fetuses, diagnostic yield = 44%*(11/25)
Cordoba (2018)[18]	Single-arm observational cohort	Argentina	NR	National Research Council Argentina	40	Consecutive series of 40 patients (adults and children) suspected of neurogenetic conditions from a neurogenetics clinic in tertiary	Singleton or trio WES, variants confirmed by Sanger sequencing Classification of variants based on ACMG and Association for Molecular Pathology; variants classified as positive,

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						hospital, mean age: 23 years (range: 3 to 70 years) Phenotypes included myopathy, ataxia, encephalopathy, developmental delay, dystonia, among others	negative, or undetermined Diagnostic yield: 40% (this includes 2 cases that were reclassified from undetermined and negative category at the time of their original report after subsequent reanalysis)
Daga (2018)[41]	Single-arm observational cohort	U.S.	2013-2016	NIH, National Research Fund of Korea, Deutsche Forschungsgemeinschaft	65 individuals, 51 families	Patients who presented at children's hospital with nephrolithiasis and/or a finding of nephrocalcinosis on renal ultrasound, before the age of 25 years and their families, study families selected for DNA available for multiple affected family members (n=49), recurrent or early-onset disease (n=7), or both parents available for trio analysis (n=15)	WES of multiple family members or trios Whole exome analysis Diagnostic yield 15 of 51 (29.4%) No comparator pathways
Dillon (2018)[17]	Single-arm observational cohort	Australia	2016	Melbourne Genomics Health Alliance, State Government of Victoria; Bioplatforms Australia	145 children	A retrospective simulation study of panel testing in 145 children who had undergone WES for diagnostic purposes; age range: 0-12 months = 46% (67); 12-24 months= 19% (28); >24 months= 35% (50) Includes participants suspected of having a genetically heterogenous condition or features. Female = 43% (63). Primary phenotype of patients consisted of: Dermatological 3% (4), dysmorphic with congenital abnormalities 45% (65), Neurometabolic 30% (43), skeletal dysplasia 9% (13); ophthalmological 3% (4), other 11% (16). Additionally, 43% (62)	WES with variants prioritized based on a phenotype-driven list. Only variants in genes known to cause human disease (the "Mendeliome") were analyzed. Variant classification was performed per the ACMG standards. Diagnostic yield with WES was 78/145 (53.8%). Comparator testing strategies were simulated by applying up to three commercial panels to each of the children who were diagnosed with WES. The three panels were chosen based on those most likely to sufficiently cover the differential diagnosis provided at recruitment

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						had an intellectual disability and 57% (83) did not. During recruitment, clinicians were required to propose commercial gene panel tests as an alternative to WES and nominate a phenotype-driven candidate gene list	
Ding (2014)[75]	Modeling Study	Australia	NR	NR	24 autosomal dominant conditions - including one semidominant condition	24 autosomal dominant conditions were selected because they were highly penetrant, asymptomatic for long periods of time, and amenable to preventive measures and/or treatment. A simple mathematical model was developed based on binomial distribution which represents the probability of reporting at least 1 incidental finding. A diagnostic panel was constructed based on the 24 ACMG-recommended minimum list of genes to be reported	No sequencing was performed during the course of this study. This is exclusively a mathematical modeling paper
Dragojlovic (2018)[23]	Modeling Study	Canada	2016	British Columbia Children's Hospital Foundation, Canadian Institutes of Health Research	167 families were sequenced, but final outcomes not completed in 2016, the year of the analysis so outcomes unknown.	A cost modeling study for the Clinical Assessment of the Utility of Sequencing and Evaluation as a Service study to test a delivery model for diagnostic exome sequencing in pediatric patients. No further information on study population provided	Evaluated both singleton and trio WES, in separate scenarios; targeted analysis focused on known disease genes; variants classified as definite or probable were confirmed with Sanger sequencing; reanalysis of negative results every 6 or 12 months until end of study. Diagnostic yield Trio WES after genomics consultation: 34.3% (95% CI, 23.2 to 46.5) Singleton WES: 28.1% (95% CI, 12.9 to 42.9)

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							Trio WES without clinical genomics consultation first: 34.0% (95%CI, NR)
Evers (2017)[52]	Single-arm observational cohort	Germany	2013 - 2015	NR	72 patients from 60 families	WES was performed in a cohort of 72 patients from 60 families with undiagnosed, suspected genetic conditions. Patients were phenotypically characterized prior to WES. The cohort was comprised of 45 index patients with developmental delay and/or congenital malformations, eight patients with infantile dystonia, and seven patients with a neurometabolic disorder. All patients were evaluated by an experienced clinical geneticist and/or neuro-pediatrician. The patient had a mean age at diagnosis of 8.5 years compared to a mean age at WES analysis of 6.4. 50% of patients were female, most were of German and Turkish origin (55% and 28%, respectively), 25% of families reported consanguinity (mainly those of Turkish descent), 70% of index patients with known family history were sporadic cases, 30% had at least one affected sibling. Patients displayed a wide range of symptoms, with 77% having developmental delay/intellectual delay; other common phenotypes	Trio-based (a few cases include affected or unaffected siblings), WES (allowed for novel variant discovery), excluded variants with MAF >1% in ExAC or 1KGP3 and local controls to exclude other common alleles/technical artifacts. Annotated using ANNOVAR. Assessed by 7 variant effect prediction tools (e.g., SIFT). ACMG guidelines used to classify, additional criteria for variants in genes not previously associated with phenotype. Diagnostic yield: 21/60 families (35%) overall 16/45 (36%) neurodevelopmental disorders 3/7 (43%) neuromuscular disorders 2/8 (25%) dystonias Comparator: NA

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						were micro or macrocephaly (53% and 12%, respectively), dysmorphic signs (40%), short stature (32%), epilepsy (28%), and behavioral abnormalities including autism spectrum disorders (18%). 32% had congenital malformations, most often congenital heart disease. Characteristics of the congenital malformations group of 45 patients were: Female = 23 (51%); Age at molecular diagnosis < 10 years = 11 (69%); ≥ 10 years = 5 (31%); Age at WES < 10 years = 14 (61%); ≥10 years = 9 (39%)	
Ewans (2018)[21]	Single-arm observational cohort	Australia	2013-2014	Australian National Health and Medical Research Council	54 patients from 37 families	Adults and children recruited from clinical genetics units with distinctive phenotype likely to have a monogenic etiology, a family structure consistent with Mendelian inheritance, and prior diagnostic investigations that were all negative. Phenotypes included syndromic intellectual disability (49%), skeletal (13%), hematological (11%), nonsyndromic intellectual disability (8%), visual (8%), neurological (5%), metabolic (3%) and other syndromal disorder (3%) Age: 68% children Sex: NR	Mixed approach of singleton, trio, including multiple affected family members; whole exome analysis with variants prioritized by pedigree structure (tested all possible inheritance patterns); used ACMG pathogenicity criteria and required adequate relationship of variant with published gene-disease evidence, Sanger validation. 12-month reanalysis: undertaken for undiagnosed families after initial testing Diagnostic yield for initial WES: 11/37 families (30%) 46% of trios had molecular diagnosis from WES 22% of singletons had molecular diagnosis from WES 20% of multiple affected individual

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							families had molecular diagnosis from WES. Diagnostic yield for WES reanalysis: 4 additional families diagnosed. Overall diagnostic rate from 30% to 41% Counterfactual comparison of WES to "traditional diagnostic pathway" 14 patients with intellectual disability and available medical records used for comparison 1) WES available at initial clinical genetics service contact 2) WES available at initial presentation "with clinical symptoms that would warrant genetic testing" 3) traditional pathway
Hauer (2017)[51]	Single-arm observational cohort	Germany	NR	Centre for Clinical Research of the University of Erlangen-Nurnberg	565 enrolled, 200 exome analysis patients	565 patients were systematically phenotyped, patients referred by local medical specialists for evaluation of growth retardation/ short stature, 551 were of European descent, 13 of Asian and 1 of Arab descent. At the time of enrollment, 83% were under the age of 18 years: < 4y = 102 (18%); > 4y =463 (82%); female = 349 (62%); male = 216 (38%) 81% presented with a height of 2 SDs below the age related mean, remaining 19% were 2 SDs below the estimated family target height. Overall 20% showed mild learning disabilities and 21% microcephaly, 30% underwent	Trio analysis In 100 probands and singleton in another 100 probands Targeted WES (1000 known short stature genes from MedGen and Human Phenotype ontology) Variant reporting: variants assessed according to inheritance pattern using in-house tool. Only variants called with GATKHap, GATKUG, or SNVer were analyzed, had at least 10% of average coverage of patient's exome, and for at least 5 novel alleles were detected. Excluded variants with MAF <= 0.001 in 1KG, Exome Variant Server, or ExAC, or <= 0.15% in in-house variant database, different cutoffs used for different zygosities Sanger sequencing done for confirmation and familial segregation, applied ACMG criteria for variant

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						bone age evaluation and of those 84% had either delayed or accelerated bone ages. All 565 underwent extensive prior endocrinological and diagnostic workup to exclude defects of the growth hormone pathway and organic causes of their growth deficit. A representative group of 200 patients selected from the 565 patients and their families, where unbiased exome sequencing was performed. These patients had short stature of unknown origin Patients were ages: < 4 years = 33 (17%); > 4 years = 167 (83%); female = 122 (61%) and male = 78 (39%)	classification Diagnostic yield: 33/200 (16.5%) No comparator pathway
Howell (2018)[28]	Other	Australia	2011-2015	NR	114 evaluated, but of these only 49 had unknown etiology/diagnosis, and only some of these received WES testing.	Population based study of 86 infants with severe epilepsies of infancy. Infants were born in Victoria, Australia during 2011 - 2015 and identified through EEG laboratories, NICU databases, and neurologist referrals. Severe epilepsies of infancy was defined as age <18 months with 1) frequent seizures (>/= daily for 1 week or >/= weekly for 1 month), 2) ongoing seizures despite trials of 2 appropriate antiepileptic drugs, and 3) epileptiform EEG abnormality. Infantile spasms were automatically included.	All participants received one or more of the following testing pathways. "Research genetic testing" defined as targeted WES (n=40), molecular inversion probes with panels of 39 to 65 epilepsy genes (n=32), single gene sequencing (n=1), and whole genome sequencing (n=1), singleton WES with targeted analysis of 341 genes (n= NR). Tier 1 testing defined as brain MRI, CMA, blood count, electrolytes, urea, creatinine, glucose, calcium, magnesium, phosphate, liver function tests, lactate, ammonia, amino acids,

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						Mean age: NR; % Female: NR; Race/ethnicity: NR	acylcarnitines, biotinidase, uric acid, urine tests for organic and amino acids, piperideine-6-carboxylate, S-sulfocysteine, guianidioacetic acid, purines, pyriminidines Tier 2 testing defined as common mitochondrial mutations, polymerase gamma common mutations, transferrin isoforms, copper, ceruloplasmin, very long chain fatty acids, white cell enzymes, paired blood-CSF evaluation, CSF neurotransmitters Tier 3 testing defined as skin biopsy, electron microscopy for changes of neuronal ceroid lipofuscinosis, lysosomal and mitochondrial disorders, fibroblast culture, liver and muscle biopsies for histopathology, histochemistry, electron microscopy, respiratory chain enzyme analysis Diagnostic Yield By Pathway Path 1 (Tier 1, Tier 2, Repeat MRI, Tier 3) ->39/86= 45.3% Path 2 (Tier 1, Tier 2, Repeat MRI, Tier 3, WES)->48/86=55.8% Path 3 (Tier 1, Tier 2, Repeat MRI, WES, Tier 3)->48/86= 55.8% Path 4 (Tier 1, Tier 2, WES, Repeat MRI, Tier 3)->48/86= 55.8% Path 5 (Tier 1, WES, Tier 2, Repeat MRI, Tier 3)->48=55.8% Path 6 (Tier 1, WES, Repeat MRI, Tier 2)->48/86=55.8%

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							Path 7 (Tier 1, WES, Repeat MRI)->46/86=53.5%
Iglesias (2014)[46]	Single-arm observational cohort	U.S.	2011-2013	NR	115	Retrospective chart review of 115 patients whose WES results were clinically evaluated at an academic health care center with a variety of phenotypes, including 25.2% (29) developmental delay/intellectual disability, 24.3% (28) birth defects, and 12.1% (14) seizures, 78.9% (94) children, 3 (2.6%) were terminated fetuses, 48.6% (56) female, 61.7% (71) white	95/115 (92.6%) had parent and proband trio submitted 3/115 (2.6%) proband only not explicit, but discover novel candidate genes, so suspect whole exome analysis Clinical interpretation of WES done by ordering geneticist Diagnostic yield = 37/115 (32.2%) 15/28 (53.5%) for birth defects 10/29 (34.4%) for developmental delay/ intellectual disability 3/7 (42.9%*) for cardiomyopathy 3/4 (75%*) for ophthalmologic disease 2/4 (50%*) myopathies 2/4 (50%*) dermatologic disease 2/2 (100%*) neurological/neurodegenerative disorders 1/2 (50%*) metabolic disorder No comparator testing pathway.
Jones (2018)[50]	Qualitative research design	U.S.	2015-2016	Regeneron Genetics Center, Geisinger	28 participants assessed; 23 included	A retrospective chart review was performed to monitor disease manifestation and medication management after learning Familial hypercholesterolemia (FH) genetic results. The 28 individuals were invited to participate in semi-structured interviews to understand their experience learning these results. Only individuals with a Geisinger primary care provider were included in the chart review portion of this study (N=23) due	Singleton Not explicitly stated targeted or whole exome WES procedures NR (MyCode program) Diagnostic yield: NA Comparator testing: NA

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						to availability of documentation about disease management and control within the electronic health record. Female = 15 (65%), median age = 66 years (range: 27 to 85). Conditions included high prevalence of hyperlipidemia 19 (83%), coronary atherosclerosis 11 (48%), and peripheral vascular disease 8 (35%). Thirteen (57%) had documented FH on their problem list after receipt of the test result, whereas only 5 (22%) had a diagnosis on their problem list before receipt of their result. Seven (30%) had a history of myocardial infarction or cerebrovascular disease. Nearly half had a diagnosis of hypertension n = 11 (48%) and 8 (35%) had a prior history of smoking, 2 (8%) were active smokers	
Jurgens (2015)[65]	Single-arm observational cohort	U.S.	NR	NIH	232 individuals from 89 families analyzed	232 individuals from 89 families sequenced Underwent WES for variety of potential Mendelian disorders Sequenced at Johns Hopkins University, a tertiary academic health care center/research university 73% self-identified as European descent	At least some were family-based WES Targeted for this report (only 56 genes in ACMG guidelines analyzed) Other genes probably analyzed for diagnosis Web-based system PhenoDB. Variant classification using HGMD, ClinVar, and Emory Genetics Laboratory Variant Classification Catalog. Classification of variants within these databases was often discordant (~45.8% shared variants

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							discordant). To determine what variants are reportable, followed criteria from Dorschner et al. Reported pathogenic and likely pathogenic variants to participants. diagnostic yield: NR
Lee (2015)[73]	Single-arm observational cohort	U.S.	2012-2013	NIH	29 eligible, 26 (approx. 90%) enrolled	Patients with presumed hereditary retinal dystrophies were enrolled during clinical appointments in a university-based ophthalmic genetics clinic during initial or follow-up visits. Return patients were eligible if the molecular etiology of their retinal disorder was unknown 5 of 26 participants (19%) were under 18 years of age; adults ranged from 22 to 69 years. 3 of 26 participants (11%) had an uncertain clinical diagnosis at time of enrollment. 14 of 26 participants (54%) did not have a known family history of retinal dystrophy	Exome sequencing used Agilent's SureSelect XT Target Enrichment System for Illumina paired-end sequencing on the HiSeq 2000 instrument. Average coverage depth across the entire region targeted for enrichment was 58.19. Custom pipeline developed for the NCGENES project used to process raw sequence data from FASTQ files to generate variant calls. Filtered variants using a list of 186 genes associated with syndromic and nonsyndromic retinopathies. Variants where then prioritized to select ones previously reported as pathogenic, truncating or missense variants with MAF <1%, and other categories. Diagnostic yield: 15 of 26 participants (58%) No comparator testing
Li (2019)[67]	Qualitative research design	U.S.	2015-NR	NR	38 families eligible, 15 consented, 14 analyzed (including 1 husband-wife dyad)	14 telephone interviews with 15 parents or legal guardians (1 interview with both parents) who received WES results for their children in the past 6 months that included variant(s) of uncertain significance at a large academic hospital, various phenotypes	Type of WES not specified Targeted vs whole exome analysis not specified Participants were restricted to those with WES completed after May 2015 due to timing of ACMG guidelines that were the focus of this paper. Diagnostic yield: NA

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						including macrocephaly, microcephaly, encephalopathy, failure to thrive, developmental delay, intellectual disability, learning disabilities, language disorder, epilepsy, gait abnormality, hemiparesis, autism spectrum disorder, attention deficit hyperactivity disorder, self-injurious behavior, congenital hip dysplasia, and heart defect, mean parent age: 45 years (range: 29 to 62), 12 female, 7 White, 8 with post-graduate degrees, mean child age: 7.5 years (range: 1.5 years to 15 years)	Comparator testing pathways: NA, but no patient had clinical genetic diagnosis prior to WES
Mann (2019)[48]	Single-arm observational cohort	U.S.	Patient renal transplants - 2007 to 2017 WES completed after transplant, implies 2018	NIH, Yale Center for Mendelian Genomics	272 probands met inclusion criteria, 41 excluded for care at different hospital, 18 excluded for inability to provide consent, 2 excluded for death, 23 excluded for secondary renal disease instead of primary, 45 declined, and	Patients with chronic kidney disease that developed disease before 25 years of age and were transplanted between 2007 and 2017 at Boston Children's Hospital 55/104 (52.9%) diagnosed with congenital anomalies of the kidney and urinary tract, 21/104 (20.2%) with steroid-refractory nephrotic syndrome, 7/107 (6.8%) with chronic glomerulonephritis, 9/104 (8.6%) with renal cystic ciliopathy, and 3/104 (2.9%) with nephrolithiasis, 9/104 (8.6%) cause of renal disease unknown	Singleton (not explicitly stated) Targeted exome (396 CKD genes) variant filtering using population databases (Exome Sequencing Project, ExAC, gnomAD, 1KG) to include only MAF < 0.01 except for NPHS2 R229Q allele. Excluded synonymous and intronic variants outside splice site regions. Six/396 genes did not achieve 30X coverage Ranked variants based on likelihood of causing disease using conservation metrics and pathogenicity prediction (PolyPhen2, SIFT, MutationTaster), then subjected to literature review, clinician/scientist review, and ACMG criteria to report pathogenic or likely pathogenic for molecular diagnosis. Sanger sequencing confirmed.

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
					39 not contacted 104 enrolled and analyzed	male = 62/104 (59.6%) race/ethnicity = NR age = NR 9/104 (8.7%) from consanguineous families	WES not used to identify novel CNVs, but if SNP array showed pathogenic CNV and WES negative for SNV/indels, performed CNV analysis on WES data using CoNIFER diagnostic yield: 34/104 (32.7%) had monogenic cause of CKD. Among patients with history of consanguinity, diagnostic yield was 67%, extra-renal manifestations = 45%, and patients with a positive family history = 48% Comparator strategy: Not explicitly done, not compared systematically, 6 patients out of 34 with WES diagnostics had previously obtained molecular diagnosis from clinical genetic testing (6/34=17.6%*) and 5 families had molecular diagnosis from targeted gene sequencing (5/34=14.7%*) 23/34 (82.4%*) individuals who underwent WES received diagnosis for first time due to WES However, it was not stated how many of 104 underwent previous diagnostic odysseys in search of a molecular diagnosis and with what tests
Matias (2019)[49]	Controlled (two or more groups) observational cohort	U.S.	2013-2015	NR	102 eligible, 78 analyzed	Children referred for WES at a tertiary children's hospital who received either positive (n=37) or negative (n=41) results with phenotypes including 38% (30)	Singleton = 3/78 (4%), doubleton = 3/78 (4%), trio = 61/78 (79%), and more than trio = 10/78 (13%) Not explicitly stated targeted vs whole exome analysis

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						neurologic, 24% (19) immune, and 19% (15) neurologic + multiple congenital anomalies/DF, mean age: 7.0 years (range 2.8 to 14.3 years), 55% (43) female, 87% (67) White	NR on method reporting Diagnostic yield = 37/78 (47.4%*) No comparator analysis
McConkie-Rosell (2018)[69]	Single-arm observational cohort	U.S.	NR	NIH	65 parents of 39 affected children probands were offered the study; 50 parents of 31 probands were enrolled	Data for the study were collected prospectively at the clinical site. Parents completed study measures on the first day of the Undiagnosed Diseases Network evaluation. Female = 60% (30), ages of 50 parents: male ages 25 - 39 = 9; 40-54 =11, female ages 25-39 = 17; 40-54 = 13, race/Ethnicity of parents (self-reported), Caucasian = 86%, age of the 31 children: mean +/- SD and minimum-maximum in years): 7.83 +/- 4.96 (1-18)	NR
Meng (2017)[40]	Single-arm observational cohort	U.S.	2011-2017	March of Dimes, NIH	278	Infants less than 100 days old at time of testing at a large academic children's hospital referred for exome sequencing for a range of medical concerns, median (SEM) patient age at sample submission: 28.5 days (1.7), 45.7% female	Proband WES, n=176 (63%); Trio WES, n=39 (14%), Critical Trio WES, n=63 (22%) Whole exome analysis Variants interpreted according to ACMG guidelines and Baylor Genetics guidelines Diagnostic yield, 102 of 278 (36.7%). Critical exome sequencing, 50.8% (p=0.01). Dual diagnoses, 3.9%. Diagnosis not recognized on initial examination: 4 of 102. No comparator-testing pathways.
Monies (2017)[61]	Single-arm observational cohort	Saudi Arabia	2016	The laboratory (Medical Diagnostic	First 1013 families referred to	Sole major referral NGS laboratory in Saudi Arabia	92.5%* had singleton WES, 4.9%* had trio, 2.6%* had duo. Whole exome analysis performed

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
				Laboratory) is revenue-generating for KFSHRC.	NGS diagnostics at this laboratory 347 families received WES in at least proband, including 15 families after negative NGS panel	Families referred to reference lab for NGS-based assays in Saudi Arabia for tests including multigene panels and WES. No particular selection criteria applied. 7 "clinically-themed" multigene panels offered, others got WES. WES n=347 families: 321 Solo (proband) only tested, parents included in trio tests (n=17). Couples with history of prior affected children offered duo tests if no affected children available for testing. Duo testing also requested in some cases of two affected siblings (total duo = 9). However, duo testing may also include parents who have lost children. Solo WES = 321/347 (92.5%*) Trio WES = 17/347 (4.9%*) Duo WES = 9/347 (2.6%*) Female = 150/347 (43.2%*) Consanguinity = 136/347 (39.2%*) mean age = 8.9*, sd = 9.6*	Used variant calling/annotation pipeline based on BWA, Samtools, GATK, and ANNOVAR using public domain data from ANNOVAR and in-house databases for Saudi disease variants. Reported variants based on previously reported disease-causing variants relevant to patient's phenotype & checked for pathogenicity (likely causal). If none identified, searched for other variants, including evaluating novel variants for pathogenicity if loss-of-function; = likely causal. Missense and in-frame indels usually reported as VOUS If only one heterozygous candidate variant identified, reported as ambiguous If no candidate variants in no disease genes, considered variants in genes not previously linked to human diseases with suspicions, but considered ambiguous Positive results = "pathogenic or likely pathogenic variants in known disease genes that explain the phenotype in the correct zygosity" Variable Sanger validation Diagnostic yield: 43% of those tested using WES 666 families subjected to one of 7 offered panel testing with 27% positive result (referring physician decision for panel vs WES)
Monroe (2016)[80]	Single-arm observational cohort	Netherlands	2011	The Wellcome Trust	17	17 patients seen in a tertiary specialty clinic that specializes in diagnosing children with	Trio WES, variants validated with Sanger Sequencing Diagnostic yield: 5 (29.4%)

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						intellectual disability. The patients met the following criteria: patient was born to healthy, unaffected parents; the parents were nonconsanguineous; both parents could be contacted and were able to give consent; and the patient was undiagnosed at the time of the study. Patients first visited the clinic at a median of 1.1 years and an average of 3.0 years., range from 0 to 11.8 years;% female = 59%	The comparator strategy included traditional diagnostic evaluation, which included labs, imaging, and other genetic tests other than WES
Muramatsu (2017)[70]	Single-arm observational cohort	Japan	2011-2013	Ministry of Health, Labor and Welfare of Japan	371 IBMFS patients: 121 targeted sequencing, 250 (WES)	371 patients with Inherited Bone Marrow Failure Syndrome (IBMFS). Targeted sequencing: 121, WES: 250 WES patients included patients diagnosed with Fanconi Anemia (FA) (73); diamond blackfan anemia (61); Hemolytic Anemia (44); dyskeratosis congenita (29); congenital dyserythropoietic anemia (12); congenital sideroblastic anemia (9); congenital amegaryocytic thrombocytopenia (7); hereditary hemophagocytic lymphohistiocystosis (6); severe congenital neutropenia (3); unclassified/other (6) . Most of the patients 182 (73%) underwent various genetic tests with	Singleton WES Whole exome analysis Variant allele frequency >0.20 used as cut-off value for variant detection. VAF >0.01 in ESP6500 or 1000 genomes considered common polymorphisms. Diagnostic yield of WES: 68 of 250 (27%) Diagnostic yield of targeted sequencing (184 genes): 53 of 121 (44%)

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						negative results before WES analysis	
Niguidula (2018)[39]	Single-arm observational cohort	U.S.	2015-2016	Ambry Genetics	62 health care providers who returned surveys regarding patients referred for WES	Survey of health care providers receiving patient WES report from commercial laboratory, 2,876 surveys sent and 2.2% (62) returned, patient phenotypes included 33.9% (21) non-specific and complex neurodevelopmental disorder, 8.1% (5) multiple congenital anomalies, 6.5% (4) cancer susceptibility, 4..8% (3) movement disorders, and 4.8% (3) cardiovascular symptoms, patients median age 5.5 years, 28 (45.2%) female	WES testing not described, findings in clinically characterized genes were classified in four categories: 1) positive, relevant alteration detected; 2) likely positive, relevant alteration detected; 3) uncertain, alterations of uncertain clinical relevance detected; 4) negative, no relevant alterations detected Of survey respondents, 37.1% were from providers that had reports with a positive or likely positive pathogenic alteration
Nolan (2016)[24]	Single-arm observational cohort	U.S.	2011-2015	no specific grant or funding source	135: WES recommended, 53: WES done, 50: Had WES results at time of analysis	Patients in an academic pediatric neurology clinic who were referred for diagnostic WES testing, 88% with neurodevelopmental delay, mean age: 7 years, 5 months, 46% female, 85% White	Singleton and/or Trio plus affected sibs WES with whole exome analysis. Analysis performed by two outside laboratories. Variants called as pathogenic or likely pathogenic were considered diagnostic. Diagnostic yield: 24 (48%)
Palmer (2018)[27]	Single-arm observational cohort	Australia	NR	SEALS Genetics Laboratory, Garvan Institute, Kinghorn Foundation, National Health and Medical Research Council	48 eligible; 32 enrolled, 30 analyzed	Children with infantile-onset epileptic encephalopathy, who remained undiagnosed after “first-tier” testing at a children's hospital, mean age: 46.6 months, 47% (15) female. Criteria for infantile-onset epileptic encephalopathy based on ILAE definition (Berg et al. 2010)	First-tier testing comprised pediatric neurology and clinical genetics consultation, brain MRI, routine EEG, urine, blood, and cerebrospinal fluid studies (basic biochemistry, blood gas, TORCH screen, urine metabolic screen, B12, folate, copper, ceruloplasmin, selenium, zinc, plasma amino acids, AASA and P6C, lactate, glucose,), CMA, and single gene testing if a single monogenic condition was suggested by the patient's phenotype.

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							Second-tier testing comprised multiple other blood, urine and CSF tests, screening for common expansions in ARX, common mitochondrial deletions and duplications, methylation, sequencing of specific genes, next-generation sequencing panel for EE, PET scan, MRS scan, CT scan, Tc99m radionucleotide scan, trio WES conducted using in-house platform. Studies compared standard diagnostic pathway (first and second tier testing without WES) to exome diagnostic pathway (first and second tier testing + trio WES +Sanger confirmation). Diagnostic yield: Standard path: 6.3% (2 of 32 tested) Exome path: 53% (16 of 30 tested)
Perucca (2017)[34]	Single-arm observational cohort	Australia	2014	National Health and Medical Research Council of Australia	42 eligible; 40 consented and enrolled	Consecutive patients >4 weeks old, diagnosis of focal epilepsy, no epileptogenic lesion on MRI, and ≥1 1st or 2nd degree relative with history of febrile seizures or any epilepsy type. Exclusions: Previous genetic testing except chromosomal microarray, severe intellectual disability, benign epilepsy with centro-temporal spikes, and benign occipital epilepsy. 24/40 (60%) diagnosed with temporal lobe epilepsy, 6/40 (15%) with frontal lobe epilepsy,	singleton Initial analysis of 27 focal epilepsy genes and 35 nonfocal epilepsy genes, then included 2 additional focal epilepsy genes later discovered (1 likely pathogenic variant detected) Identified variants reviewed by expert panel, population databases, online tools (e.g., SIFT, PolyPhen). Used ACMG classifications as pathogenic or likely pathogenic. Validated by Sanger sequencing and family segregation when possible 5/40 (12.5%) had pathogenic or likely pathogenic; 1 detected after re-analysis NA comparator pathways

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						1/40 (2.5%) with parietal lobe epilepsy, and 1/40 (2.5%) with occipital lobe epilepsy. Undefined localization in 8/40 (20%) of patients female: 16/40 (40%) age: median 32.5, range 2-74 80% had single first or second degree affected relative	
Posey (2015)[63]	Single-arm observational cohort	U.S.	2011-2014	NIH	4476 individuals with diagnostic singleton WES; 505 adults over age 18; 486 excluding related individuals and those referred without clinical indication. 272 included in previous reports	Unrelated adults with varied diagnosis referred for WES for clinical diagnosis age: 18-30, 255/486 (52.5%); >70 12/486 (2.5%) Mean/median age NR Females = 247/486 (50.8%*) Mixed European Caucasian descent = 71.7% African American = 3.6% Hispanic = 12.6% Mixed ethnicity = 6.0% Unknown ethnicity = 72/486* (14.8%) Parental consanguinity = 22/486 (4.5%)	Singleton WES Parental samples used for Sanger confirmation) Whole exome analysis (No specified conditions or genes, report of secondary findings) Coding SNP array for QC Mitochondrial sequencing Variant classification consistent with ACMG guidelines Diagnosis required pathogenic or likely pathogenic variant in Mendelian disease genes consistent with phenotype and inheritance pattern observed clinically. Diagnostic yield: 82*/486 (16.9%*). Excludes 3 diagnoses from mitochondrial sequencing. No comparator pathways
Ream (2014)[58]	Single-arm observational cohort	U.S.	NR	NR	37 new patients (19 boys) with DRE of which	New patients at tertiary care center pediatric epilepsy clinic diagnosed with pediatric drug resistance epilepsy in a 12-month	Singleton vs. trio = NR; Targeted vs whole exome analysis =NR; WES analysis and interpretation done by clinical laboratory.

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
					25 underwent genetic testing. 4 established patients with WES. Total WES: 6, 2 new and 4 established.	period and patients initially seen prior to the availability of WES. Data collection: retrospective chart review. Patients underwent one of the following genetic tests: karyotype, chromosomal microarray, gene sequencing of specific single genes, gene sequencing using gene sequencing panels, and/or WES. New patients 12 (48%)* were male. Age at initial evaluation was 6.8 (+/- 6.8, med: 5) years; Age at epilepsy onset (2.5 (+/- 3..1, med: 0.92) years. Diagnoses: developmental delay 96% (24); history of regression 20% (5); seizure frequency: daily 56% (14) and less than daily 44% (11); epileptic encephalopathy 56% (14) and seizure types: focal= 32% (8) and generalized = 68% (17). Established patients: 2 males mean age at epilepsy onset was 1.5 years, 2 had MRI abnormalities, 3 had daily seizures, 2 had a history of developmental regression, all had developmental delay, 3 had generalized seizures	Diagnostic yield: any genetic testing: 34.5%; karyotype: 1/7, 14.3%; microarray: 2/12 (16.7%); single gene sequencing: 2/13 (15.4%); epilepsy gene panel: 6/13 (46.2%); WES: 1/6, 16.7%
Retterer (2016)[64]	Single-arm observational cohort	U.S.	2012-2014	GeneDx, Takeda, Pathway Genomics,	3,040 analyzed	Consecutive WES cases including 17.5% (532) proband-only cases, 6.6% (200) with one	Mix of singleton and 2 other family members (trio if available, or up to two additional affected family members if

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
				BioReference Laboratories		additional family member, 68.4% (2,081) with two additional family members, and 7.5% (227) with three or more additional family members referred to a commercial laboratory with a wide variety of primary phenotypes including 35.6% (1,082) abnormality of the nervous system, 24.0% (729) multiple congenital anomalies, 5.7% (173) abnormality of the mitochondrion, 5.1% (154) seizures, and 4.3% (190) autisms spectrum disorders, mean proband age was 11.4 years (standard deviation = 13.2 years)	available) 532/3040 (17.5%) proband only 200/3040 (6.6%) proband + 1 additional family member 2081/3040 (68.4%) proband + two additional family members (most often trio but not necessarily) 227/3040 (7.5%) proband + 3 or more additional family members Whole exome analysis ACMG interpretation guidelines, definitive result = pathogenic or likely pathogenic in known disease gene associated with reported phenotype. Identified uniparental disomy and regions of homozygosity from WES data using custom Perl script for 80% homozygosity over 8Mb minimum region size. Called CNV using WES data. Confirmed UPD and CNV results by appropriate measures Did mitochondrial genome sequencing by request (1221/3040 (40%)) Novel candidate gene is a possible result Diagnostic yield = 28.8% 23.6% in proband-only cases 31.0% in cases with three family members analyzed 55% (n=11) in hearing disorders 47% (n=60) in vision disorders Definitive result = 23.6% in proband-only group Definitive result = 31.0% when 3 members of family had WES

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							Definitive result = 20.8% when proband age ≤ 30 years Definitive result = 32.0% when proband age ≤ 12 months Candidate gene result as only finding in 7.6%
Roche (2019)[76]	Single-arm observational cohort	U.S.	2013-2013	NIH	622 participants at enrollment, 335 eligible; 171 control group, 155 decision group	1:1 ratio randomized-controlled trial. Control group did not receive education about nonmedically actionable secondary findings (NMASF) and was not eligible to request NMASF. Decision group received education about NMASF. Study focuses on participants randomized to the decision group. 9 participants in decision group failed to attend the disclosure visit and were excluded leaving 155 participants. The sample was moderately ethnically diverse (21% Hispanic and/or nonwhite). Approximately 75% were female and the average participant age was 47 years. Participants were eligible to request up to six categories of NMASF (A) single-nucleotide polymorphisms for risk assessment of common diseases. (B) pharmacogenomic variants, (C) heterozygous variants indicating carrier status	WES procedures/information not reported in this paper. NMASF reporting procedures: A or B, telephone; C, D, or E in-person visit; F, in-person visits

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						(D) specific alleles of the APOE gene associated with risks for Alzheimer disease, (E) variants associated with rare Mendelian diseases for which no effective pre-symptomatic interventions exist, and (F) variants associated with rare, highly penetrant, progressive, neurodegenerative Mendelian diseases that cannot be prevented or effectively treated Participants could request some types of NMASF without having to request them all	
Rosell (2016)[62]	Qualitative research design	U.S.	NR	NR	24 parents contacted and invited to participate. Each set of parents elected to only have one parent participate. 19 parents were consented and interviewed.	Interviews with parents whose child had undergone WES and had results returned in Duke Genome sequencing clinic in accordance with protocol including evaluation by medical geneticists and pre- and post-WES counseling. 16/19 (84.2%) female parents interviewed 19/19 (100%) Caucasian 19/19 (100%) non-Hispanic age categories 31-35 years: 5/19 (26.3%) 36-40 years: 2/19 (10.5%) 41-45 years: 7/19 (36.8%) 46-50 years: 3/19 (15.8%) 51-55 years: 2/19 (10.5%)	Trio WES Unclear if targeted or whole exome analysis, but suspect whole exome based on reporting of incidental findings NR reporting variants in analysis Diagnostic categories were: definite, likely, partial, possible, and no diagnosis Diagnostic yield: Definite = 2/19 (10.5%) Likely = 6/19 (31.6%) Partial (definite or likely) = 3/19 (15.8%) Possible with VUS of interest = 3/19 (15.8%) No diagnosis = 5/19 (26.3%) No comparator testing

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
Sawyer (2016)[55]	Single-arm observational cohort	Canada	NR	Canadian Institute of Health Research	362 families were submitted to project for WES, 105 enrolled	A retrospective study of patients enrolled in the FORGE project (Finding of Rare Disease GEnes) were ascertained by physicians, mainly geneticists from 21 participating academic centers across the country. Diseases studied included neurodevelopmental phenotypes and dysmorphic syndromes. Patients underwent WES at one of three centralized Genome Canada Science and Technology Innovative Centers. The success rate ranged from 12% (immunological disorders) to 44% (ciliopathies). These patients had already received standard of care genetic evaluation and diagnostic testing. Patients were accepted with either a recognized clinical diagnosis (Dubowitz syndrome, etc.) or with a description of their clinical presentation (microcephaly, short stature, etc.)	Singleton Whole exome analysis Variant filtering using internal exome database for MAF < 1% diagnosis required variant in gene previously known to cause disease Diagnostic yield: 105/362 (29%) neurodevelopmental phenotypes: 31/98 (31.6%) dysmorphic syndromes: 18/80 (22.5%) ocular: 11/40 (27.5% metabolic: 12/31 (38.7%) neuromuscular: 7/30 (23.3%) ciliopathy: 12/27 (44.4%) congenital malformation syndromes: 4/19 (21.1%) immunological: 2/17 (11.8%) other: 8/20 (40.0%) Comparator: NA
Schofield (2017)[26]	Controlled (two or more groups) observational cohort	Australia	1998-2013	National Health and Medical Research Council of Australia and European Union Collaborative Research Grant Scheme	58 enrolled, 56 analyzed	Patients seen over 15 years at a publicly funded tertiary neuromuscular center and identified through clinical records and Muscle research Biospecimen Bank. Phenotype: 38 (67.9%) were diagnosed with congenital muscular dystrophies (CMD) and 18 (32.1%) were diagnosed with nemaline myopathy (NM).	Traditional diagnostic pathway included creatine kinase, nerve conduction studies, MRI imaging of brain/muscles, metabolic investigations, genetic investigations as first-tier tests, with muscle biopsy, protein-based studies of muscle biopsy specimens, candidate gene sequencing and CMA as second tier tests. Neuromuscular gene panel included traditional pathway followed by

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						Female: 26(46.4%). Age at onset: Birth: 34 (60.7%) 1st year: 11 (19.6%) 2nd year: 8 (14.3%) >2nd year = 3 (5.4%). Congenital Muscular Dystrophy patients were included if their presentation was consistent with CMD elevated CK level >200 and muscle biopsy showed dystrophic changes or nonspecific myopathic findings. Nemaline myopathy patients were included if their presentation was consistent with a congenital onset or childhood-onset myopathy and muscle biopsy showed nemaline rods	commercially available panel of 464 genes among those who remained undiagnosed; this pathway was used prior to muscle biopsy in the traditional pathway WES pathway included traditional testing followed by singleton WES and then trio WES if remained undiagnosed; type of analysis (whole exome vs. targeted) not explicitly stated, but likely whole exome analysis. This pathway was used prior to muscle biopsy in the traditional pathway. Diagnostic yield: Traditional pathway: 26 (46%*) Neuromuscular gene panel: pathway 42/56 (75%*) WES pathway: 44/56 (78.6%*)
Shamriz (2016)[53]	Case series	Israel	NR	Hebrew University and Hadassah Medical Center	6 patients included	WES was utilized in six patients with malignant infantile osteopetrosis (MIOP) and identified mutations in four MIOP-related genes. Of six patients included, five were born to consanguineous families. In four children, the initial clinical presentation included blindness. Median and mean ages at disease onset were 1 and 13.4 (range 0.5 - 72) months, respectively. Family history of osteopetrosis was recorded in four out of six children. 4 (67%)* male patients; 2 (33%)* female	Singleton WES Not explicit about targeted vs whole exome, suspect whole exome analysis based on "the choice of using WES rather than deep sequencing of an osteopetrosis-specific panel..." Excluded heterozygous variants in patients with consanguinity. Excluded variants with MAF >0.05 in ExAC or >1% in Hadassah inhouse database. Excluded if predicted benign by Mutation Taster. Diagnostic yield: 6/6 (100%*)

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						patients. In cases where more than one child from the same family was affected, WES was performed on one of the children and the genetic findings were confirmed by Sanger sequencing in the siblings and other family members	
Shashi (2015)[74]	Single-arm observational cohort	U.S.	2011 - 2013	NR	188 patients eligible for chart review, 93 (49.5%) enrolled and underwent WES during period of review,	93 patients who underwent clinical WES Of participants enrolled, 53 (57%) were male, 66.7% Caucasians, 9.7% African Americans, 11.8% Hispanic, 5.4% Asian and 6.5% Others. The mean age was 7.59 +_8.08 years, ranging from newborn to 48 years. The majority of patients were younger than 18 years of age (n=85, 91.4%)	Four clinical laboratories performed the WES with 35 (37.6%), 49 (52.6%,) 6 (6.4%) and 3 (3.2%), respectively. Trio WES in 68 of 93, Proband and mother in 19 of 93, proband only in 6. Whole exome analysis; clinical laboratory's interpretation of variants. Diagnostic yield, laboratory interpretation: 24/93 (25.8%) Diagnostic yield, lab + clinician: 22/93 (23.6%)
Skinner (2018)[59]	Qualitative research design	U.S.	NR	NIH	32	Adults (n=21) and children (n=11) with uncertain exome sequencing results at an academic tertiary health care center. Study population included: 15.6% (5)* with cancer, 6.3% (2)* cardiogenetic disease, 37.5% (12)* neuromuscular or neurocognitive conditions, 9.4% (3)* ophthalmological disorders 31.3% (10)* intellectual disability and/or congenital malformations, adult mean age: 50 years (range: 19 to 84 years), child mean age: 6.5 years (range: 1 to 16 years),	Exome sequencing. Singleton versus trios, NR. Targeted vs. whole exome, NR. Results classified as diagnostic, possibly diagnostic/uncertain, or negative determined by panel of clinical experts

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						68.8% (22)* female, 84.4% (27)* White	
Snoeijen-Schouwenaars (2019)[32]	Single-arm observational cohort	Netherlands	2016 to NR	NR	100 enrolled and analyzed	Diagnostic WES performed in all patients who were undiagnosed by previous targeted DNA diagnostic tests and clinical indication for WES. Patients referred to multidisciplinary outpatient clinic at Academic Center for Epileptology at Kempenhaeghe, Heeze, the Netherlands or Maastricht University Medical Center, Maastricht, the Netherlands 61/100 (61%*) with neuropsychiatric symptoms, 51/100 (51%*) with no family history of ID or epilepsy, 25/100 (25%*) with dysmorphic features, 32/86 (37.2%*) with abnormal brain MRI (denominator=MRI performed) Female = 45/100 (45%*) 98/100 Caucasian (98%*), 2/100 (2*) African mean age = 24.1 years, SD = 16.2, range = 2.8-67.6 consanguinity NR	Preferentially trio (66/100 (66%*), 34/100 (34%) was singleton due to either consent or DNA availability lacking for both parents. Segregation analysis done when possible) Targeted (known epilepsy and/or ID genes) first, and those with negative targeted underwent whole exome interrogation Sanger confirmation of putative causal variants. Variants classified from Dutch guidelines for pathogenicity evaluation and interpreted according to ACMG guidelines 25/100 (25%*) patients had pathogenic/likely pathogenic by ACMG criteria from WES. 6/49 (12.2%*) from Epilepsy gene panel, 2/17 (11.8%*) from intellectual disability panel, 10/34 (29.4%*) from combined epilepsy/intellectual disability panel. 56/100 proceeded to whole exome analysis (26 not consented for this), and 7/56 (12.5%*) undiagnosed by panel testing who went on to whole exome testing were diagnosed by whole exome Previous diagnostic investigations: 4/100 (4%*) none, 9/100 (9%*) specific DNA tests, 32/100 (32%*) genome-wide

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
							chromosomal analysis, 27/100 (27%*) had specific DNA tests + genome-wide chromosomal analysis, 4/100 (4&*) had specific DNA + metabolic screening, 2/100 (2%*) had chromosomal + metabolic screening, and 22/100 (22%*) had DNA + chromosomal + metabolic screening
Soden (2014)[25]	Single-arm observational cohort	U.S.	NR	NIH, Marion Merrill Dow Foundation, Children's Mercy Kansas City, Patton Trust, William T. Kemper Foundation, Pat and Gil Clements Foundation, Claire Giannini Foundation, Black and Veatch	119 children (from 100 families)	85 families followed in ambulatory clinics at a children's hospital with children with neurodevelopmental disorders (global developmental delay, intellectual disability, encephalopathy, muscular weakness, failure to thrive, microcephaly, developmental regression). Mean age was about 7 years at enrollment	Trio WES; variant classification as defined by ACMG. Diagnostic yield: 38.8% (33 of 85 families; data not reported by participant)
Srivastava (2014)[57]	Single-arm observational cohort	U.S.	2011-2014	NR	78 enrolled	Retrospective cohort study of patients with neurodevelopmental disabilities and unrevealing workup prior to WES. Mean patient age 8.6 +-5.8 years (range =1.6 - 26.3 years); 53% (41) were male. Family history, 14% (11) had >/= 1 affected sibling with the same phenotype, 3% (2) had an affected parent, and 12% (9) were born to consanguineous parents..	Singleton vs. trio NR Whole exome analysis Diagnostic yield was 41% (32 of 78). WES analysis was performed by outside diagnostic laboratories No comparator pathways
Stark (2016, 2017, 2019)[13-16]	Single-arm observational cohort	Australia	2014-2016	Melbourne Genomics Health Alliance, State	89 eligible; 80 enrolled	Children age 0 to 2 years with suspected monogenic disorders (multiple congenital	Singleton WES as a first-tier evaluation with pathogenic and likely pathogenic variants confirmed by Sanger

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
				Government of Victoria, Bioplatforms Australia		abnormalities, dysmorphic features, or others highly suggestive) prospectively recruited from a single tertiary pediatric center. Excluded if had specific clinical presentations that were genetically clear (e.g., achondroplasia) unless test for that disorder was not commercially available. Excluded if undergone previous sequencing tests or novel phenotypes. All participants had undergone CMA with negative results. Female 30 (38%) Age at enrollment 0-6 months: 37 (46z%) 6-12 months: 25 (31%) 12-36 months: 18 (23%)	sequencing. in parallel with standard non-WES investigations. Analysis was limited to genes known to cause monogenic disorders (i.e. the "Mendeliome" panel). Only variants relevant to phenotype were assessed for pathogenicity. Standard clinical care: basic investigations (biochemical, imaging, neurophysiological studies, subspecialist assessments); complex investigations (biochemical testing in specialized laboratories, invasive tissue biopsies), commercial single-gene or multigene panel sequencing. Sanger sequencing of single genes, methylation studies, mitochondrial mutation panels. For participants without a diagnosis, sequences were reanalyzed every 6 months against the updated bioinformatics database for up to 18 months. 43 (53.8%) diagnosed after 1 round of WES testing; 47(58.8%) diagnosed after reanalysis by 18 months. [1 participant diagnosed by standard pathway and not WES] Counterfactual models for cost comparison: 1) WES as last resort, 2) WES replacing some tests, 3) WES replacing most tests
Stark (2018)[22]	Controlled (two or more groups) observational cohort	Australia	2016-2017	Melbourne Genomics Health Alliance and the State Government of Victoria,	40 in rapid WES cohort; 40 in standard WES cohort and in historical	Acutely ill infants and children with suspected monogenic disorders from two tertiary pediatric hospitals; participants received either rapid singleton WES (n=40) or standard	Singleton WES not explicitly stated as targeted vs whole exome analysis, but given diversity of phenotypes likely whole exome analysis, with variants in customized gene list prioritized for each patient; only variants relevant to a

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
				Bioplatforms Australia	standard WES cohort.	turnaround WES (n=80). Female Rapid WES: 45% Standard WES: 37.5% Median (IQR) age at enrollment Rapid WES: 28 days (12 to 204) Standard WES: 271 days (77 to 409) Principle phenotypic feature: Congenital abnormalities and dysmorphic features Rapid WES: 22%43% (17) Standard WES: 54% Neurometabolic disorder Rapid WES: 43% Standard WES: 24% Other Rapid WES: 35% Standard WES: 22%	particular phenotype assessed with regard to pathogenicity. Variants classified according to ACMG and reviewed by expert panel. Diagnostic yield of rapid WES: 21 of 40 (53%) Diagnostic yield of standard WES: 25 of 40 (58%) Historical diagnostic yield of standard WES cohort prior to WES testing: 7 of 40 (17.5%)
Strauss (2017)[60]	Single-arm observational cohort	U.S.	1998-2015	Charitable contributions from Old Order Amish and Mennonite Communities of Pennsylvania and surrounding states Howard Hughes Medical Institute	79 probands identified 7 diagnosed by molecular karyotype 72 analyzed using WES	Clinic for Special Children, medical home for children of Old Order Amish and Mennonite populations. Presented for evaluation between September 1998 and 2015 with clinical signs of underlying genetic disorder and remained undiagnosed following biochemical and genetic investigations. All except 3 probands were from Old Order Amish or Mennonite founder populations. 64% probands had central nervous system disease	68/79 (86%) had CMA array to detect CMVs. Those with uninformative CMA went on to receive WES. WES performed in eligible probands and all available members of nuclear family and relevant additional family members. Whole exome analysis. Called variants filtered to MAF <= 0.01 within public, RGC internal, and CSC-population specific allele frequency databases, then annotated using publicly available annotation algorithms (e.g., SIFT). Primary analysis performed using RGC's trio-based pipeline and then refined with segregation analysis incorporating additional family members who

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						7% had auditory or visual impairment 6% had neuromuscular weakness 5% had growth delay 4% had hepatopathy 4% had skeletal dysplasia of 52 probands with neurological disease, 85% had developmental delay (diverse phenotypes), 73% global developmental delay/intellectual disability, 60% motor disability with or without hypotonia, 44% executive dysfunction, 44% epilepsy, 27% autism, 17% extrapyramidal movement disorders, 15% affective illness. Of probands with developmental disability, 23% had microcephaly, 12% macrocephaly, and/or 13% cortical malformation. female: 36/79 (45.6%*) probands identified age: mean 6.9 years, +/- 9.4, range newborn-49.8 years (probands identified)	underwent WES. ACMG guidelines used for pathogenicity determinations. Pathogenic and likely pathogenic used. Validated in CLIA lab prior to reporting. 37/72 (51%) probands subjected to WES were diagnosed using WES. 5/72 (7%) received negative WES that was considered to exclude monogenic disease. Comparator: Uses previously published costs of testing strategies to calculate cost per molecular diagnosis of "standard approach" vs theoretical genomic evaluation
Tammimies (2015)[72]	Single-arm observational cohort	Canada	2008- 2013	Autism Speak Canada; Autism Speaks; NeuroDevNet; Canadian Institute for Advanced	258 enrolled, 95 analyzed further after quality control	The study sample included children who were consecutively referred from both of the developmental pediatric clinics in the province. that perform multidisciplinary team	Trio Not explicit about targeted vs whole exome, incidental findings therefore whole exome analysis probable Diagnostic yield: 8/95 (9.4%) Comparator: chromosomal microarray

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
				Research; Univ of Toronto; Genome Canada and Ontario Genomics Institute; Canadian Institute of Health Research; Ontario Brain Institute; Hospital for Sick Children; Janeway Research Foundation		assessments for Autism Spectrum disorders (ASD). Each assessment was led by a developmental pediatrician. Age at diagnosis = 4.5 (mean 2.8); boys = 216 (84%)* girls = 42 (16%)* Autism Spectrum Disorder subtypes: Asperger = 27 (10.5%); Autistic disorder = 143 (55.4%); Pervasive developmental disorder, Not otherwise specified = 88 (34.1%). 95 probands were analyzed further after quality control of WES data. 8 (8.9%) children with 9 mutations received and ASD molecular diagnosis	24/258 (9.3%) received molecular diagnosis from chromosomal microarray. 15/95 who underwent both CMA and WES (15.8%) received diagnosis. 2/95 who underwent both CMA and WES received molecular diagnosis from both tests
Tan (2017)[19]	Single-arm observational cohort	Australia	2015-2015	Melbourne Genomics Health Alliance, State Government of Victoria, Australian Genome Research Facility sponsored by Bioplatforms Australia	61 assessed for eligibility 3 excluded for novel phenotype 7 enrolled in another genomic project 5 declined or withdrew consent 2 diagnosed by microarray	Tertiary health care center Prospective recruitment of ambulatory children aged 2-18 years suspected of having monogenic condition Recruited from outpatient clinics of Victorian Clinical Genetics Services at Royal Children's Hospital, Melbourne, Australia May 1 to November 30, 2015 Panel of experts determined eligibility Excluded those whose diagnosis usually made by clinical assessment (e.g., achondroplasia or neurofibromatosis type 1)	Singleton WES Targeted; analyzed only variants in HUGO Gene Nomenclature Committee genes associated with mendelian disease before the end of 2015 (3203 genes) Variants assessed using Melbourne Genomics variant curation database, a modification of Leiden Open Variation Database, prioritized based on phenotype-driven gene lists for each participants (Gene Prioritization Index) and predicted effect (Variant Prioritization Index) Only assessed pathogenicity of variants relevant to participant's phenotype based

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
					44 enrolled and analyzed	All had previous nondiagnostic SNP microarray but no prior single gene or panel sequencing tests. Methylation or triplet repeat analysis allowed. Excluded children deemed to have novel phenotypes Primary phenotype among those enrolled and analyzed dysmorphic with multiple congenital anomalies = 21/44 (47.7%*) neurometabolic = 8/44 (18.2%*) intellectual disability without congenital anomalies = 7/44 (15.9%*) skeletal dysplasia = 4/44 (9.1%*) dermatological = 4/44 (9.1%*) female = 23/44 (52%) age at enrollment 2-10 years = 30/44 (68%) 10-18 years = 14/44 (32%)	on ACMG standards for interpretation. Reviewed at multidisciplinary meeting. Parents underwent Sanger sequencing to confirm phase and segregation Reanalyzed unsolved cases (unsure when) Counterfactual comparator testing scenarios: 1) "standard diagnostic pathway" without WES, includes microarray 2) "standard diagnostic pathway" with WES as final test 3) WES at first genetics appointment 4) WES at initial tertiary presentation 23/44 (52%) received molecular diagnosis from WES
Tarailo-Graovac (2016)[44]	Single-arm observational cohort	Canada	2012-2015	BC Children's Hospital Foundation, BC Clinical Genomics Network, the Rare Diseases Foundation, Canadian Institutes of Health Research, British Heart Foundation, National Institute	47 eligible, 41 analyzed	Consecutively enrolled patients with intellectual developmental disorder and unexplained metabolic phenotypes undergoing WES and deep clinical phenotyping at an academic medical center, median age: 5.9 years (range, 8 months-31 years), 37% (15) female, 63% (26) white	Trio + (WES done on proband, both parents, and affected siblings if available) Targeted vs whole exome analysis not explicitly stated. They allowed for novel candidate genes, so I would guess whole exome analysis Used ACMG guidelines to classify pathogenicity of variants. Novel candidate genes allowed. Diagnostic yield: 28/41 probands (68%) with variants either pathogenic or

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
				of General Medical Sciences, Leenaards Foundation, Rare Disease Initiative Zurich			probably pathogenic. Includes 2 genes newly implicated in disease No comparator testing. Patients undergone biochemical testing from published diagnostic algorithm for treatable intellectual developmental disorder and clinical genetic testing but remained undiagnosed
Tsiplova (2017)[79]	Modeling Study	Canada	2013-2014	Genome Canada and Ontario Genomics Institute, Centre for Applied Genomics and Genome Diagnostics at the Hospital for Sick Children	NA, synthetic population for cost modeling	Modeling study using a bottoms up micro-costing approach from an institutional perspective based on the laboratory practices at the Hospital for Sick Children, Canada. The target population approach was children in the referral and diagnostic pathway for ASD	Model assumptions: Singleton WES, assumed follow-up Sanger sequencing for proband and 2 parents in 50% of cases Diagnostic yield assumptions On average 2 variants per participants (range 0 to 4) 3 to 5% with secondary (incidental) findings Strategies evaluated: CMA alone CMA + WES
Valencia (2015)[54]	Single-arm observational cohort	U.S.	NR	National Human Genome Research Institute	40 pediatric cases, 12 (30%) had genetic defects	Retrospective review of 40 pediatric patients referred by medical specialists (medical geneticists 77%, Immunologists 15%, Cardiologists 3% and others 3%) for exome sequencing. The patients in this cohort had diverse clinical features: 30% congenital anomalies, 22% neurological disorders, 17% immunodeficiencies, 25% mitochondrial disorders	Singleton Whole exome analysis Diagnostic yield: 12/40 (30%) Used ACMG guidelines for category 1 or 2 Scrutinized putative causal variants in literature review, used in silico prediction programs and Sanger sequencing for familial segregation Defined full molecular diagnosis as gene variant(s) classified as pathogenic or likely pathogenic that explains most/all of clinical features

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						All patients were under 17 years of age at time of exome analysis (average age 83.2 months) and much younger at the time of clinical presentation (average age 5.3 months). Prior to referral, all patients had undergone extensive diagnostic evaluations. Males 27 (68%)* and females (32%) *; 37 (97%)* Caucasian; 14/40 (36.7%*) non-Caucasian or of mixed ethnicity, including the individual with Ashkenazi ancestry, who would potentially need different reference panels	Partial molecular diagnosis equaled gene variant(s) classified as pathogenic or likely pathogenic that explains one or several clinical features. Comparator: NA
Vanderver (2016)[71]	Single-arm observational cohort	Australia	2009-2013	Illumina Inc.	191 cases identified; 71 families enrolled	71 patients with persistently unresolved white matter abnormalities with a suspected diagnosis of leukodystrophy or genetic leukoencephalopathy. WES analyses performed on trio, or greater family groups. Patients had high quality samples available for complete trios. Patients included 30 female and 47 male individuals who all had abnormal white matter signal on neuroimaging. Individuals ranged in age from 3 years to 26 years at the time of sequencing, but symptom onset ranged from birth to 19 years. Ethnicities varied and included individuals of mixed and northern European descent, as well as African American, Arab,	Trio or trio + additional family members Not explicitly stated targeted vs whole exome Used custom variant annotation and interpretation software to identify causal mutations Interpretation included disease association in public database or published literature ACMG criteria for pathogenic or likely pathogenic mutations in known disease genes and clinical feature correlation with disease were classified as "diagnostically resolved" Diagnostic yield: 25/71 (35%) Potentially pathogenic variants: 5/71 (7%) "clinical diagnoses" =42% Comparator testing pathway: NA

(Continued)

Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						African, Asian, and Latin American origin	
Vissers (2017)[20]	Single-arm observational cohort	Netherlands	2011-2015	Netherlands organization of Health Research and Development	150 consecutive patients with nonacute neurological symptoms of suspected genetic origin selected.	150 consecutive patients with nonacute neurological symptoms of suspected genetic origin selected. Referred by GP (n=11), medical specialist (n=55), previously referred but remained undiagnosed (n=84). Tertiary referral center. Excluded with well-known, clinically diagnosable disorders (e.g. NF1) Median age: 5years 7months (range: 5 months to 18 years) 53.3% male 78 intellectual disability (52%*) 20 movement disorders (13.3%*) 8 neuromuscular disease (5.3%*) 5 epilepsy (3.3%*) 39 combination of above (26%*)	Singleton WES in 7/150 patients Trio 143/150 patients 1st step was in-silico panel test using WES sequencing, 2nd step looked at variants outside the panel WES "panel" determined by presenting phenotype Performed variant calling for SNV and CNV Standard pathway was determined at discretion of pediatric neurologists, may have included single gene tests and arrays Standard pathway and WES received in parallel and patients followed for a minimum of 6 months after starting WES (median 17mo, range 6-42months) Diagnostic yield by WES = 44/150 (29.3%) Diagnostic yield by standard pathway = 11/150 (7.3%)
Vrijenhoek (2018)[77]	Single-arm observational cohort	Netherlands	2015	European Union's Horizon 2020 research and innovation programme	370	Retrospective study that analyzed medical records of 370 patients with intellectual disabilities (ID) who had undergone WES at various stages of diagnosis at the Wilhelmina Children Hospital, University Medical Centre, Utrecht Age, sex, and race/ethnicity: NR	Trio WES; targeted vs whole exome analysis not explicitly stated ESHG recommendations informed variant filtering Diagnostic yield: 128 (35%)
Waldrop (2019)[47]	Single-arm observational cohort	U.S.	2013-2017	NIH	31 patients, 30 families	Pediatric patients seen in a neuromuscular clinic who had WES performed since 2013,	Trio sequencing Report provided to ordering clinician only included genes predicted to be related to patient's clinical phenotype + medically

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						WES performed at Baylor or Gene Dx	actionable variants, ACMG/ACOG carrier status guidelines WES performed (due to presence of incidental findings) Pathogenic, likely pathogenic, or VUS. Focused report on genes predicted to patient's clinical phenotype Diagnostic yield: 11/30 (37%) of families got genetic diagnosis No comparator testing, but range between 2-12 prior genetic tests before going to WES
Walsh (2017)[78]	Single-arm observational cohort	Australia	2014-2015	Melbourne Genomics Health Alliance, State government of Victoria, Bioplatforms Australia	53 eligible, 50 enrolled, and analyzed	50 adults and children with peripheral neuropathies prospectively enrolled by neurologist, genetics, genetic counselor at Royal Children's Hospital or Royal Melbourne Hospital. All had neurophysiologically confirmed peripheral neuropathy of likely monogenic cause. If suspected based on clinical symptoms, CMT1A from PMP22 duplication was excluded using non-WES analysis prior to study enrollment Female: 17 (34%) Race/ethnicity: NR Age: median: 18 years, range 2-68 Phenotype Demyelinating sensorimotor neuropathy: 9 (18%) Axonal sensorimotor neuropathy: 17 (34%)	Singleton WES initially targeted to 55 genes associated with peripheral neuropathies as of 2013; uninformative patients expanded to 88 gene panel plus a SNP array; patients with additional syndromic features had customized gene panel generated. If all else failed, variants from whole exome analysis considered. Variants classified by ACMG standards, discussed by expert panel, and confirmed with Sanger sequencing. Family segregation studies done as needed. Diagnostic yield Initial 55 gene panel: 12 (24%) SNP Microarray after undiagnosed on initial panel: 2 of 38 remaining undiagnosed (37) or in case where 2nd diagnosis suspected (1) Expanded WES analysis: 8 of 36 remaining undiagnosed (22%), cumulative diagnostic yield 20 of 50

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						Intermediate sensorimotor neuropathy: 10 (20%) Pure motor neuropathy: 11 (22%), Pure sensory neuropathy: 3 (6%)	(40%) Comparator strategy: Hypothetical scenario: WES replaces sequencing-based genetic tests, repeated nerve conduction studies, complex biochemical tests, and tissue biopsies. Limits diagnostic neurology appointments to 2/patient
Werner-Lin (2018)[68]	Qualitative research design	U.S.	NR	National Human Genome Research Institute	10	Interviews with adolescents (aged 12 to 19 years at recruitment) and their parents recruited from disease specific clinics, phenotypes included: 60% (6) cardiac arrhythmia, 20% (2) hearing loss, and 20% (2) platelet disorders, 30% (3) aged 12 to 15 years and 70%(7) aged 16 to 19 years, 60% (6) female, 70% (7), White	Type of WES: NR Targeted vs whole exome: NR Variant reporting: allowed carrier variants and VUS Diagnostic yield = 3/10 (30%*) but this isn't a meaningful number Comparator testing: NA
Willing (2015)[56]	Single-arm observational cohort	U.S.	2011 - 2014	Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Human Genome Research Institute, National Center for Advancing Translational Services	49 enrolled, 35 infants eligible	Retrospective comparison of STATseq and standard genetic testing in a case series from the level 4 NICU and PICU of a quaternary children's hospital. The participants were families with an infant younger than 4 months with an acute illness of suspected genetic cause and did not have a genetic diagnosis. Study compared diagnostic rate, time to diagnosis, and types of molecular diagnoses of standard clinical genetic testing. Affected children were nominated for STATseq by the treating	STATseq = rapid WGS STATseq of trios Whole exome analysis Identified causative variants using VIKING software Classified as definitive diagnosis if ACMG pathogenic or likely pathogenic in disease gene that overlapped with reported phenotype in medical record Sanger sequencing to confirm likely causative Diagnostic yield: 20/35 (57%) by STATseq Comparator: standard genetic testing based on clinical judgment (may have

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						physician, typically a neonatologist. 18 (51%) were male; median age at enrollment: 26 days/ range (1-71 days) Clinical features of affected infants were ascertained through physician and family interviews and review of medical records. STATseq was done in the lab at Children's Mercy- Kansas City on both parents and affected infants simultaneously. Principal phenotypes included: multisystem congenital anomalies = 9 (26%); neurological = 7 (20%); cardiac or heterotaxy = 5 (14%); hydrops or pleural effusion = 4 (11%); metabolic findings, including hypoglycaemia = 4 (11%); renal = 1 (3%); Arthrogryposis = 2 (6%); respiratory = 1 (3%); hepatic = 1 (3)%; dermatological = 1 (3%) Of the 35 infants who had STATseq, 32 had standard genetic testing based on physician's clinical judgment	included gene panel sequencing), yield: 3/32 (9%)
Yang (2014)[66]	Single-arm observational cohort	U.S.	2012-2014	National Human Genome Research Institute	2000 analyzed	Clinical WES at Whole Genome Laboratory of Baylor College of Medicine, CLIA-certified, tertiary care center 2000 consecutive patients with	Singleton Whole exome Molecularly diagnosed defined as pathogenic or likely pathogenic variant detected in Mendelian disease genes that overlapped with described

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						WES ordered by patient's physician. Exclusion was for financial reasons only. mean age 6 years. Categorized as "neurological" (n=526) , "neurological plus other organ systems" (n=1147), "specific neurological" (n=83), and "nonneurological" (n=244) Could have had previous workup that did not yield molecular diagnosis phenotype = 82.2% had non-neurological female = 888/2000 = 44% (11 fetuses with gender unknown, 1%) race/ethnicity NR 900/2000 (45%) <5years, 845/2000 (42.2%) 5-18years, 244/2000 (12.2%) adults >18years, and 11/2000 terminated fetal samples (0.6%)	phenotype, and biallelic variants required for recessive disorders. 2 tiers of reporting: tier 1 included 1) pathogenic variants related to disease phenotype, 2) VUS related to disease phenotype, 3) medically actionable mutations including ACMD 56, 4) carrier status for ACMG-recommended population screening panel, 5) defined number of pharmacogenetic variants, and 6) clinically relevant mitochondrial mutations. Tier 2 included deleterious mutations or VUS unrelated to disease phenotype, and predicted deleterious mutations in nondisease genes Diagnostic yield: 504/2000 = 25.2% overall, 143/526 (27.2%) neurological, 282/1147 (24.6%) neurological + other organ systems, 30/83 (36.1%) specific neurological, 49/244 (20.1%) non-neurological Diagnostic yield excluding fetuses: Overall = 498/1989 (25%*), neurological =143/526 (27.2%), neurological + other organ systems = 277/1140 (24.3%*), specific neurological = 29/82 (36.3%*), non-neurological = 49/241 (20.3%*) Comparator testing: NA
Zhu (2015)[45]	Single-arm observational cohort	U.S.	NR	UCB Celltech	119 patients analyzed 113 first analyses 6 re-analyses	65 trios recruited from Genome Sequencing Clinic at Duke University Medical Center, (54.6%*) 48 trios recruited from Sheba Medical Center in Tel HaShomer,	Trio WES Whole exome analysis Variant reporting: used two independent sources of population controls: Center for Human Genome Variation at Duke

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Author (Year)	Study Design	Country	Year (s) Conducted	Study Funder	Number of participants	Study setting and population	Description of test or testing strategy; comparator strategies evaluated (if applicable); and reported diagnostic yield
						Israel (40.3%*) 6 trios previously recruited and unresolved (0.05%*), I think from Duke 113/119 trios reported for the first time 6/119 trios reinterpreted (previously unresolved) mean age = 9.5*, sd = 8.7* female: 52/119 = 68.1* Clinical phenotypes vary widely	controls (phenotypes not analyzed), and NHLBI Grand Opportunity Exome Sequencing Project. Qualifying genes from analysis checked against OMIM for phenotypic overlap, consistency with inheritance pattern, similarity of mutation in reported data Diagnostic yield 29/119 = 24% No comparators

Abbreviations: ACMG = American College of Medical Genetics; CI = confidence interval; CMA = chromosomal micro-array; CNV = copy number variant; EEG = Electroencephalographic; FH = familial hypercholesterolemia; ID = intellectual disability; NA = not applicable; NGS = next-generation sequencing; NICU = neonatal intensive care unit; NMASF = nonmedically actionable secondary findings; NR = not reported; SD = standard deviation; SNP = single-nucleotide polymorphisms; UPD = uniparental disomy; VUS = variance of unknown significance; WES = whole exome sequencing; * = calculated value

Table C-2. Clinical Utility Outcomes

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
Balridge (2017)[43]	Some	NR	8 (12% of those with a diagnosis, 5% of those tested) had directly altered clinical care	18 (11% of those tested, 26% of those diagnosed)
Bourchany (2017)[42]	High	2/13 (15.4%*) of those with WES diagnosis had change in prognosis. 6/13 (46.2%) of those with WES diagnosis had change in inheritance pattern of presumed diagnosis	1/13 (7.7%*) of those with WES diagnosis had investigation of systemic involvement. 2/13 (15.4%*) of those with WES diagnosis included in clinical trials	12/13 (92.3%*) of those diagnosed using WES received prenatal counseling/testing
Cordboba (2018)[18]	Some	NR	43.8%* (7of 16) of those with a diagnosis 17.5%* (7 of 40) of those tested 6.3%*(1) of those with a diagnosis had endocrine monitoring 25%*(4) of those with a diagnosis were treated with a with new medication 12.5% (2) of those with a diagnosis were advised to avoid a medication	NR
Daga (2018)[41]	Some	46%* (7 of 15) of families with diagnosis, (14%* of families tested) received a diagnosis that resulted in a potential change in treatment	20% (3 of 15) of diagnosed families received screening for other symptoms of their genetic disease	NR
Evers (2017)[52]	Some	NR	8 (38%) of 21 cases had management changes 2 (8%) change in medication or biotherapy 7 (33%) began surveillance for disease complications	20 (95%) of 21 said results were important for family planning 19% (4 cases in 21 families) have used results for prenatal diagnosis
Hauer (2017)[51]	High	NR	31 families (15.5% of 200 exome individuals) led to preventive measures 23 families (11.5%) orthopedic support and developmental evaluation 9 families (4.5%) had recommendations for symptomatic treatment or screening for associated malformations 4 families (2%) received new medications to treat their specific genetic defect	NR

(Continued)

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
Howell (2018)[28]	High	NR	Genetic diagnosis led to a management change in 1 participant (SCN2A mutation with sodium channel blocking AEDs used); unclear what % this represents since not calculable based on data reported in article	100% of those with a genetic diagnosis (unclear N); a significant recurrent risk was identified in 5 families
Iglesias (2014)[46]	Some	NR	Of the 37 with a diagnosis: 22%* (8) were screened for other manifestations of the disease 38%* (14) had changes in management 5%* (2) changed treatment	14%*(5 of 37) identifying other family member mutation carriers 16%* (6 of 37) reproductive planning
Jones (2018)[50]	High	NR	Of patients with FH molecular diagnosis 18 (78% of 23) prescribed lipid-lowering therapy 8 (47% of 17) changes to intensity of medication management 9 (39% of 23) changes made to their treatment regiments 1 (11% of 9) was initiated on new therapy	8 (42% of 19) discussed genetic results with clinical genomics specialist
Mann (2019)[48]	Some	5 probands (4 had correct clinical diagnosis) where molecular genetic etiology had clinical consequences 5/104 = 4.8%* This is a counterfactual potential change in management, as they had already been transplanted	NR	NR
Matias (2019)[49]	Some	NR	Change from pre-WES to post-WES Any change (Not significant (NS)) 100% (37 of 37) of those with a diagnosis 95% (31 of 41) of those without a diagnosis Imaging tests (NS) 46% (17 of 37) of those with a diagnosis 56% (23 of 41) of those without a diagnosis Metabolic testing (NS) 43% (16 of 37) of those with a diagnosis 46% (19 of 41) of those without a diagnosis Genetic testing (NS)	Any genetic counseling change: (p <0.001) 97% (36 of 37) with a diagnosis 5% (2 of 41) of those without a diagnosis Recurrence risk (p <0.001) 95% (35 of 37) with a diagnosis 0% (o of 41) of those without a diagnosis Reproductive counseling: (p <0.001) 97% (36 of 37) of those with a diagnosis 0% (o of 41) of those without a diagnosis Family Testing: (p <0.001)

(Continued)

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
			73% (27 of 37) of those with a diagnosis 80% (33 of 41) of those without a diagnosis Received specialist referrals (p=0.05) 43% (16 of 37) of those with a diagnosis 46% (19 of 41) of those without a diagnosis Lifestyle recommendations (NS, significant with 4 group analysis) 24% (9 of 37) of those with a diagnosis 12% (5 of 41) of those without a diagnosis	97% (36 of 37) of those with a diagnosis 0% (0 of 0) of those without a diagnosis
Meng (2017)[40]	Some	NR	52.0% (53 of 102) of those with diagnosis had a change in medical management 35.8%(19 of 53) of those with diagnosis had a redirection in care 50.9% (27 of 53) of those with a diagnosis had initiation of subspecialist care 13.2% (7 of 53) of those with a diagnosis a change in medication or diet 9.4% (5 of 53) of those with a diagnosis had a major procedure completed	88% (90 of 102) of families with diagnosed received genetic counseling
Niguidula (2018)[39]	High	NR	Medication change: 11% of those tested (17% of those with diagnosis, 29% of those with uncertain results, 3% of those with negative results) Discontinue diagnostic studies: 58% of those tested (96% of those with positive test, 86% of those with uncertain test, 25% of those with negative test) Medical management change: 40% of those tested (78% of those with diagnosis, 71% of those with uncertain diagnosis, 9% of those with negative diagnosis) Psychosocial support: 27% of those tested (65% of those with positive diagnosis, 29% of those with uncertain diagnosis, and 0% of those with negative diagnosis)	Reproductive planning: 45% of those tested (87% of those with diagnosis, 86% of those with uncertain results, 6% of those with negative results)

(Continued)

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
Nolan (2016)[24]	Some	NR	10 (18.9%) of those tested and (41.7%) of those with a diagnosis	11 (22%) of those tested and (46%) of those with a diagnosis
Palmer (2018)[27]	High	NR	31.3% (5) of those diagnosed had changes in management 6.3% (1) of those with a diagnosis had palliative care initiated 6.3% (1) of those with diagnosis had reduced invasive/costly diagnostic investigations 6.3 % (1) had targeted management (not specified) 12.5% (2) of those with a diagnosis received guidance on AED therapy	43.7% (7) of those with diagnosis had reproductive planning
Perucca (2017)[34]	High	NR	1/5 of those with molecular diagnosis (20%*) had a change in medication	NR
Ream (2014)[58]	Some	0/6 (0%) of patients diagnosed by WES 4/23 (17%) patients diagnosed by other genetic tests had diagnoses defined a priori as having potential therapeutic implications	0/6 (0%) of patients diagnosed by WES 13%* (3/23) patients diagnosed by other genetic tests had a change in medication. 4%* (1/23) patients diagnosed by other genetic tests was prescribed a special diet	50% (3 of 6) of WES patients received genetic counseling regarding the implications of heterozygous autosomal recessive mutations with potential diagnostic significance
Sawyer (2016)[55]	High	NR	6 (26%) of 105 families 3 had adjustment of therapy and 3 had therapy initiated	NR
Shamriz (2016)[53]	High	NR	One patient, decision to defer allogenic hematopoietic stem cell transplantation based on clinical and genetic findings, treatment included palliative care only	NR
Snoeijen-Schouwenaars (2019)[32]	High	10/25 (40%) had a potential change in management from their WES results 5/25 (20%) of those with pathogenic/likely pathogenic variance had potential consequence for clinical approach An additional 5/25 (20%), variants with possible consequence for daily clinical care (5/100 (5%*) of those analyzed)	1/25 (4%*) of those with pathogenic/likely pathogenic variance had a change in management (medication change) resulting from the WES results	NR
Soden (2014)[25]	High	NR	49% (22 families with a diagnosis) had a change in patient management and/or clinical impression of the pathophysiology 23% (10 families with a diagnosis) had a change in	NR

(Continued)

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
			drug or dietary treatment (this either occurred or were planned) 6.7% (3 families with a diagnosis) had a discontinuation of unnecessary treatments 20% (9 families with a diagnosis) had additional evaluation for possible disease complications	
Srivastava (2014)[57]	High	NR	WES testing affected management in 41% (32 of 78) of patients, in 100% (32 of 32) of those with a presumptive diagnosis 5% (4) started disease monitoring after diagnosis 6% (5) discontinued medication 3% (2) started medication 8% (6) received further workup for systemic involvement	135%* (27 of 78) of patients had results essential for reproductive planning
Stark (2016, 2017, 2019)[13-16]	Some	NR	16/47 (34%) of those diagnosed using WES, 16/80 (20%) of those tested; includes 13/16 who added new treatment or surveillance and 4/16 who stopped treatment/surveillance	Testing was offered to all available parents and some siblings where clinically indicated. 79/88 eligible first-degree relatives underwent cascade testing (including those only diagnosed with standard care); 12 relatives of WES-diagnosed probands received a genetic diagnosis from cascade testing. 5 relatives would have received genetic diagnosis if proband diagnosed using standard of care pathway; 28 couples were identified as high risk of recurrence from WES. 13 couples would have been identified using standard of care pathway (counterfactual); 14/47 (30%) of families with a WES diagnosis sought reproductive counseling services: 2 preimplantation genetic counseling, 12 prenatal genetic diagnosis. 2 (6%) of families without a diagnosis sought reproductive counseling services
Stark (2018)[22]	High	NR	Reported for the Rapid WES Cohort Only 20% (16) overall had change in management 10%*(4) medication started/adjusted	NR

(Continued)

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
			3%*(1) medication stopped 18%*(7) surveillance initiated 0%*(0) surveillance stopped 8%*(3) avoidance of tissue biopsy 5%*(2) redirection to palliative care	
Tan (2017)[19]	Some	NR	7 (30% of those diagnosed, 16% of those tested) had change in management (specific changes unspecified) 6 (26% of those diagnosed, 14% of those tested) had 1 (4% of those diagnosed, 2% of those tested) of those stopped planned investigations	1 (4% of those diagnosed, 2% of those tested) had a prenatal implantation genetic diagnosis planned
Tarailo-Graovac (2016)[44]	Some	NR	44% (18) with pathogenic or probably pathogenic variant had impact on clinical treatment, including: 4 of 18 had preventive measures: regular cancer screening from patients with high risk of malignancies or avoidance of disease triggers 3 of 18 immune-modulating therapies 5 of 18 more precise symptomatic treatment 7 of 18 treatments targeting the identified abnormality at a cellular or molecular level	NR
Valencia (2015)[54]	Some	12.5% (5 of 40)	2 (5%) had change in management 12 (30%) altered medical management including genetic counseling	NR
Waldrop (2019)[47]	Some	NR	25% (3 of 12) develop plan for disease surveillance (e.g. cardiac, immune or eye) 8%* (1 of 12) discontinue medication 8%* (1 of 12) certainty of malignant hyperthermia risk 8%* (1 of 12) with diagnosis started palliative care	100% (12 of 12) of those with a diagnosis
Willing (2015)[56]	High	NR	12/20 (60%) had a change in management 13 (65%) of those with a STATseq diagnosis report acute clinical usefulness, 4 (20%) had diagnoses with favorable effects on management and 6 (30%) were started on palliative care	NR
Zhu (2015)[45]	High	NR	4/119 tested (3.4%*) 4/29 diagnosed (13.8%*) 2/119 (1.7%*) tested had specific pharmacotherapies	NR

(Continued)

Author (Year)	Risk of Bias	Number and Proportion of Participants with a Potential Change in Management	Number and Proportion of Participants with an Actual Change in Management	Number and proportion of participants with results Leading to Additional Genetic Counseling or Testing in Family
			result from WES results 2/119 (1.7%*) tested had specific diet interventions result from WES	

Abbreviations: AED = antiepileptic drugs; FH = Familial hypercholesterolemia; NA = not applicable; NR = not reported; NS = not significant; WES = whole exome sequencing; * = calculated value

Table C-3. Health Outcomes

Author (Year)	Risk of Bias	Mortality	Length of Survival	Other health outcomes (morbidity, cognitive ability, functional outcomes)
Meng (2017)[40]	Some	5-yr death rate: Diagnosed: 39 of 102 (38.2%) Not diagnose:, 41 of 170 (24.1%) 120-day death rate: Diagnosed: 30 of 102 (29.4%) Not diagnosed: 28 of 170 (16.5%)	NR	NR
Perucca (2017)[34]	High	NR	NR	1/5 of those with molecular diagnosis (20%) (1 of 1 with change in management) experienced change from "uncontrolled monthly seizures" to seizure-free for 12 months since implementing change in management
Ream (2014)[58]	High	NR	NR	Seizure control. 0%* (0/6) of WES patients had improved seizure control. 1 of 23 (4%) patients diagnosed with other genetic tests had improved seizure control receiving stiripentol based on the gene test result
Shamriz (2016)[53]	High	1 patient of 6 (16.7%*) with diagnosis from WES died after parent refusal of treatment 2 years after initial diagnosis Total follow-up: 2.5 years Length of follow-up for all patients: 0.28 to 8.96 years Patients were not assessed for a minimum amount of time to record outcomes	NR	1/6 (16.7%) with diagnosis from WES experienced progressive neurological deterioration 4/6 (66.7%) with diagnosis from WES were alive and well
Snoeijen-Schouwenaars (2019)[32]	High	NR	NR	1 (4%*) of 25 patients with likely pathogenic variant had improved behavior and mood following medication change based on WES result
Stark (2018)[22]	Some	Unclear length of follow-up 9 (23%) of rapid WES cohort 9 (11%) of standard WES cohort	NR	NR
Willing (2015)[56]	High	14 (40%) of 35 infants died within 120 days 120-day mortality was 57% (12 of 21) in infants with a genetic diagnosis (ALM during QC: this number includes infants with a diagnosis by either STATseq or standard testing) 4 infants died within 4 days of enrollment	NR	NR

Abbreviations: AED = antiepileptic drugs; NA = not applicable; NR = not reported, NS = not significant; WES = whole exome sequencing

Table C-4. Safety Outcomes

Author (Year)	Risk of Bias	Misdiagnosis (False positives/False Negatives)	Proportion of participants with ACMG-defined medically actionable variants	Psychosocial harms
Baldridge (2017)[43]	Some	NR	141 (97% of the 146 who were given choice to opt in or out) elected to receive incidental findings. 14 (10% of those tested who opted in) had incidental findings in one or more of the 56 ACMG-defined genes	NR
Bourchany (2017)[42]	Low	NR	0/29 (0%*) of those tested had any ACMG 56 incidental findings	NR
Ding (2014)[75]	Some	NR	Modeling confirms that 1.5%–6.5% of screened individuals will have a significant reportable finding	NR
Jones (2018)[50]	NA- Qualitative Study	NR	NR	Some shock related to a participant's discovery of nonpaternity as a result of family discussions regarding family history of heart disease
Jurgens (2015)[65]	Some	NR	2/232 (0.86%) individuals had a reportable variant in an ACMG gene	NR
Lee (2015)[73]	Low	NR	1 of 26 (4%)* of those tested	NR
Li (2019)[67]	NA- Qualitative Study	NR	NR	Participants reported a range of emotions upon receiving a report of variants of unknown significance including confusion, anger, stress, fear, relief, and disappointment The majority of participants reported it did not affect their ability to take care of their child, or alter their perception of their child's condition.
McConkie-Rosell (2018)[69]	Low	NR	NR	Anxiety and Depression: 44 parents who completed GAD-7 and PHQ - 9, 29 (65.9%) did not meet criteria for depressive disorder, 8 (18.2%) had mild depression, and 7 (15.9%) had moderate depression. For anxiety 26 (59.1%) did not meet criteria for anxiety, 6 (13.7%) had moderate anxiety, and 1 (2.3%) had severe anxiety Among those whose children underwent prior WES : PHQ-9 (mean +/- sd) = 5.45 +/- 5.99 GAD-7 = 5.36 +- 4.96 CSE = 188.24 +/- 37.97

(Continued)

Author (Year)	Risk of Bias	Misdiagnosis (False positives/False Negatives)	Proportion of participants with ACMG-defined medically actionable variants	Psychosocial harms
				Health care engagement = 18.52 +/- 1.75 Uncertainty tolerance = 16.24 +/- 2.66
Meng (2017)[40]	Some	NR	7.9% (21 of 267) of those who agreed to receive information	NR
Monies (2017)[61]	Some	NR	1.2% of cohort tested (panel + WES)	NR
Muramatsu (2017)[70]	Low	NR	0 of 250 (0%)	NR
Nolan (2016)[24]	Some	NR	5 (10%) of total tested Not specifically reported in the study as ACMG-defined medically actionable variants; however, study authors reported that all 5 findings affected patient management	NR
Posey (2015)[63]	Low	NR	Medically actionable findings ACMG criteria, 6/482 = 1.2% Outside of ACMG criteria findings = 6/481 = 1.2%	NR
Ream (2014)[58]	High	NR	67% (4 of 6) WES patients had a cytochrome enzyme mutation affecting drug metabolism	NR
Retterer (2016)[64]	Low	NR	12.2% (291of 2,382) participants opted out of receiving secondary findings 6.2% (129 of 2,091) of those who opted to receive secondary findings had reportable secondary findings	NR
Roche (2019)[76]	High	NR	2% (13 of 622) participants ineligible as a result of medically actionable SF	5 of 36 respondents to a survey of participants who did not request nonmedically actionable results reason for not requesting results were concern that information would be an emotional burden
Rosell (2016)[62]	NA	NR	No incidental findings identified	All parents hoped for diagnosis: 4/19 had high expectations of diagnosis; 13/19 had tempered expectations, not wanting to get their hopes up only to be disappointed; 2 parents had low expectations Some parents voiced frustration and disappointment with waiting and not getting complete answers

(Continued)

Author (Year)	Risk of Bias	Misdiagnosis (False positives/False Negatives)	Proportion of participants with ACMG-defined medically actionable variants	Psychosocial harms
				Some families felt need for more follow-up counseling or outreach Some expressed need to help families manage expectations
Shashi (2016)[74]	Low	NR	3.3% (2/59 patients tested after publication of ACMG guidelines) with an incidental mutation All patients opted to receive results	NR
Skinner (2018)[59]	NA- Qualitative Study	NR	NR	Only 1/32 (3.1%) misinterpreted an uncertain result as a definitive answer. The clinicians reported it as a possible but uncertain explanation, but the patient interpreted it as definitive and described it as 'life-changing'. She did understand the VUS did not cause her symptoms when her unaffected father was found to carry the same variant. Some adult participants for whom family testing was recommended did not pursue it because they did not want to pressure family members. Patients pursuing testing did not worry while waiting on results. Some commented that uncertainty was not new. One participant reported experiencing distress related to the uncertain result. No participants expressed regret at learning the uncertain result. No participants reacted to the uncertain result in ways that could cause harm. Most regarded the information as potentially valuable in the future.
Strauss (2017)[60]	Low	NR	490/502 (98%) subjects subjected to family-based WES elected to receive secondary findings. 21 (4.2%) subjects had 1 of 4 pathogenic/likely pathogenic variants in 3 genes (BRCA2, APOB, and DSC2) and received these results	NR
Tammimies (2015)[72]	Low	NR	8 of 95 probands (8.4%) reported incidental findings	NR

(Continued)

Author (Year)	Risk of Bias	Misdiagnosis (False positives/False Negatives)	Proportion of participants with ACMG-defined medically actionable variants	Psychosocial harms
			6 (6.2%) were deemed medically actionable	
Valencia (2015)[54]	Low	16% of variants identified by WES and carried forward to Sanger sequencing did not survive Sanger sequencing and were therefore WES false positives. However, because Sanger sequencing was part of the pipeline prior to diagnosis, they are not false positives	8%* (3) had reported medically actionable findings in 3 ACMG-recommended reportable genes (MYL2, FBN1, BRCA2)	NR
Vanderver (2016)[71]	Low	NR	Unaffected adults screened = 142 Incidental findings = 3 (2.1%) Affected children screened = 79 Incidental findings = 3 (3.7%) Unaffected siblings = 0/10 (0%) with incidental findings 3/71 (4.2%*) families screened had incidental findings Incidental findings included the 56 adult and 49 pediatric ACMG-recommended genes	NR
Vissers (2017)[20]	Some	3 patients received diagnosis through non-WES pathway but NOT through WES (9bp duplication, repeat expansion, mosaic duplication of Chr7). 3/150 (2%*) of those tested received a false negative diagnosis by	0/150 (0%*) tested had incidental findings (study did not define incidental findings)	NR

(Continued)

Author (Year)	Risk of Bias	Misdiagnosis (False positives/False Negatives)	Proportion of participants with ACMG-defined medically actionable variants	Psychosocial harms
		WES 36 patients (76.6%) received diagnosis through WES pathway but not through standard diagnostic pathway. 36/150 received a false negative diagnosis by standard care pathway (24%)		
Werner-Lin (2018)[68]	NA (qualitative study)	NR	10% (1) nonimmediately actionable childhood-onset finding 8/10 (80%) had positive carrier findings (in accordance with ACMG)	Families were initially disappointed when uncertain results were conveyed; they experienced frustration, disappointment, and fear. These feelings evolved over time; and moved toward acceptance and satisfaction, generally within the ensuing 3 months.
Yang (2014)[66]	Low	NR	59/2000 (3%) ACMG-defined by local definition: 95 variants found in 92/2000 patients (4.6%) with incidental findings that had immediate implications for management	Of the 92 patients with incidental findings, 33 parents from 19 families have requested testing for medically actionable variants found in proband.

Abbreviations: NA = not applicable; NR = not reported.

Table C-5. Characteristics of Included Studies Reporting Cost Outcomes

Author (Year)	Cost Study Design	Year and Unit of Currency Reported	Perspective Used	Time Horizon and Discounting	Description of Costs Included	Description of Benefit and/or Utility Measures Used
Cordoba (2018)[18]	Other	US$; currency year NR	Payer	NA	Actual costs of tests, procedures, and visits encountered by enrolled participants; repetitive procedures and visits considered unnecessary and expendable; others considered nonexpendable	NA
Dillon (2018)[17]	Other : Cost simulation	2016 AU$	Payer	NA	WES AU$ 2,000; comparison gene panels cost NR	NA
Dragojlovic (2018)[23]	Cost analysis	2016, CAD$	Payer	NA	Costs of clinical and laboratory staff labor, infrastructure, WES laboratory, and bioinformatics	NA
Ewans (2018)[21]	Cost-benefit analysis	2016, reported in US$	Payer	NA	Only n=14 patients in this analysis (all with intellectual disability) Costs for diagnostic encounters and procedures recorded in the medical record (determined by using local salary data to estimate staff time, procedure; investigation costs from the Australian Medicare Benefits Schedule. Cost of single gene and Sanger sequencing, deletion/duplication studies, and biochemical tests were obtained from referral labs, WES costs were obtained from local labs	NA
Howell (2018)[28]	Cost-benefit analysis	2016; reported in US$ (converted from AU$)	Payer	NA	Calculated from data from the Australian Medicare Benefits Schedule, Royal Children's Hospital Decision Support Unit, Victorian Clinical Genetics Service, and State Neuropathology Service. Only diagnostic costs and costs related to diagnosis (e.g., anesthesia, operating room costs, ward/nursing costs, drugs related to sedation for testing, etc.) were considered, the cost of each test within each tier was aggregated for a total tier cost. Reported cost of WES gene panel: $1,639	Number of diagnoses
Monroe (2016)[80]	Cost analysis	2014; USD (converted from Euros)	Payer	NA	Reimbursement prices from Dutch Healthcare Authority were used for medical interventions, imaging and diagnostics, biochemical analysis, and surgeries; inpatient days, health professional visits, day admissions, blood products WES costs estimated at $3,972 per trio and includes cost of blood draw, DNA isolation, sample	NA

(Continued)

Author (Year)	Cost Study Design	Year and Unit of Currency Reported	Perspective Used	Time Horizon and Discounting	Description of Costs Included	Description of Benefit and/or Utility Measures Used
					preparation, exome enrichment, sequencing, interpretation, reporting of results, data storage, and infrastructure In comparative analysis, WES replaces all genetic costs except CMA and SNP and all metabolic assessments. Also, assumed a scenario where WES testing would result in 50% reduction in health care utilization related to additional testing	
Nolan (2016)[24]	Cost analysis	U.S. $, year NR	Payer	NA	Costs for initial and secondary genetic and metabolic tests estimated from data from private laboratories and included karyotype, chromosomal microarray, fragile X, methylation PCR, urine organic acids, plasma amino acids, acylcarnitine profile and lactate, single gene tests or gene panels Source of cost of WES not explicitly reported but presumed to be from the two laboratories that conducted the diagnostic WES testing	NA
Palmer (2018)[27]	Cost-benefit analysis	Australian $, Year NR	Payer	NA	Actual costs of diagnostic tests of the patients enrolled based on case files, pathology databases, public hospital, and commercial costs Costs included billed cost of the test, courier costs, workforce costs associated with diagnostic procedures, patient admission for diagnostic tests, costs of specialist consultations, costs associated with functional testing to assess the pathogenicity of novel findings Costs of WES included cost of DNA extraction, costs related to sequencing, and costs of medical genomicist to prioritize variants and a genetic pathologist to assess pathogenicity and compile a report	Additional diagnosis
Schofield (2017)[26]	Cost-benefit analysis	2016, Australian $	Payer	NA	Traditional pathway: Cost of all diagnostic investigations and procedures, Sanger sequencing of candidate genes in DNA extracted from biopsy specimens, confirmation in parents Neuromuscular gene panel: costs of traditional	NA

(Continued)

Author (Year)	Cost Study Design	Year and Unit of Currency Reported	Perspective Used	Time Horizon and Discounting	Description of Costs Included	Description of Benefit and/or Utility Measures Used
					pathway, cost of commercially available 464 neuromuscular gene panel, cost of confirmation with Sanger sequencing in proband and parents WES: cost of traditional pathway, cost of Sanger sequencing confirmation, cost of singleton WES, cost of trio WES	
Soden (2014)[25]	Cost analysis	NR	Payer	NA	Total costs of prior negative diagnostic testing for children who received a diagnosis, including laboratory tests, radiologic procedures, electromyograms, nerve conduction velocity studies Not considered: tests performed at outside institutions, tests necessary for patient management (e.g. EEG), physician visits, phlebotomy, other health care charges	NA
Stark (2016, 2017, 2019)[13-16]	Cost-benefit analysis, Cost-effectiveness analysis	2015, Australian $	Payer	18 months; 20 years; 5%	Medications, imaging, pathology, biochemical testing, genetic tests, specialty medical and genetic consultations, hospital admissions, reproductive counseling or services or testing in family members. Costs obtained from hospital, state government, and testing laboratories. General patient care costs were not included	In initial publication, clinicians determined QALY's gained based on their prognosis of disease progress in the absence of a diagnosis and thus no changes in management For reproductive outcomes, utility was estimated based on health condition at the time of birth of subsequent pregnancies and parents were assumed to benefit from an additional 0.07 QALY each as result of the birth In follow-up publication, published population norm utility values were used
Stark (2018)[22]	Cost-benefit analysis	Year NR, AU$	Payer	NA	Authors extracted all diagnostic investigations, procedures, and assessments from the medical record; costs of those were obtained from the hospital, state government medical benefits schedule, and testing laboratories	NA

(Continued)

Author (Year)	Cost Study Design	Year and Unit of Currency Reported	Perspective Used	Time Horizon and Discounting	Description of Costs Included	Description of Benefit and/or Utility Measures Used
Tan (2017)[19]	Cost-benefit analysis	2015, US$	Payer	NA	All costs from initial presentation to tertiary services for diagnostic assessments, first clinical genetic assessment and WES testing, all diagnostic inpatient and outpatient episodes of care including investigations, specialists consulted, duration of admission, and travel, costs of case conferences, costs incurred to the health system for travel from home	Additional diagnoses
Tsiplova (2017)[79]	Other: Cost-consequence analysis	2015, CAD$	Payer	Costs were estimated in each year of a 5-year program, 3% discount rate	Labor (specimen prep, DNA extraction, library preparation, microarray processing, sequencing, analysis, including bioinformatics for WES, clinical interpretation, reporting), supplies (sample handling, library preparation kits, sequencing reagents, scanner consumables), follow-up testing (qPCR,, FISH, Sanger sequencing, bioinformatics computation use, small equipment, large equipment (service contracts)	NR
Vissers (2017)[20]	Cost-benefit analysis	2016, Euro	Payer	NA	Actual costs of diagnostic tests performed both prior to and after inclusion in the study, unit cost prices from the Dutch Healthcare Authority and cover the cost of the test, interpretation of results, and physician fee. Cost of singleton WES was E1800 and trio WES E3,500 Assumed that when WES resulted in a conclusive diagnosis that tests performed in the standard pathway could have been precluded. When WES did not result in conclusive diagnosis, assumed costs would be identical except that the costs associated with genetic testing would be replaced by costs of diagnostic WES. In the WES-first pathway, assumed that once a conclusive diagnosis was reached, no additional tests would be performed	NA
Vrijenhoek (2018)[77]	Other: Cost of Illness	Year NR; Euro	Payer	NA	Costs on all healthcare activities performed at the university medical center as indicated in the patient's medical records and hospital information systems, starting with the first visit to the university medical center. All health care activities were linked to their	NA

(Continued)

Author (Year)	Cost Study Design	Year and Unit of Currency Reported	Perspective Used	Time Horizon and Discounting	Description of Costs Included	Description of Benefit and/or Utility Measures Used
					unit costs derived from price lists issued by the Dutch Healthcare Authority Costs for WES were excluded except for WES-first strategies	
Walsh (2017)[78]	Cost-benefit analysis	Year NR; Australian $	Payer	NA	Costs for all investigations, diagnostic procedures, first three neurology appointments for pediatric participants, first appointment with neurologist for adult patients (these visits were considered for diagnostic purposes)	NA

Abbreviations: AU = Australian; CAD = Canadian; CI = confidence interval; CMA = chromosomal microarray; E = Euro; NA = not applicable; NR = not reported; PCR = Polymerase Chain Reaction; QALY = quality-adjusted life year; SNP = single-nucleotide polymorphisms; U.S. = United States.

Table C-6. Findings from Studies Reporting Cost Outcomes

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
Cordoba (2018)[18]	High	$1,000	Cost of expendable diagnostic workup: $1,646 (95% CI, 1,439 to 1,835)	NR	NR	NR	NR
Dillon (2018)[17]	High	AU$ 2,000	NR	In 26% of WES-diagnosed children for whom a comparator panel would have been diagnostic, the least costly panel had a higher price than the price of WES in this study	NR	NR	NR
Dragojlovic (2018)[23]	Some	Singleton; CAD$ 2,576 Trio; CAD$ 6,437	Cost per patient Last resort trio WES after clinical genomics consultation: CAD$ 6,138 Last resort singleton WES: CAD$ 5,125 Last resort trio WES without clinical genomics consultation: CAD$ 5,263	Cost per diagnosis Trio WES after clinical genomics consultation: CAD$ 14,405 Singleton WES: CAD$ 18,223 Trio WES without clinical genomics consultation: CAD$ 15,495	NR	NR	NR
Ewans (2018)[21]	Some	Singleton; $ 1,200 Trio; $3,150	Mean cost per patient Traditional pathway: $6,742 (95% CI, $5,262 to $8,432) WES at initial symptoms presentation: $6,574 (95% CI, $4,831 to $8,524) WES at clinical genetics review: $6,918 (95% CI, 5,358 to $8,763) WES at initial symptoms presentation	Mean cost per diagnosis Traditional pathway: $0 (no diagnoses made) WES at initial symptoms presentation: $23,010 (95% CI, $10,135 to $102,147) (4 diagnoses) WES at clinical genetics review: $24,215 ($11,195 to $103,173) (4 diagnoses) WES at initial symptoms presentation and	Cost per additional diagnosis compared to traditional pathway WES at initial symptoms presentation: $-586 (95% CI, $-3769 to $16,144) WES at clinical genetics review: $618 (95% CI, $-2,431 to $17,439) WES at initial	NA	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
			and reanalysis at 12 months: $6,709 (95% CI, 4,937 to $8,688) WES at clinical genetics review and reanalysis at 12 months: $7,053 (95% CI, $5,458 to $8,929)	reanalysis at 12 months: $15,653 (95% CI, $7,619 to $49,752) (6 total diagnoses) WES at clinical genetics review and reanalysis at 12 months: $16,457 (95% CI, 8521 to $50,531) (6 total diagnoses)	symptoms presentation and reanalysis at 12 months: $-77 (95%CI, $-2,990 to $7,334) WES at clinical genetics review and reanalysis at 12 months: $726 (95% CI, $-1,873 to $8,060)		
Howell (2018)[28]	Some	Commercial WES gene pane; $1,639	Path 1: $7,687 Path 2: $8,538 Path 3: $8,027 Path 4: $8,069 Path 5: $7,873 Path 6: $6,453 Path 7: $5,298	Path 1: $16,951 Path 2: $15,378 Path 3: $14,382 Path 4: $14,457 Path 5: $14,106 Path 6: $11,530 Path 7: $9,904	Compared to Path 1 Path 2: $8,559 Path 3: $3,250 Path 4: $3,650 Path 5: $1,775 Path 6: Dominates (i.e., identified more diagnoses at lower cost) Path 7: Dominates (i.e., identifies more diagnoses at lower cost) Sensitivity analysis varied diagnostic yield of WES and cost of WES; Path 5 also dominated under assumptions of somewhat higher diagnostic yield and 20% lower WES costs	NR	NR
Monroe (2016)[80]	Some	Trio; $3,972	Median (range) cost per patient Traditional diagnostic pathway: $14,153 ($6,343 to $47,841)	NR	NR	NR	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
			Median cost savings from early WES Diagnosed participants: $5,342 ($0 to $10,684) Undiagnosed participants: $4,854 ($890 to $18,696) Cost savings from early WES leading to 50% reduction in number and cost of diagnostic trajectory Diagnosed participants: $1,660 Undiagnosed participants: $4,269				
Nolan (2016)[24]	High	Range $2,000 to $15,000	Average cost of initial and secondary genetic and metabolic testing prior to WES: $4,853 Cost of WES testing: range $2,000 to $15,000 If WES was performed after initial but prior to secondary testing, estimated average savings of $2,968	NR	NR	NR	NR
Palmer (2018)[27]	Some	Trio; AU$4,036 to AU $12,362 (varied by commercial lab)	Standard path: AU$11,827 (95% CI, $10,677 to $13,027) In-house Exome path:	Standard path: AU$182,243 (95% CI, $72,703 to $406,142) In-house exome path:	AU$-5,236 (95% CI, $2,483 to $-9,784) [Exome path was cost saving relative to standard path]	NR	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
			AU$9,536 (95% CI, $9,412 to $9,683)	AU$ 19,074 (95% CI, $14,421 to $27,969)	Sensitivity analyses using costs of four commercial trio WES platforms demonstrated the exome path provided additional diagnoses at less costs >95% of the time for three of the four platforms. The fourth platform (which was the most expensive) resulted in an additional cost per diagnosis of $13,113 (95% CI, $8,610 to $23,728)		
Schofield (2017)[26]	Some	Singleton; AU$1,718	Mean cost per patient (95% CI) Traditional pathway: AU$ 10,491 (AU$ 9,115 to AU$11,848) Neuromuscular gene pathway: AU$3,808 (AU$3,293 to AU$4,373) WES pathway: AU$6,077 (AU$ 5,284 to AU$6,846)	Mean cost per diagnosis (95% CI) Traditional pathway: AU$22,596 (AU$17,004 to AU$31,498) Neuromuscular gene pathway: AU$5,077 (AU$4,228 to AU$6,100) WES pathway: AU$7,734 (AU$6,166 to AU$9,696)	Cost per additional diagnosis compared to the traditional pathway Neuromuscular gene pathway: AU$-23,390 (AU$-14,595 to AU$-41,184) WES pathway: AU$-13,732 (AU$-7,938 to AU$-473)	NA	NR
Soden (2014)[25]	High	NR	NR	At an average cost of prior testing of $19,100 (range $3,248 to $55,321) per family, authors estimate that WES would be cost-effective at a cost of $2,996 per individual ($7,640 per trio)	NR	NR	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
Stark (2016, 2017, 2019)[13-16]	High	Singleton; AU$ 1,500 to $3,100	Mean cost per patient (95% CI) Standard clinical pathway: AU$ 4,734 (AU$3,693 to AU$ 5,895) WES after basic and complex investigations: AU$ 8,384 (AU$ 7,079 to AU$ 9,619) WES after basic investigations: AU$ 5,914 (AU$ 5,243 to AU$ 6,641) WES as first-tier test: AU$3,752 (AU$ 3,752 to AU$ 3,752) For those with noninformative initial testing: WES reanalysis at 18 months: AU$ 391 (95% CI, AU$ 360 to AU$ 433) WES reanalysis every 6 months: AU$ 1,031 (AU$ 988 to AU$ 1,071) No reanalysis: AU$ 537 (95% CI, AU$ 159 to AU$ 1,051)	Mean cost per diagnosis (95% CI) Standard clinical pathway: AU$ 27,050 (AU$ 15,366 to AU$ 68,530) WES after basic and complex investigations: AU$13,415 (AU$ 10,165 to AU$ 18,351) WES after basic investigations: AU$ 9,462 (AU$ 7,497 to AU$ 12,619) WES as first-tier test: AU$ 6,003 (AU$4,841 to AU$ 7,899) For those with non-informative initial testing: WES reanalysis at 18 months: AU$ 2,838 (95% CI, 1,569 to 10,450) WES reanalysis every 6 months: AU$ 7,475 (95% CI, 3,625 to 30,400) No reanalysis: NA	Incremental cost per additional diagnosis compared to standard pathway: WES after basic and complex investigations: AU$ 8,112(AU$ 5,851 to AU$ 11,967) WES after basic investigations: AU$ 2,622 (AU$ 847 to AU$ 4,459) WES as first-tier test: AU$ -2,182 (AU$ -5,855 to AU$ 130) In 97% of simulations, WES as first-tier test was dominant (less cost with more diagnoses compared to standard care). Compared to no reanalysis: WES reanalysis at 18 months: AU$ -1,059 (95% CI, AU$ -10,502 to AU$ 1,937) WES reanalysis every 6 months: AU$ 3,578 (95% CI, AU$ -232 to AU$ 17,003)	Results from 2017 publication: [13] Compared to standard care after a median follow-up of 473 days: Diagnosis with WES and resulting changes in management for proband only: Cost per QALY gained AU$ -1,578 (95% CI, AU$ -205,450 to AU$ 19,780). In simulations to assess uncertainty of findings, 48.5% of simulations demonstrated cost savings from diagnosis and changes in management. Diagnosis with WES with resulting changes in management, cascade testing, and reproductive planning in first-degree relatives: Cost per QALY gained AU$ 8,119 (95% CI, AU$ 1,962 to AU$ 38,944). In simulations to assess uncertainty	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
						of findings, 97.8% of simulations demonstrated additional costs from diagnosis and changes in management and additional family member testing and counseling. Results from 2019 publication projecting health outcomes over 20 years compared to standard care:[15] WES after basic investigations: cost per QALY gained AU$ 31,144 (probands only); AU$ 20,840 (probands plus cascade outcomes in 1st degree relatives); AU$ 14,235 (probands, cascade outcomes in 1st degree relatives, reproductive outcomes)	
Stark (2018)[22]	Some	NR	Usual care + conventional sequencing costs (no WES): AU$ 4,734 Standard WES: AU$	Usual care + conventional sequencing costs (no WES): AU$27,050 (95% CI, AU$15,366 to AU$68, 530)	NR	NR	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
			6,777 Rapid WES: AU$ 7,029	Standard WES: AU$ 10,843 (95% CI, AU$7,488 to AU$14,090) Rapid WES: AU$ 13,388 (95% CI, AU$9,269 to AU$17,507)			
Tan (2017)[19]	Some	Singleton; < AU$ 2,300	Mean cost per patient (95% CI) Standard pathway no WES: $7,515 ($5,743 to $9,486) Standard pathway with WES: $9,800 ($8,033 to $11,758) WES at first genetics appointment: $5,349 ($4,583 to $6,295) WES at first tertiary presentation: $3,927 ($3,520 to $4,413)	Mean cost per diagnosis (95% CI) Standard pathway no WES: NA (study design assumed no diagnoses made) Standard pathway with WES: $18,762 ($13,640 to $26,628) WES at first genetics appointment: $10,239 ($7,667 to $14,614) WES at first tertiary presentation: $7,534 ($5,832 to $10,494)	Mean cost per additional diagnosis (95% CI) Compared to standard pathway: Standard pathway with WES: $4,804 ($3,904 to $6,523) WES at first genetics appointment: $-3,709 ($-7,491 to $ -694) WES at first tertiary presentation: $-6,412 ($-11,192 to $-2,887)	NR	NR
Tsiplova (2017)[79]	Some	CAD$ 1,655 (CAD$ 1,611 to CAD$ 1,699)	Cost per sample (95% CI) CMA: $CAD 744 (CAD$ 714 to CAD$ 773) CMA + WES: CAD$1,655 (CAD$ 1,611 to CAD$ 1,699)	NR	Incremental sample cost per diagnosis of CMA +WES compared to CMA alone: CAD$ 25,458	NR	NR
Vissers (2017)[20]	Some	€ 3,240	Mean costs (95% CI) per patient Standard pathway: E10,685 (9,544 to 11,909) WES pathway: E9,941* WES-first pathway: E8,356 (E7,591 to E9,247)	NR	NR	NR	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
Vrijenhoek (2018)[77]	High	Trio; € 3,600	Average health care cost before WES : E16,346 Average health care costs before and including WES as last test in diagnostic trajectory: E19,946 (median E8,734, range E0 to E316,860) Costs after receiving WES as last test in diagnostic trajectory were 82% lower than healthcare costs before WES testing. Costs after receiving WES as first-tier test (i.e., no other genetic test performed) 58% lower than before WES testing	NR	NR	NR	Average health care cost before WES : E16,346 Average health care costs before and including WES as last test in diagnostic trajectory: E19,946 (median E8,734, range E0 to E316,860) Costs after receiving WES as last test in diagnostic trajectory were 82% lower than healthcare costs before WES testing Costs after receiving WES as first-tier test (i.e. no other genetic test performed) were 58% lower than costs before WES testing
Walsh (2017)[78]	High	Singleton; AU$2,000	Mean cost per patient on standard investigations prior to WES: AU$ 4,013 (SD $2,761) Mean cost per patient of	Mean cost per diagnosis: Standard investigations and WES as last resort strategy: AU$ 16,027 Early WES in	Mean cost per additional diagnosis compared to standard investigations: WES as last resort strategy: AU$ 5,889	NA	NR

(Continued)

Author (Year)	Risk of bias	Cost of WES	Cost per patient	Cost per diagnosis	Cost per additional diagnosis	Cost-utility or cost-effectiveness	Other cost outcomes
			standard investigations and WES: AU$ 6,344 (SD NR)	hypothetical scenario: AU$ 12,413	Early WES in hypothetical scenario: AU$ 2,276		

Abbreviations: AU = Australian; CAD = Canadian; CI; confidence interval; E = Euro; NA = not applicable; NR = not reported; QALY = quality-adjusted life year; SD = standard deviation; U.S. = United States; * = calculated value.

Appendix D. Excluded Articles

List of Exclusion Codes

X1: Ineligible publication type or study design

X2: Ineligible population

X3: Ineligible test

X4: Ineligible outcome

X5: Non-English full text

X6: Systematic reviews for hand search

X7: Study protocol or in progress

X8: Duplicate or superseded

X9: Ineligible country

X10: Not retrievable

1. NCGENES: North Carolina clinical genomic evaluation by nextgen exome sequencing. Https://clinicaltrials.gov/show/nct01969370 https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01581945/full. Published 2013. Exclude: X8
2. Genomic sequencing in acutely ill neonates. Https://clinicaltrials.gov/show/nct02225522 https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01583543/full. Published 2014. Exclude: X8
3. Whole-genome sequencing can improve care of severely ill infants: study finds technique yields high rate of diagnoses, aids decision making related to treatment. Am J Med Genet A. 2015;167a(8):vi-vii. PMID: 26204861. doi: 10.1002/ajmg.a.37241. Exclude: X1
4. Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases. Genome Biol. 2015;16:134. PMID: 26112015. doi: 10.1186/s13059-015-0693-2. Exclude: X4
5. Enhancing genomic laboratory reports to enhance communication and empower patients. Https://clinicaltrials.gov/show/nct02504502 https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01491117/full. Published 2015. Exclude: X8
6. Whole-exome sequencing strategy proposed as first-line test: WES for well-phenotyped infants leads to high diagnostic yield. Am J Med Genet A. 2016;170(6):1387-1388. PMID: 27191527. doi: 10.1002/ajmg.a.37317. Exclude: X1
7. Patients express satisfaction, understanding of whole-genome sequencing: in primary care and cardiology, patients were generally satisfied with their physicians' communication of WGS results, but expectations about its clinical benefits were not met. Am J Med Genet A. 2018;176(4):754-755. PMID: 29575633. doi: 10.1002/ajmg.a.38669. Exclude: X1

8. Abela L, Steindl K, Simmons L, et al. A combined metabolic-genetic approach to early-onset epileptic encephalopathies: results from a Swiss study cohort. Neuropediatrics. 2016;47. PMID. doi: 10.1055/s-0036-1583731. Exclude: X1

9. Ackerman JP, Bartos DC, Kapplinger JD, Tester DJ, Delisle BP, Ackerman MJ. The promise and peril of precision medicine: phenotyping still matters most. Mayo Clin Proc. 2016. PMID: 27810088. doi: 10.1016/j.mayocp.2016.08.008. Exclude: X1

10. Adam S, Friedman JM. Controversy and debate on clinical genomics sequencing-paper 2: clinical genome-wide sequencing: don't throw out the baby with the bathwater! J Clin Epidemiol. 2017;92:7-10. PMID: 28916491. doi: 10.1016/j.jclinepi.2017.08.020. Exclude: X1

11. Alfares A, Alfadhel M, Wani T, et al. A multicenter clinical exome study in unselected cohorts from a consanguineous population of Saudi Arabia demonstrated a high diagnostic yield. Mol Genet Metab. 2017;121(2):91-95. PMID: 28454995. doi: 10.1016/j.ymgme.2017.04.002. Exclude: X4

12. Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. Genet Med. 2018;20(11):1328-1333. PMID: 29565419. doi: 10.1038/gim.2018.41. Exclude: X4

13. Al-Murshedi F, Meftah D, Scott P. Underdiagnoses resulting from variant misinterpretation: time for systematic reanalysis of whole exome data? Eur J Med Genet. 2019;62(1):39-43. PMID: 29709712. doi: 10.1016/j.ejmg.2018.04.016. Exclude: X1

14. Al-Nabhani M, Al-Rashdi S, Al-Murshedi F, et al. Reanalysis of exome sequencing data of intellectual disability samples: yields and benefits. Clin Genet. 2018;94(6):495-501. PMID: 30125339. doi: 10.1111/cge.13438. Exclude: X9

15. Al-Shamsi A, Hertecant JL, Souid AK, Al-Jasmi FA. Whole exome sequencing diagnosis of inborn errors of metabolism and other disorders in United Arab Emirates. Orphanet J Rare Dis. 2016;11(1):94. PMID: 27391121. doi: 10.1186/s13023-016-0474-3. Exclude: X4

16. Alsultan A, Al-Suliman AM, Aleem A, AlGahtani FH, Alfadhel M. Utilizing whole-exome sequencing to characterize the phenotypic variability of sickle cell disease. Genet Test Mol Biomarkers. 2018;22(9):561-567. PMID: 30183354. doi: 10.1089/gtmb.2018.0058. Exclude: X10

17. Ammann S, Lehmberg K, Zur Stadt U, et al. Effective immunological guidance of genetic analyses including exome sequencing in patients evaluated for hemophagocytic lymphohistiocytosis. J Clin Immunol. 2017;37(8):770-780. PMID: 28936583. doi: 10.1007/s10875-017-0443-1. Exclude: X4

18. Anderson JH, Tester DJ, Will ML, Ackerman MJ. Whole-exome molecular autopsy after exertion-related sudden unexplained death in the young. Circ Cardiovasc Genet. 2016;9(3):259-265. PMID: 27114410. doi: 10.1161/circgenetics.115.001370. Exclude: X4

19. Angione K, Eschbach K, Smith G, Joshi C, Demarest S. Genetic testing in a cohort of patients with potential epilepsy with myoclonic-atonic seizures. Epilepsy Res. 2019;150:70-77. PMID: 30660939. doi: 10.1016/j.eplepsyres.2019.01.008. Exclude: X4

20. Asan, Xu Y, Jiang H, et al. Comprehensive comparison of three commercial human whole-exome capture platforms. Genome Biol. 2011;12(9):R95. PMID: 21955857. doi: 10.1186/gb-2011-12-9-r95. Exclude: X9

21. Assistance Publique Hopitaux De Marseille. New diagnostic strategy in hypertrophic cardiomyopathy. https://ClinicalTrials.gov/show/NCT02520856. Published 2015. Updated July. Exclude: X7

22. Atwal PS, Brennan ML, Cox R, et al. Clinical whole-exome sequencing: are we there yet? Genet Med. 2014;16(9):717-719. PMID: 24525916. doi: 10.1038/gim.2014.10. Exclude: X1

23. Ayuso C, Millan JM, Dal-Re R. Management and return of incidental genomic findings in clinical trials. Pharmacogenomics J. 2015;15(1):1-5. PMID: 25348616. doi: 10.1038/tpj.2014.62. Exclude: X1

24. Bacchelli C, Williams HJ. Opportunities and technical challenges in next-generation sequencing for diagnosis of rare pediatric diseases. Expert Rev Mol Diagn. 2016;16(10):1073-1082. PMID: 27560481. doi: 10.1080/14737159.2016.1222906. Exclude: X1

25. Bademci G, Diaz-Horta O, Guo S, et al. Identification of copy number variants through whole-exome sequencing in autosomal recessive nonsyndromic hearing loss. Genet Test Mol Biomarkers. 2014;18(9):658-661. PMID: 25062256. doi: 10.1089/gtmb.2014.0121. Exclude: X4

26. Bagnall RD, Das KJ, Duflou J, Semsarian C. Exome analysis-based molecular autopsy in cases of sudden unexplained death in the young. Heart Rhythm. 2014;11(4):655-662. PMID: 24440382. doi: 10.1016/j.hrthm.2014.01.017. Exclude: X2

27. Bahamat AA, Assidi M, Lary SA, et al. Use of array comparative genomic hybridization for the diagnosis of DiGeorge Syndrome in Saudi Arabian population. Cytogenet Genome Res. 2018;154(1):20-29. PMID: 29455205. doi: 10.1159/000487094. Exclude: X3

28. Bainbridge MN, Wiszniewski W, Murdock DR, et al. Whole-genome sequencing for optimized patient management. Sci Transl Med. 2011;3(87):87re83. PMID: 21677200. doi: 10.1126/scitranslmed.3002243. Exclude: X1

29. Baker M. Increasing precision in medicine - tackling the bottleneck of variant interpretation. Drugs Today (Barc). 2016;52(7):395-398. PMID: 27540598. doi: 10.1358/dot.2016.52.7.2533694. Exclude: X1

30. Balci TB, Hartley T, Xi Y, et al. Debunking Occam's razor: diagnosing multiple genetic diseases in families by whole-exome sequencing. Clin Genet. 2017;92(3):281-289. PMID: 28170084. doi: 10.1111/cge.12987. Exclude: X4

31. Bardakjian TM, Helbig I, Quinn C, et al. Genetic test utilization and diagnostic yield in adult patients with neurological disorders. Neurogenetics. 2018;19(2):105-110. PMID: 29589152. doi: 10.1007/s10048-018-0544-x. Exclude: X4

32. Bartholdi D, Miny P. [Genetic testing in the fetus and child]. Ther Umsch. 2013;70(11):621-631. PMID: 24168795. doi: 10.1024/0040-5930/a000457. Exclude: X5

33. Basel D, McCarrier J. Ending a diagnostic odyssey: family education, counseling, and response to eventual diagnosis. Pediatr Clin North Am. 2017;64(1):265-272. PMID: 27894449. doi: 10.1016/j.pcl.2016.08.017. Exclude: X1

34. Basha M, Demeer B, Revencu N, et al. Whole exome sequencing identifies mutations in 10% of patients with familial non-syndromic cleft lip and/or palate in genes mutated in well-known syndromes. J Med Genet. 2018;55(7):449-458. PMID: 29500247. doi: 10.1136/jmedgenet-2017-105110. Exclude: X1

35. Bauer P, Kandaswamy KK, Weiss MER, et al. Development of an evidence-based algorithm that optimizes sensitivity and specificity in ES-based diagnostics of a clinically heterogeneous patient population. Genet Med. 2019;21(1):53-61. PMID: 30100613. doi: 10.1038/s41436-018-0016-6. Exclude: X4

36. Beale S, Sanderson D, Sanniti A, Dundar Y, Boland A. A scoping study to explore the cost-effectiveness of next-generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children. Health Technol Assess. 2015;19(46):1-90. PMID: 26132578. doi: 10.3310/hta19460. Exclude: X6

37. Becherucci F, Mazzinghi B, Landini S, et al. Whole-exome sequencing for personalized managementof idiopathic nephrotic syndrome. Nephrology Dialysis Transplantation. 2018;33:i43. PMID. doi: 10.1093/ndt/gfy104.FO057. Exclude: X1

38. Beheshtian M, Saee Rad S, Babanejad M, et al. Impact of whole exome sequencing among Iranian patients with autosomal recessive retinitis pigmentosa. Arch Iran Med. 2015;18(11):776-785. PMID: 26497376. doi: 0151811/aim.009. Exclude: X9

39. Bell SG. Ethical implications of rapid whole-genome sequencing in neonates. Neonatal Netw. 2018;37(1):42-44. PMID: 29436358. doi: 10.1891/0730-0832.37.1.42. Exclude: X1

40. Bergant G, Maver A, Lovrecic L, Cuturilo G, Hodzic A, Peterlin B. Comprehensive use of extended exome analysis improves diagnostic yield in rare disease: a retrospective survey in 1,059 cases. Genet Med. 2018;20(3):303-312. PMID: 28914264. doi: 10.1038/gim.2017.142. Exclude: X3

41. Bernardini L, Alesi V, Loddo S, et al. High-resolution SNP arrays in mental retardation diagnostics: how much do we gain? Eur J Hum Genet. 2010;18(2):178-185. PMID: 19809473. doi: 10.1038/ejhg.2009.154. Exclude: X3

42. Bettencourt C, Lopez-Sendon JL, Garcia-Caldentey J, et al. Exome sequencing is a useful diagnostic tool for complicated forms of hereditary spastic paraplegia. Clin Genet. 2014;85(2):154-158. PMID: 23438842. doi: 10.1111/cge.12133. Exclude: X1

43. Biesecker LG, Nussbaum RL, Rehm HL. Distinguishing variant pathogenicity from genetic diagnosis: how to know whether a variant causes a condition. JAMA. 2018;320(18):1929-1930. PMID: 30326012. doi: 10.1001/jama.2018.14900. Exclude: X1

44. Bittles AH. Genetics and global healthcare. J R Coll Physicians Edinb. 2013;43(1):7-10. PMID: 23516683. doi: 10.4997/jrcpe.2013.102. Exclude: X1

45. Bochud M, Currat C, Chapatte L, Roth C, Mooser V. High participation rate among 25 721 patients with broad age range in a hospital-based research project involving whole-genome sequencing - the Lausanne Institutional Biobank. Swiss Med Wkly. 2017;147:w14528. PMID: 29063527. doi: 10.4414/smw.2017.14528. Exclude: X2

46. Bodian DL, Klein E, Iyer RK, et al. Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. Genet Med. 2016;18(3):221-230. PMID: 26334177. doi: 10.1038/gim.2015.111. Exclude: X2

47. Borghesi A, Mencarelli MA, Memo L, et al. Intersociety policy statement on the use of whole-exome sequencing in the critically ill newborn infant. Ital J Pediatr. 2017;43(1):100. PMID: 29100554. doi: 10.1186/s13052-017-0418-0. Exclude: X1

48. Bourgeron T. Current knowledge on the genetics of autism and propositions for future research. C R Biol. 2016;339(7-8):300-307. PMID: 27289453. doi: 10.1016/j.crvi.2016.05.004. Exclude: X1

49. Bowdin S, Ray PN, Cohn RD, Meyn MS. The genome clinic: a multidisciplinary approach to assessing the opportunities and challenges of integrating genomic analysis into clinical care. Hum Mutat. 2014;35(5):513-519. PMID: 24599881. doi: 10.1002/humu.22536. Exclude: X1

50. Bowdin SC, Hayeems RZ, Monfared N, Cohn RD, Meyn MS. The SickKids Genome Clinic: developing and evaluating a pediatric model for individualized genomic medicine. Clin Genet. 2016;89(1):10-19. PMID: 25813238. doi: 10.1111/cge.12579. Exclude: X1

51. Brett GR, Wilkins EJ, Creed ET, et al. Genetic counseling in the era of genomics: what's all the fuss about? J Genet Couns. 2018;27(5):1010-1021. PMID: 29368275. doi: 10.1007/s10897-018-0216-x. Exclude: X1

52. Brunham LR, Hayden MR. Medicine. Whole-genome sequencing: the new standard of care? Science. 2012;336(6085):1112-1113. PMID: 22654044. doi: 10.1126/science.1220967. Exclude: X1

53. Bujakowska KM, Fernandez-Godino R, Place E, et al. Copy-number variation is an important contributor to the genetic causality of inherited retinal degenerations. Genet Med. 2017;19(6):643-651. PMID: 27735924. doi: 10.1038/gim.2016.158. Exclude: X3

54. Cai Y, Huang T. Accelerating precision medicine through genetic and genomic big data analysis. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2018;1864(6):2215-2217. PMID. doi: 10.1016/j.bbadis.2018.03.012. Exclude: X1

55. Centre Hospitalier Universitaire de Besancon. Molecular diagnosis of syndromic or isolated severe intellectual disability using whole exome sequencing : a pilot study. https://ClinicalTrials.gov/show/NCT02862808. Published 2017. Updated September 20. Exclude: X7

56. Centre Hospitalier Universitaire Dijon. Evaluate and understand preferences and representations in families of patients with regard to high-throughput sequencing technology for diagnostic purposes. Published. Exclude: X10

57. Centre Hospitalier Universitaire Dijon. Evaluation of the diagnostic contribution of high-throughput exome sequencing for patients with convulsive encephalopathy of unknown etiology: pilot study to improve genetic counselling. https://ClinicalTrials.gov/show/NCT03652246. Published 2013. Updated September. Exclude: X7

58. Centre Hospitalier Universitaire Dijon. Screening for genes in patients with congenital neutropenia. https://ClinicalTrials.gov/show/NCT02866162. Published 2013. Updated September. Exclude: X8

59. Centre Hospitalier Universitaire Dijon. Medico-economic evaluation of different high-throughput sequencing strategies in the diagnosis of patients with intellectual deficiency. https://ClinicalTrials.gov/show/NCT03287206. Published 2017. Updated June 28. Exclude: X7

60. Centre Hospitalier Universitaire Dijon. Secondary findings from high-throughput sequencing: how to announce them with respect to the patient's needs. https://ClinicalTrials.gov/show/NCT03288727. Published 2017. Updated November 4. Exclude: X7

61. Centre Hospitalier Universitaire Dijon. Identification of the molecular and/or pathophysiological bases of developmental diseases. https://ClinicalTrials.gov/show/NCT03287193. Published 2017. Updated March 13. Exclude: X7

62. Centre Hospitalier Universitaire Dijon. Contribution of high throughput RNA sequencing combined with sequencing of whole genomes in the diagnosis of intellectual disability. https://ClinicalTrials.gov/show/NCT03857997. Published 2019. Updated February 4. Exclude: X7

63. Chacon-Camacho OF, Garcia-Montano LA, Zenteno JC. The clinical implications of molecular monitoring and analyses of inherited retinal diseases. Expert Rev Mol Diagn. 2017;17(11):1009-1021. PMID: 28945154. doi: 10.1080/14737159.2017.1384314. Exclude: X1

64. Chan LF, Campbell DC, Novoselova TV, Clark AJ, Metherell LA. Whole-exome sequencing in the differential diagnosis of primary adrenal insufficiency in children. Front Endocrinol (Lausanne). 2015;6:113. PMID: 26300845. doi: 10.3389/fendo.2015.00113. Exclude: X4

65. Charbit-Henrion F, Parlato M, Hanein S, et al. Diagnostic yield of next-generation sequencing in very early-onset inflammatory bowel diseases: a multicenter study. J Crohns Colitis. 2018. PMID: 29788237. doi: 10.1093/ecco-jcc/jjy068. Exclude: X4

66. Charite University; German Federal Ministry of Education Research. Mutation exploration in non-acquired, genetic disorders and its impact on health economy and life quality. https://ClinicalTrials.gov/show/NCT02380729. Published 2015. Updated January 31. Exclude: X7

67. Charng WL, Karaca E, Coban Akdemir Z, et al. Exome sequencing in mostly consanguineous Arab families with neurologic disease provides a high potential molecular diagnosis rate. BMC Med Genomics. 2016;9(1):42. PMID: 27435318. doi: 10.1186/s12920-016-0208-3. Exclude: X4

68. Chen Z, Wang JL, Tang BS, et al. Using next-generation sequencing as a genetic diagnostic tool in rare autosomal recessive neurologic Mendelian disorders. Neurobiol Aging. 2013;34(10):2442.e2411-2447. PMID: 23726790. doi: 10.1016/j.neurobiolaging.2013.04.029. Exclude: X9

69. Cherot E, Keren B, Dubourg C, et al. Using medical exome sequencing to identify the causes of neurodevelopmental disorders: experience of 2 clinical units and 216 patients. Clin Genet. 2018;93(3):567-576. PMID: 28708303. doi: 10.1111/cge.13102. Exclude: X3

70. Chiara M, Pavesi G. Evaluation of quality assessment protocols for high throughput genome resequencing data. Front Genet. 2017;8:94. PMID: 28736571. doi: 10.3389/fgene.2017.00094. Exclude: X1

71. Children's Hospital of Fudan University. Etiology and treatment of neonatal seizure. https://ClinicalTrials.gov/show/NCT03822741. Published 2016. Updated August 8. Exclude: X7

72. Children's Hospital of Philadelphia. LeukoSEQ: whole genome sequencing as a first-line diagnostic tool for leukodystrophies. https://ClinicalTrials.gov/show/NCT02699190. Published 2017. Updated January 6. Exclude: X7

73. Children's Hospital of Philadelphia. The Myelin disorders biorepository project. https://ClinicalTrials.gov/show/NCT03047369. Published 2016. Updated December 8. Exclude: X7

74. Children's Mercy Hospital Kansas City. Genomic sequencing in acutely ill neonates. https://ClinicalTrials.gov/show/NCT02225522. Published 2014. Updated October. Exclude: X8

75. Choi BO, Koo SK, Park MH, et al. Exome sequencing is an efficient tool for genetic screening of Charcot-Marie-Tooth disease. Hum Mutat. 2012;33(11):1610-1615. PMID: 22730194. doi: 10.1002/humu.22143. Exclude: X4

76. Christensen KD, Dukhovny D, Siebert U, Green RC. Assessing the costs and cost-effectiveness of genomic sequencing. J Pers Med. 2015;5(4):470-486. PMID: 26690481. doi: 10.3390/jpm5040470. Exclude: X1

77. Christensen KD, Phillips KA, Green RC, Dukhovny D. The cost of integrating whole genome sequencing into the care of cardiomyopathy patients: sensitivity and Scenario analyses. Value Health. 2018;21:S56-S57. PMID: CN-01630917. Exclude: X1

78. Christensen KD, Vassy JL, Phillips KA, et al. Short-term costs of integrating whole-genome sequencing into primary care and cardiology settings: a pilot randomized trial. Genet Med. 2018;20(12):1544-1553. PMID: 29565423. doi: 10.1038/gim.2018.35. Exclude: X3

79. Christensen KD, Vassy JL, Phillips KA, et al. Short-term costs of whole genome sequencing in cardiology and primary care: findings from the medseq project. Value Health. 2017;20(5):A30-. PMID: CN-01407756. Exclude: X3

80. Chrystoja CC, Diamandis EP. Whole genome sequencing as a diagnostic test: challenges and opportunities. Clin Chem. 2014;60(5):724-733. PMID: 24227285. doi: 10.1373/clinchem.2013.209213. Exclude: X1

81. Chung JH, Cai J, Suskin BG, Zhang Z, Coleman K, Morrow BE. Whole-genome sequencing and integrative genomic analysis approach on two 22q11.2 Deletion syndrome family trios for genotype to phenotype correlations. Hum Mutat. 2015;36(8):797-807. PMID: 25981510. doi: 10.1002/humu.22814. Exclude: X1

82. Cirino AL, Lakdawala NK, McDonough B, et al. A comparison of whole genome sequencing to multigene panel testing in hypertrophic cardiomyopathy patients. Circ Cardiovasc Genet. 2017;10(5). PMID: 29030401. doi: 10.1161/circgenetics.117.001768. Exclude: X3

83. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med. 2018;3:16. PMID: 30002876. doi: 10.1038/s41525-018-0053-8. Exclude: X6

84. Classen CF, Riehmer V, Landwehr C, et al. Dissecting the genotype in syndromic intellectual disability using whole exome sequencing in addition to genome-wide copy number analysis. Hum Genet. 2013;132(7):825-841. PMID: 23552953. doi: 10.1007/s00439-013-1296-1. Exclude: X1

85. Cohen L, Orenstein N, Weisz-Hubshman M, et al. [Utilization of whole exome sequencing in diagnostics of genetic disease: Rabin Medical Center's experience]. Harefuah. 2017;156(4):212-216. PMID: 28551919. Exclude: X5

86. Consugar MB, Navarro-Gomez D, Place EM, et al. Panel-based genetic diagnostic testing for inherited eye diseases is highly accurate and reproducible, and more sensitive for variant detection, than exome sequencing. Genet Med. 2015;17(4):253-261. PMID: 25412400. doi: 10.1038/gim.2014.172. Exclude: X3

87. Coorg R, Weisenberg JL, Wong M. Clinical neurogenetics: recent advances in the genetics of epilepsy. Neurol Clin. 2013;31(4):891-913. PMID: 24176415. doi: 10.1016/j.ncl.2013.04.003. Exclude: X1

88. Cornelis C, Tibben A, Dondorp W, et al. Whole-exome sequencing in pediatrics: parents' considerations toward return of unsolicited findings for their child. Eur J Hum Genet. 2016;24(12):1681-1687. PMID: 27460421. doi: 10.1038/ejhg.2016.100. Exclude: X4

89. Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. Eur J Hum Genet. 2018;26(5):740-744. PMID: 29453418. doi: 10.1038/s41431-018-0114-6. Exclude: X3

90. Darin N, Leckstrom K, Sikora P, Lindgren J, Almen G, Asin-Cayuela J. gamma-glutamyl transpeptidase deficiency caused by a large homozygous intragenic deletion in GGT1. Eur J Hum Genet. 2018;26(6):808-817. PMID: 29483667. doi: 10.1038/s41431-018-0122-6. Exclude: X1

91. Das AS, Agamanolis DP, Cohen BH. Use of next-generation sequencing as a diagnostic tool for congenital myasthenic syndrome. Pediatr Neurol. 2014;51(5):717-720. PMID: 25194721. doi: 10.1016/j.pediatrneurol.2014.07.032. Exclude: X1

92. de Araujo Lima L, Wang K. PennCNV in whole-genome sequencing data. BMC Bioinformatics. 2017;18(Suppl 11):383. PMID: 28984186. doi: 10.1186/s12859-017-1802-x. Exclude: X3

93. de Castro-Miro M, Pomares E, Lores-Motta L, et al. Combined genetic and high-throughput strategies for molecular diagnosis of inherited retinal dystrophies. PLoS One. 2014;9(2):e88410. PMID: 24516651. doi: 10.1371/journal.pone.0088410. Exclude: X3

94. de Castro-Miro M, Tonda R, Escudero-Ferruz P, et al. Novel candidate genes and a wide spectrum of structural and point mutations responsible for inherited retinal dystrophies revealed by exome sequencing. PLoS One. 2016;11(12):e0168966. PMID: 28005958. doi: 10.1371/journal.pone.0168966. Exclude: X4

95. de Ligt J, Boone PM, Pfundt R, et al. Detection of clinically relevant copy number variants with whole-exome sequencing. Hum Mutat. 2013;34(10):1439-1448. PMID: 23893877. doi: 10.1002/humu.22387. Exclude: X3

96. de Villartay JP. When natural mutants do not fit our expectations: the intriguing case of patients with XRCC4 mutations revealed by whole-exome sequencing. EMBO Mol Med. 2015;7(7):862-864. PMID: 25962386. doi: 10.15252/emmm.201505307. Exclude: X1

97. Demougeot L, Houdayer F, Pelissier A, et al. [Changes in clinical practice related to the arrival of next-generation sequencing in the genetic diagnosis of developmental diseases]. Arch Pediatr. 2018;25(2):77-83. PMID: 29395884. doi: 10.1016/j.arcped.2017.12.006. Exclude: X5

98. Dewey FE, Murray MF, Overton JD, et al. Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. Science. 2016;354(6319). PMID: 28008009. doi: 10.1126/science.aaf6814. Exclude: X2

99. Dhamija R, Chambers C. Diagnostic NGS for severe neuromuscular disorders. Pediatr Neurol Briefs. 2015;29(11):82. PMID: 26933539. doi: 10.15844/pedneurbriefs-29-11-1. Exclude: X1

100. Dong Z, Zhang J, Hu P, et al. Low-pass whole-genome sequencing in clinical cytogenetics: a validated approach. Genet Med. 2016;18(9):940-948. PMID: 26820068. doi: 10.1038/gim.2015.199. Exclude: X3

101. Douglas MP, Ladabaum U, Pletcher MJ, Marshall DA, Phillips KA. Economic evidence on identifying clinically actionable findings with whole-genome sequencing: a scoping review. Genet Med. 2016;18(2):111-116. PMID: 25996638. doi: 10.1038/gim.2015.69. Exclude: X6

102. Du X, Gao X, Liu X, et al. Genetic diagnostic evaluation of trio-based whole exome sequencing among children with diagnosed or suspected autism spectrum disorder. Front Genet. 2018;9:594. PMID: 30555518. doi: 10.3389/fgene.2018.00594. Exclude: X9

103. Eilbeck K, Quinlan A, Yandell M. Settling the score: variant prioritization and Mendelian disease. Nat Rev Genet. 2017;18(10):599-612. PMID: 28804138. doi: 10.1038/nrg.2017.52. Exclude: X1

104. Eldomery MK, Coban-Akdemir Z, Harel T, et al. Lessons learned from additional research analyses of unsolved clinical exome cases. Genome Med. 2017;9(1):26. PMID: 28327206. doi: 10.1186/s13073-017-0412-6. Exclude: X3

105. Ellingford JM, Barton S, Bhaskar S, et al. Whole genome sequencing increases molecular diagnostic yield compared with current diagnostic testing for inherited retinal disease. Ophthalmology. 2016;123(5):1143-1150. PMID: 26872967. doi: 10.1016/j.ophtha.2016.01.009. Exclude: X3

106. Elmas M, Yildiz H, Erdogan M, Gogus B, Avci K, Solak M. Comparison of clinical parameters with whole exome sequencing analysis results of autosomal recessive patients; a center experience. Mol Biol Rep. 2018. PMID: 30426380. doi: 10.1007/s11033-018-4470-7. Exclude: X9

107. Emad A, Lamoureux J, Ouellet A, Drouin R. Rapid aneuploidy detection of chromosomes 13, 18, 21, X and Y using quantitative fluorescent polymerase chain reaction with few microdissected fetal cells. Fetal Diagn Ther. 2015;38(1):65-76. PMID: 25999366. doi: 10.1159/000365810. Exclude: X3

108. Eunice Kennedy Shriver National Institute of Child Health. Evaluation of children with endocrine and metabolic-related conditions. https://ClinicalTrials.gov/show/NCT02769975. Published 2016. Updated May 11. Exclude: X7

109. Fahiminiya S, Majewski J, Mort J, Moffatt P, Glorieux FH, Rauch F. Mutations in WNT1 are a cause of osteogenesis imperfecta. J Med Genet. 2013;50(5):345-348. PMID: 23434763. doi: 10.1136/jmedgenet-2013-101567. Exclude: X1

110. Fan J, Wang L, Wang H, et al. The clinical utility of next-generation sequencing for identifying chromosome disease syndromes in human embryos. Reprod Biomed Online. 2015;31(1):62-70. PMID: 25985995. doi: 10.1016/j.rbmo.2015.03.010. Exclude: X2

111. Fang H, Wu Y, Yang H, et al. Whole genome sequencing of one complex pedigree illustrates challenges with genomic medicine. BMC Med Genomics. 2017;10(1):10. PMID: 28228131. doi: 10.1186/s12920-017-0246-5. Exclude: X1

112. Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med. 2018;3:10. PMID: 29644095. doi: 10.1038/s41525-018-0049-4. Exclude: X3

113. Farrell CP, Parker CJ, Phillips JD. Exome sequencing for molecular characterization of non-HFE hereditary hemochromatosis. Blood Cells Mol Dis. 2015;55(2):101-103. PMID: 26142323. doi: 10.1016/j.bcmd.2015.04.002. Exclude: X1

114. Farwell Hagman KD, Shinde DN, Mroske C, et al. Candidate-gene criteria for clinical reporting: diagnostic exome sequencing identifies altered candidate genes among 8% of patients with undiagnosed diseases. Genet Med. 2017;19(2):224-235. PMID: 27513193. doi: 10.1038/gim.2016.95. Exclude: X1

115. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015;17(7):578-586. PMID: 25356970. doi: 10.1038/gim.2014.154. Exclude: X4

116. Fattahi Z, Kalhor Z, Fadaee M, et al. Improved diagnostic yield of neuromuscular disorders applying clinical exome sequencing in patients arising from a consanguineous population. Clin Genet. 2017;91(3):386-402. PMID: 27234031. doi: 10.1111/cge.12810. Exclude: X9

117. Fedida J, Fressart V, Charron P, et al. Contribution of exome sequencing for genetic diagnostic in arrhythmogenic right ventricular cardiomyopathy/dysplasia. PLoS One. 2017;12(8):e0181840. PMID: 28767663. doi: 10.1371/journal.pone.0181840. Exclude: X4

118. Feero WG, Wicklund CA, Veenstra D. Precision medicine, genome sequencing, and improved population health. JAMA. 2018;319(19):1979-1980. PMID: 29547675. doi: 10.1001/jama.2018.2925. Exclude: X1

119. Fichna JP, Macias A, Piechota M, et al. Whole-exome sequencing identifies novel pathogenic mutations and putative phenotype-influencing variants in Polish limb-girdle muscular dystrophy patients. Hum Genomics. 2018;12(1):34. PMID: 29970176. doi: 10.1186/s40246-018-0167-1. Exclude: X4

120. Fierman AH. Advances in whole-genome genetic testing: from chromosomes to microarrays; solving the puzzle: case examples of array comparative genomic hybridization as a tool to end the diagnostic odyssey. Foreword. Curr Probl Pediatr Adolesc Health Care. 2012;42(3):45-46. PMID: 22325473. doi: 10.1016/j.cppeds.2011.10.005. Exclude: X1

121. Flore LA, Milunsky JM. Updates in the genetic evaluation of the child with global developmental delay or intellectual disability. Semin Pediatr Neurol. 2012;19(4):173-180. PMID: 23245550. doi: 10.1016/j.spen.2012.09.004. Exclude: X1

122. Fokstuen S, Makrythanasis P, Hammar E, et al. Experience of a multidisciplinary task force with exome sequencing for Mendelian disorders. Hum Genomics. 2016;10(1):24. PMID: 27353043. doi: 10.1186/s40246-016-0080-4. Exclude: X4

123. Foley AR, Pitceathly RD, He J, et al. Whole-genome sequencing and the clinician: a tale of two cities. J Neurol Neurosurg Psychiatry. 2014;85(9):1012-1015. PMID: 24706943. doi: 10.1136/jnnp-2013-306264. Exclude: X1

124. Fong K, Bailey CV, Tuttle P, Cunningham B, McGrath JA, Cho RJ. Questioning the clinical utility of exome sequencing in developing countries. Pediatr Dermatol. 2017;34(1):e32-e34. PMID: 27874213. doi: 10.1111/pde.13029. Exclude: X1

125. Frederix GW, Monroe G, Hovels AM, van Haaften G. Whole exome sequencing as a diagnostic tool for complex neurological disorders. Value Health. 2014;17(7):A396. PMID: 27200932. doi: 10.1016/j.jval.2014.08.886. Exclude: X1

126. French CE, Delon I, Dolling H, et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. Intensive Care Med. 2019. PMID: 30847515. doi: 10.1007/s00134-019-05552-x. Exclude: X3

127. Gadalla SM, Ballew BJ, Haagenson MD, et al. Germline mutations in patients receiving unrelated donor hematopoietic cell transplant for severe aplastic anemia. Blood. Conference: 58th annual meeting of the american society of hematology, ASH 2016. United states. Conference start: 20161203. Conference end: 20161206. 2016;128(22) (no pagination). PMID: CN-01303036. Exclude: X1

128. Gallo V, Dotta L, Giardino G, et al. Diagnostics of primary immunodeficiencies through next-generation sequencing. Front Immunol. 2016;7:466. PMID: 27872624. doi: 10.3389/fimmu.2016.00466. Exclude: X4

129. Gambin T, Akdemir ZC, Yuan B, et al. Homozygous and hemizygous CNV detection from exome sequencing data in a Mendelian disease cohort. Nucleic Acids Res. 2017;45(4):1633-1648. PMID: 27980096. doi: 10.1093/nar/gkw1237. Exclude: X3

130. Gambin T, Jhangiani SN, Below JE, et al. Secondary findings and carrier test frequencies in a large multiethnic sample. Genome Med. 2015;7(1):54. PMID: 26195989. doi: 10.1186/s13073-015-0171-1. Exclude: X2

131. Gauthier-Vasserot A, Thauvin-Robinet C, Bruel AL, et al. Application of whole-exome sequencing to unravel the molecular basis of undiagnosed syndromic congenital neutropenia with intellectual disability. Am J Med Genet A. 2017;173(1):62-71. PMID: 27615324. doi: 10.1002/ajmg.a.37969. Exclude: X4

132. Geisinger Clinic Patient-Centered Outcomes Research Institute. Enhancing genomic laboratory reports to enhance communication and empower patients. https://ClinicalTrials.gov/show/NCT02504502. Published 2015. Updated August. Exclude: X8

133. George A, Marquis-Nicholson R, Zhang LT, et al. Chromosome microarray analysis in a clinical environment: new perspective and new challenge. Br J Biomed Sci. 2011;68(2):100-108. PMID: 21706924. Exclude: X1

134. Ghaoui R, Cooper ST, Lek M, et al. Use of whole-exome sequencing for diagnosis of Limb-Girdle Muscular Dystrophy: Outcomes and lessons learned. JAMA Neurol. 2015;72(12):1424-1432. PMID: 26436962. doi: 10.1001/jamaneurol.2015.2274. Exclude: X4

135. Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014;511(7509):344-347. PMID: 24896178. doi: 10.1038/nature13394. Exclude: X3

136. Goldfeder RL, Priest JR, Zook JM, et al. Medical implications of technical accuracy in genome sequencing. Genome Med. 2016;8(1):24. PMID: 26932475. doi: 10.1186/s13073-016-0269-0. Exclude: X3

137. Golding M, Paluch BE, Srivastava P, et al. Patients treated with decitabine demonstrate changes in β-catenin localization from the nucleus to the cytoplasm in circulating blasts. Blood. 2013;122(21). PMID. Exclude: X1

138. Gonzaga-Jauregui C, Lupski JR, Gibbs RA. Human genome sequencing in health and disease. Annu Rev Med. 2012;63:35-61. PMID: 22248320. doi: 10.1146/annurev-med-051010-162644. Exclude: X1

139. Gozes I, Patterson MC, Van Dijck A, et al. The eight and a half year journey of undiagnosed AD: Gene sequencing and funding of advanced genetic testing has led to hope and new beginnings. Front Endocrinol (Lausanne). 2017;8:107. PMID: 28579975. doi: 10.3389/fendo.2017.00107. Exclude: X1

140. Griffin HR, Pyle A, Blakely EL, et al. Accurate mitochondrial DNA sequencing using off-target reads provides a single test to identify pathogenic point mutations. Genet Med. 2014;16(12):962-971. PMID: 24901348. doi: 10.1038/gim.2014.66. Exclude: X3

141. Gross AM, Ajay SS, Rajan V, et al. Copy-number variants in clinical genome sequencing: deployment and interpretation for rare and undiagnosed disease. Genet Med. 2018. PMID: 30293986. doi: 10.1038/s41436-018-0295-y. Exclude: X3

142. Guo MH, Shen Y, Walvoord EC, et al. Whole exome sequencing to identify genetic causes of short stature. Horm Res Paediatr. 2014;82(1):44-52. PMID: 24970356. doi: 10.1159/000360857. Exclude: X4

143. Hadinnapola C, Bleda M, Haimel M, et al. Phenotypic characterization of EIF2AK4 mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. Circulation. 2017;136(21):2022-2033. PMID: 28972005. doi: 10.1161/circulationaha.117.028351. Exclude: X3

144. Hamilton A, Tetreault M, Dyment DA, et al. Concordance between whole-exome sequencing and clinical Sanger sequencing: implications for patient care. Mol Genet Genomic Med. 2016;4(5):504-512. PMID: 27652278. doi: 10.1002/mgg3.223. Exclude: X4

145. Hanchard NA, Murdock DR, Magoulas PL, et al. Exploring the utility of whole-exome sequencing as a diagnostic tool in a child with atypical episodic muscle weakness. Clin Genet. 2013;83(5):457-461. PMID: 22901280. doi: 10.1111/j.1399-0004.2012.01951.x. Exclude: X1

146. Harris E, Topf A, Barresi R, et al. Exome sequences versus sequential gene testing in the UK highly specialised Service for Limb Girdle Muscular Dystrophy. Orphanet J Rare Dis. 2017;12(1):151. PMID: 28877744. doi: 10.1186/s13023-017-0699-9. Exclude: X4

147. Hartley T, Wagner JD, Warman-Chardon J, et al. Whole-exome sequencing is a valuable diagnostic tool for inherited peripheral neuropathies: outcomes from a cohort of 50 families. Clin Genet. 2018;93(2):301-309. PMID: 28708278. doi: 10.1111/cge.13101. Exclude: X4

148. Hayeems RZ, Bhawra J, Tsiplova K, et al. Care and cost consequences of pediatric whole genome sequencing compared to chromosome microarray. Eur J Hum Genet. 2017;25(12):1303-1312. PMID: 29158552. doi: 10.1038/s41431-017-0020-3. Exclude: X3

149. Hehir-Kwa JY, Pfundt R, Veltman JA. Exome sequencing and whole genome sequencing for the detection of copy number variation. Expert Rev Mol Diagn. 2015;15(8):1023-1032. PMID: 26088785. doi: 10.1586/14737159.2015.1053467. Exclude: X1

150. Heitzman D, Sharma M, Pascual V, Phillips JT. Whole blood transcriptional profiling of sporadic amyotrophic lateral sclerosis patients identifies a sub-population with an inflammatory component. Neurology. 2013;80(1). PMID. Exclude: X1

151. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18(9):898-905. PMID: 26795593. doi: 10.1038/gim.2015.186. Exclude: X4

152. Helm BM, Langley K, Spangler BB, Schrier Vergano SA. Military health care dilemmas and genetic discrimination: a family's experience with whole exome sequencing. Narrat Inq Bioeth. 2015;5(2):179-186. PMID: 26300150. doi: 10.1353/nib.2015.0059. Exclude: X1

153. Helman G, Sherbini O, Cross Z, et al. Leukoseq whole genome sequencing clinical trial: an interim analysis. Neurology. 2018;90(15). PMID: CN-01608693. Exclude: X1

154. Hochstenbach R, van Binsbergen E, Schuring-Blom H, Buijs A, Ploos van Amstel HK. A survey of undetected, clinically relevant chromosome abnormalities when replacing postnatal karyotyping by whole genome sequencing. Eur J Med Genet. 2018. PMID: 30248410. doi: 10.1016/j.ejmg.2018.09.010. Exclude: X1

155. Hosen MJ, Van Nieuwerburgh F, Steyaert W, et al. Efficiency of exome sequencing for the molecular diagnosis of pseudoxanthoma elasticum. J Invest Dermatol. 2015;135(4):992-998. PMID: 25264593. doi: 10.1038/jid.2014.421. Exclude: X4

156. Houniet DT, Rahman TJ, Al Turki S, et al. Using population data for assessing next-generation sequencing performance. Bioinformatics. 2015;31(1):56-61. PMID: 25236458. doi: 10.1093/bioinformatics/btu606. Exclude: X3

157. Hu X, Li N, Xu Y, et al. Proband-only medical exome sequencing as a cost-effective first-tier genetic diagnostic test for patients without prior molecular tests and clinical diagnosis in a developing country: the China experience. Genet Med. 2018;20(9):1045-1053. PMID: 29095814. doi: 10.1038/gim.2017.195. Exclude: X3

158. Huang Z, Sun Y, Fan Y, et al. Genetic evaluation of 114 Chinese short stature children in the next generation era: a single center study. Cell Physiol Biochem. 2018;49(1):295-305. PMID: 30138938. doi: 10.1159/000492879. Exclude: X3

159. Ichimura T, Yoshida K, Okuno Y, et al. Diagnostic challenge of Diamond-Blackfan anemia in mothers and children by whole-exome sequencing. Int J Hematol. 2017;105(4):515-520. PMID: 27882484. doi: 10.1007/s12185-016-2151-7. Exclude: X1

160. Illumina I, Le Bonheur Children's Hospital, Rady Pediatric Genomics, Systems Medicine Institute, Children's Hospital of Orange County, Children's Hospital of Omaha, St. Louis Children's Hospital &, Philadelphia; CsHo. NICUSeq: a trial to evaluate the clinical utility of human whole genome sequencing (WGS) compared to standard of care in acute care neonates and infants. https://ClinicalTrials.gov/show/NCT03290469. Published 2017. Updated August 31. Exclude: X8

161. Imperial College London Diabetes Centre. Delineation of novel monogenic disorders in the United Arab Emirates population. https://ClinicalTrials.gov/show/NCT03589079. Published 2018. Updated January 1. Exclude: X7

162. Iossifov I, O'Roak BJ, Sanders SJ, et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014;515(7526):216-221. PMID: 25363768. doi: 10.1038/nature13908. Exclude: X1

163. Isaacs D. Gene expression in Kawasaki disease. J Paediatr Child Health. 2018;54(12):1400-1401. PMID. doi: 10.1111/jpc.14258. Exclude: X1

164. Iwama K, Mizuguchi T, Takeshita E, et al. Genetic landscape of Rett syndrome-like phenotypes revealed by whole exome sequencing. J Med Genet. 2019. PMID: 30842224. doi: 10.1136/jmedgenet-2018-105775. Exclude: X4

165. Jaitovich Groisman I, Hurlimann T, Godard B. Parents of a child with epilepsy: views and expectations on receiving genetic results from whole genome sequencing. Epilepsy Behav. 2019;90:178-190. PMID: 30583270. doi: 10.1016/j.yebeh.2018.11.020. Exclude: X4

166. Jalkh N, Corbani S, Haidar Z, et al. The added value of WES reanalysis in the field of genetic diagnosis: lessons learned from 200 exomes in the Lebanese population. BMC Med Genomics. 2019;12(1):11. PMID: 30665423. doi: 10.1186/s12920-019-0474-y. Exclude: X9

167. Jamal L, Robinson JO, Christensen KD, et al. When bins blur: Patient perspectives on categories of results from clinical whole genome sequencing. AJOB Empir Bioeth. 2017;8(2):82-88. PMID: 28949844. doi: 10.1080/23294515.2017.1287786. Exclude: X3

168. Jernigan TL, Brown TT, Hagler DJ, Jr., et al. The pediatric imaging, neurocognition, and genetics (PING) data repository. Neuroimage. 2016;124(Pt B):1149-1154. PMID: 25937488. doi: 10.1016/j.neuroimage.2015.04.057. Exclude: X1

169. Johnson K, Bertoli M, Phillips L, et al. Detection of variants in dystroglycanopathy-associated genes through the application of targeted whole-exome sequencing analysis to a large cohort of patients with unexplained limb-girdle muscle weakness. Skelet Muscle. 2018;8(1):23. PMID: 30060766. doi: 10.1186/s13395-018-0170-1. Exclude: X3

170. Johnson K, Topf A, Bertoli M, et al. Identification of GAA variants through whole exome sequencing targeted to a cohort of 606 patients with unexplained limb-girdle muscle weakness. Orphanet J Rare Dis. 2017;12(1):173. PMID: 29149851. doi: 10.1186/s13023-017-0722-1. Exclude: X3

171. Jones KL, McNamara EA, Longoni M, et al. Dual diagnoses in 152 patients with Turner syndrome: knowledge of the second condition may lead to modification of treatment and/or surveillance. Am J Med Genet A. 2018;176(11):2435-2445. PMID: 30079495. doi: 10.1002/ajmg.a.40470. Exclude: X1

172. Keogh MJ, Steele H, Douroudis K, et al. Frequency of rare recessive mutations in unexplained late onset cerebellar ataxia. J Neurol. 2015;262(8):1822-1827. PMID: 25976027. doi: 10.1007/s00415-015-7772-x. Exclude: X4

173. Kerschner JE. Clinical implementation of whole genome sequencing a valuable step toward personalized care. WMJ. 2013;112(5):224-225. PMID: 24734419. Exclude: X1

174. Kingsmore SF. Newborn testing and screening by whole-genome sequencing. Genet Med. 2016;18(3):214-216. PMID: 26681311. doi: 10.1038/gim.2015.172. Exclude: X1

175. Kingsmore SF, Saunders CJ. Deep sequencing of patient genomes for disease diagnosis: when will it become routine? Sci Transl Med. 2011;3(87):87ps23. PMID: 21677196. doi: 10.1126/scitranslmed.3002695. Exclude: X1

176. Klein CJ, Foroud TM. Neurology individualized medicine: When to use next-generation sequencing panels. Mayo Clin Proc. 2017;92(2):292-305. PMID: 28160876. doi: 10.1016/j.mayocp.2016.09.008. Exclude: X1

177. Kliegman RM, Bordini BJ, Basel D, Nocton JJ. How doctors think: common diagnostic errors in clinical judgment-lessons from an undiagnosed and rare disease program. Pediatr Clin North Am. 2017;64(1):1-15. PMID: 27894438. doi: 10.1016/j.pcl.2016.08.002. Exclude: X1

178. Kluska A, Kulecka M, Litwin T, et al. Whole-exome sequencing identifies novel pathogenic variants across the ATP7B gene and some modifiers of Wilson's disease phenotype. Liver Int. 2019;39(1):177-186. PMID: 30230192. doi: 10.1111/liv.13967. Exclude: X3

179. Knies K, Schuster B, Ameziane N, et al. Genotyping of fanconi anemia patients by whole exome sequencing: advantages and challenges. PLoS One. 2012;7(12):e52648. PMID: 23285130. doi: 10.1371/journal.pone.0052648. Exclude: X1

180. Krabbenborg L, Schieving J, Kleefstra T, et al. Evaluating a counselling strategy for diagnostic WES in paediatric neurology: an exploration of parents' information and communication needs. Clin Genet. 2016;89(2):244-250. PMID: 25916247. doi: 10.1111/cge.12601. Exclude: X4

181. Kwak SH, Jung CH, Ahn CH, et al. Clinical whole exome sequencing in early onset diabetes patients. Diabetes Res Clin Pract. 2016;122:71-77. PMID: 27810688. doi: 10.1016/j.diabres.2016.10.005. Exclude: X4

182. LaHaye S, Corsmeier D, Basu M, et al. Utilization of whole exome sequencing to identify causative mutations in familial congenital heart disease. Circ Cardiovasc Genet. 2016;9(4):320-329. PMID: 27418595. doi: 10.1161/circgenetics.115.001324. Exclude: X4

183. Landis BJ, Ware SM. The current landscape of genetic testing in cardiovascular malformations: opportunities and challenges. Front Cardiovasc Med. 2016;3:22. PMID: 27504451. doi: 10.3389/fcvm.2016.00022. Exclude: X1

184. Lazaridis KN, McAllister TM, Babovic-Vuksanovic D, et al. Implementing individualized medicine into the medical practice. Am J Med Genet C Semin Med Genet. 2014;166c(1):15-23. PMID: 24616301. doi: 10.1002/ajmg.c.31387. Exclude: X1

185. Lazaridis KN, Schahl KA, Cousin MA, et al. Outcome of whole exome sequencing for diagnostic odyssey cases of an individualized medicine clinic: the Mayo Clinic experience. Mayo Clin Proc. 2016;91(3):297-307. PMID: 26944241. doi: 10.1016/j.mayocp.2015.12.018. Exclude: X4

186. Lee S, Choi M. Ultra-rare disease and genomics-driven precision medicine. Genomics Inform. 2016;14(2):42-45. PMID: 27445646. doi: 10.5808/gi.2016.14.2.42. Exclude: X1

187. Legault MA, Girard S, Lemieux Perreault LP, Rouleau GA, Dube MP. Comparison of sequencing based CNV discovery methods using monozygotic twin quartets. PLoS One. 2015;10(3):e0122287. PMID: 25812131. doi: 10.1371/journal.pone.0122287. Exclude: X3

188. Leinoe E, Zetterberg E, Kinalis S, et al. Application of whole-exome sequencing to direct the specific functional testing and diagnosis of rare inherited bleeding disorders in patients from the Oresund Region, Scandinavia. Br J Haematol. 2017;179(2):308-322. PMID: 28748566. doi: 10.1111/bjh.14863. Exclude: X3

189. Levenson D. Whole-exome sequencing emerges as clinical diagnostic tool: testing method proves useful for diagnosing wide range of genetic disorders. Am J Med Genet A. 2014;164a(1):ix-x. PMID: 24352919. doi: 10.1002/ajmg.a.36385. Exclude: X1

190. Levenson D. Whole-exome sequencing effective at diagnosing elusive genetic disorders: tests diagnose about 25% of patients, find a variety of mutation types. Am J Med Genet A. 2015;167a(2):vii-viii. PMID: 25604662. doi: 10.1002/ajmg.a.36965. Exclude: X1

191. Li N, Wang L, Wang H, et al. The performance of whole genome amplification methods and next-generation sequencing for pre-implantation genetic diagnosis of chromosomal abnormalities. J Genet Genomics. 2015;42(4):151-159. PMID: 25953353. doi: 10.1016/j.jgg.2015.03.001. Exclude: X2

192. Liang D, Wang Y, Ji X, et al. Clinical application of whole-genome low-coverage next-generation sequencing to detect and characterize balanced chromosomal translocations. Clin Genet. 2017;91(4):605-610. PMID: 27491356. doi: 10.1111/cge.12844. Exclude: X4

193. Licastro D, Mutarelli M, Peluso I, et al. Molecular diagnosis of Usher syndrome: application of two different next generation sequencing-based procedures. PLoS One. 2012;7(8):e43799. PMID: 22952768. doi: 10.1371/journal.pone.0043799. Exclude: X4

194. Likar T, Hasanhodzic M, Teran N, Maver A, Peterlin B, Writzl K. Diagnostic outcomes of exome sequencing in patients with syndromic or non-syndromic hearing loss. PLoS One. 2018;13(1):e0188578. PMID: 29293505. doi: 10.1371/journal.pone.0188578. Exclude: X4

195. Lin X, Tang W, Ahmad S, et al. Applications of targeted gene capture and next-generation sequencing technologies in studies of human deafness and other genetic disabilities. Hear Res. 2012;288(1-2):67-76. PMID: 22269275. doi: 10.1016/j.heares.2012.01.004. Exclude: X1

196. Linderman MD, Brandt T, Edelmann L, et al. Analytical validation of whole exome and whole genome sequencing for clinical applications. BMC Med Genomics. 2014;7:20. PMID: 24758382. doi: 10.1186/1755-8794-7-20. Exclude: X4

197. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. Genet Med. 2018;20(4):435-443. PMID: 28771251. doi: 10.1038/gim.2017.119. Exclude: X4

198. Liskova P, Dudakova L, Evans CJ, et al. Ectopic GRHL2 expression due to non-coding mutations promotes cell state transition and causes Posterior Polymorphous Corneal Dystrophy 4. Am J Hum Genet. 2018;102(3):447-459. PMID: 29499165. doi: 10.1016/j.ajhg.2018.02.002. Exclude: X3

199. Lohmann K, Klein C. Next generation sequencing and the future of genetic diagnosis. Neurotherapeutics. 2014;11(4):699-707. PMID: 25052068. doi: 10.1007/s13311-014-0288-8. Exclude: X1

200. Long PA, Evans JM, Olson TM. Diagnostic yield of whole exome sequencing in pediatric dilated cardiomyopathy. J Cardiovasc Dev Dis. 2017;4(3). PMID: 29367541. doi: 10.3390/jcdd4030011. Exclude: X4

201. Ma A, Grigg J, Cheng A, Bennetts B, Jamieson R. Genomic diagnoses in families with anteriorsegment abnormalities and complex microphthalmia. Twin Research and Human Genetics. 2017;20(5):433. PMID. doi: 10.1017/thg.2017.46. Exclude: X1

202. Ma A, Yousoof S, Grigg J, Cheng A, Bennetts B, Jamieson R. Genomic approaches and new diagnoses in ocular anterior segment disorders. Twin Research and Human Genetics. 2016;19(5):533. PMID. doi: 10.1017/thg.2016.69. Exclude: X1

203. Maasalu K, Nikopensius T, Koks S, et al. Whole-exome sequencing identifies de novo mutation in the COL1A1 gene to underlie the severe osteogenesis imperfecta. Hum Genomics. 2015;9:6. PMID: 25958000. doi: 10.1186/s40246-015-0028-0. Exclude: X1

204. Macnamara EF, Schoch K, Kelley EG, et al. Cases from the Undiagnosed Diseases Network: the continued value of counseling skills in a new genomic era. J Genet Couns. 2019. PMID: 30680851. doi: 10.1002/jgc4.1091. Exclude: X1

205. Mak CC, Leung GK, Mok GT, et al. Exome sequencing for paediatric-onset diseases: impact of the extensive involvement of medical geneticists in the diagnostic odyssey. NPJ Genom Med. 2018;3:19. PMID: 30109123. doi: 10.1038/s41525-018-0056-5. Exclude: X9

206. Mak TSH, Lee YK, Tang CS, et al. Coverage and diagnostic yield of whole exome sequencing for the evaluation of cases with dilated and hypertrophic cardiomyopathy. Sci Rep. 2018;8(1):10846. PMID: 30022097. doi: 10.1038/s41598-018-29263-3. Exclude: X9

207. Marchuk DS, Crooks K, Strande N, et al. Increasing the diagnostic yield of exome sequencing by copy number variant analysis. PLoS One. 2018;13(12):e0209185. PMID: 30557390. doi: 10.1371/journal.pone.0209185. Exclude: X3

208. Marian AJ. Medical DNA sequencing. Curr Opin Cardiol. 2011;26(3):175-180. PMID: 21415728. doi: 10.1097/HCO.0b013e3283459857. Exclude: X1

209. Marquis-Nicholson R, Doherty E, Love JM, et al. Array-based identification of copy number changes in a diagnostic setting: simultaneous gene-focused and low resolution whole human genome analysis. Sultan Qaboos Univ Med J. 2013;13(1):69-79. PMID: 23573385. Exclude: X3

210. Marshall CR, Scherer SW, Zariwala MA, et al. Whole-exome sequencing and targeted copy number analysis in primary ciliary dyskinesia. G3 (Bethesda). 2015;5(8):1775-1781. PMID: 26139845. doi: 10.1534/g3.115.019851. Exclude: X4

211. Marshall DA, Gonzalez JM, MacDonald KV, Johnson FR. Estimating preferences for complex health technologies: Lessons learned and implications for personalized medicine. Value Health. 2017;20(1):32-39. PMID: 28212966. doi: 10.1016/j.jval.2016.08.737. Exclude: X4

212. Martin HC, Kim GE, Pagnamenta AT, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. Hum Mol Genet. 2014;23(12):3200-3211. PMID: 24463883. doi: 10.1093/hmg/ddu030. Exclude: X3

213. Massachusetts General Hospital. Investigating the feasibility and implementation of whole genome sequencing in patients with suspected genetic disorder. https://ClinicalTrials.gov/show/NCT03829176. Published 2018. Updated March 1. Exclude: X7

214. Mattick JS, Dinger M, Schonrock N, Cowley M. Whole genome sequencing provides better diagnostic yield and future value than whole exome sequencing. Med J Aust. 2018;209(5):197-199. PMID: 29621958. Exclude: X1

215. McDonell LM, Warman Chardon J, Schwartzentruber J, et al. The utility of exome sequencing for genetic diagnosis in a familial microcephaly epilepsy syndrome. BMC Neurol. 2014;14:22. PMID: 24479948. doi: 10.1186/1471-2377-14-22. Exclude: X1

216. McInerney-Leo AM, Harris JE, Leo PJ, et al. Whole exome sequencing is an efficient, sensitive and specific method for determining the genetic cause of short-rib thoracic dystrophies. Clin Genet. 2015;88(6):550-557. PMID: 25492405. doi: 10.1111/cge.12550. Exclude: X4

217. Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. J Med Genet. 2018;55(11):721-728. PMID: 30049826. doi: 10.1136/jmedgenet-2018-105396. Exclude: X3

218. Meyts I, Bosch B, Bolze A, et al. Exome and genome sequencing for inborn errors of immunity. J Allergy Clin Immunol. 2016;138(4):957-969. PMID: 27720020. doi: 10.1016/j.jaci.2016.08.003. Exclude: X1

219. Miller KA, Twigg SR, McGowan SJ, et al. Diagnostic value of exome and whole genome sequencing in craniosynostosis. J Med Genet. 2017;54(4):260-268. PMID: 27884935. doi: 10.1136/jmedgenet-2016-104215. Exclude: X4

220. Milton S. Hershey Medical Center. Whole genome sequencing in the neonatal intensive care unit. https://ClinicalTrials.gov/show/NCT03721458. Published 2019. Updated May 1. Exclude: X7

221. Moccia A, Srivastava A, Skidmore JM, et al. Genetic analysis of CHARGE syndrome identifies overlapping molecular biology. Genet Med. 2018;20(9):1022-1029. PMID: 29300383. doi: 10.1038/gim.2017.233. Exclude: X4

222. Moeschler JB, Shevell M. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014;134(3):e903-918. PMID: 25157020. doi: 10.1542/peds.2014-1839. Exclude: X1

223. Molparia B, Pham PH, Torkamani A. Symptom-driven idiopathic disease gene identification. Genet Med. 2015;17(11):859-865. PMID: 25590976. doi: 10.1038/gim.2014.202. Exclude: X1

224. Monies D, Alhindi HN, Almuhaizea MA, et al. A first-line diagnostic assay for limb-girdle muscular dystrophy and other myopathies. Hum Genomics. 2016;10(1):32. PMID: 27671536. doi: 10.1186/s40246-016-0089-8. Exclude: X4

225. Moore B, Hu H, Singleton M, De La Vega FM, Reese MG, Yandell M. Global analysis of disease-related DNA sequence variation in 10 healthy individuals: implications for whole genome-based clinical diagnostics. Genet Med. 2011;13(3):210-217. PMID: 21325948. doi: 10.1097/GIM.0b013e31820ed321. Exclude: X2

226. Mori M, Haskell G, Kazi Z, et al. Sensitivity of whole exome sequencing in detecting infantile- and late-onset Pompe disease. Mol Genet Metab. 2017;122(4):189-197. PMID: 29122469. doi: 10.1016/j.ymgme.2017.10.008. Exclude: X3

227. Morrison KE. Whole-genome sequencing informs treatment: personalized medicine takes another step forward. Clin Chem. 2011;57(12):1638-1640. PMID: 21956236. doi: 10.1373/clinchem.2011.172684. Exclude: X1

228. Mtatiro SN, Mgaya J, Singh T, et al. Genetic association of fetal-hemoglobin levels in individuals with sickle cell disease in Tanzania maps to conserved regulatory elements within the MYB core enhancer. BMC Med Genet. 2015;16:4. PMID: 25928412. doi: 10.1186/s12881-015-0148-3. Exclude: X3

229. Mu W, Schiess N, Orthmann-Murphy JL, El-Hattab AW. The utility of whole exome sequencing in diagnosing neurological disorders in adults from a highly consanguineous population. J Neurogenet. 2019:1-6. PMID: 30724636. doi: 10.1080/01677063.2018.1555249. Exclude: X4

230. Nambot S, Thevenon J, Kuentz P, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: substantial interest of prospective annual reanalysis. Genet Med. 2018;20(6):645-654. PMID: 29095811. doi: 10.1038/gim.2017.162. Exclude: X4

231. Naseer MI, Faheem M, Chaudhary AG, et al. Genome wide analysis of novel copy number variations duplications/deletions of different epileptic patients in Saudi Arabia. BMC Genomics. 2015;16 Suppl 1:S10. PMID: 25923336. doi: 10.1186/1471-2164-16-s1-s10. Exclude: X3

232. National Eye Institute. Whole exome and whole genome sequencing for genotyping of inherited and congenital eye conditions. https://ClinicalTrials.gov/show/NCT02077894. Published 2014. Updated February 28. Exclude: X7

233. National Human Genome Research Institute. Whole genome medical sequencing for genome discovery. https://ClinicalTrials.gov/show/NCT01087320. Published 2010. Updated February 17. Exclude: X7

234. National Human Genome Research Institute. A study of consent forms for whole exome and whole genome sequencing. https://ClinicalTrials.gov/show/NCT01927770. Published 2013. Updated August 20. Exclude: X7

235. National Human Genome Research Institute. Adult patients with undiagnosed conditions and their responses to clinically uncertain results from exome sequencing. https://ClinicalTrials.gov/show/NCT03605004. Published 2019. Updated April 12. Exclude: X7

236. National Taiwan University Hospital. Rapid genetic diagnosis employing next generation sequencing for critical illness in infants and children. https://ClinicalTrials.gov/show/NCT03175692. Published 2017. Updated June 14. Exclude: X7

237. Need AC, Shashi V, Hitomi Y, et al. Clinical application of exome sequencing in undiagnosed genetic conditions. J Med Genet. 2012;49(6):353-361. PMID: 22581936. doi: 10.1136/jmedgenet-2012-100819. Exclude: X4

238. Need AC, Shashi V, Schoch K, Petrovski S, Goldstein DB. The importance of dynamic re-analysis in diagnostic whole exome sequencing. J Med Genet. 2017;54(3):155-156. PMID: 27899421. doi: 10.1136/jmedgenet-2016-104306. Exclude: X4

239. Nelen M, Veltman JA. Genome and exome sequencing in the clinic: unbiased genomic approaches with a high diagnostic yield. Pharmacogenomics. 2012;13(5):511-514. PMID: 22462741. doi: 10.2217/pgs.12.23. Exclude: X1

240. Neubauer J, Lecca MR, Russo G, et al. Post-mortem whole-exome analysis in a large sudden infant death syndrome cohort with a focus on cardiovascular and metabolic genetic diseases. Eur J Hum Genet. 2017;25(4):404-409. PMID: 28074886. doi: 10.1038/ejhg.2016.199. Exclude: X2

241. Nguyen MT, Charlebois K. The clinical utility of whole-exome sequencing in the context of rare diseases - the changing tides of medical practice. Clin Genet. 2015;88(4):313-319. PMID: 25421945. doi: 10.1111/cge.12546. Exclude: X1

242. Nicklaus Children's Hospital f/k/a Miami Children's Hospital; Rady Pediatric Genomics; Systems Medicine Institute. Diagnostic odyssey: Whole genome sequencing (WGS). https://ClinicalTrials.gov/show/NCT03458962. Published 2018. Updated February 20. Exclude: X7

243. Nuytemans K, Vance JM. [Whole exome sequencing]. Rinsho Shinkeigaku. 2010;50(11):952-955. PMID: 21921524. Exclude: X1

244. Ohba C, Osaka H, Iai M, et al. Diagnostic utility of whole exome sequencing in patients showing cerebellar and/or vermis atrophy in childhood. Neurogenetics. 2013;14(3-4):225-232. PMID: 24091540. doi: 10.1007/s10048-013-0375-8. Exclude: X4

245. Olson HE, Tambunan D, LaCoursiere C, et al. Mutations in epilepsy and intellectual disability genes in patients with features of Rett syndrome. Am J Med Genet A. 2015;167a(9):2017-2025. PMID: 25914188. doi: 10.1002/ajmg.a.37132. Exclude: X4

246. Omran H, Hoben IM, Hjeij R, et al. Mutations in C11ORF70 cause primary ciliary dyskinesia with randomization of left-right body asymmetry due to outer and inner dynein arm defects. Am J Respir Crit Care Med. 2018;197(MeetingAbstracts). PMID: CN-01619234. Exclude: X1

247. Ostergaard E, Risom L, Ek J, Gronborg S, Duno M, Skovby F. [Exome sequencing for syndrome diagnostics]. Ugeskr Laeger. 2017;179(17). PMID: 28473029. Exclude: X5

248. Ostrander BEP, Butterfield RJ, Pedersen BS, et al. Whole-genome analysis for effective clinical diagnosis and gene discovery in early infantile epileptic encephalopathy. NPJ Genom Med. 2018;3:22. PMID: 30109124. doi: 10.1038/s41525-018-0061-8. Exclude: X4

249. Pal LR, Kundu K, Yin Y, Moult J. CAGI4 SickKids clinical genomes challenge: a pipeline for identifying pathogenic variants. Hum Mutat. 2017;38(9):1169-1181. PMID: 28512736. doi: 10.1002/humu.23257. Exclude: X3

250. Park ST, Kim J. Trends in next-generation sequencing and a new era for whole genome sequencing. Int Neurourol J. 2016;20(Suppl 2):S76-83. PMID: 27915479. doi: 10.5213/inj.1632742.371. Exclude: X1

251. Pasche B, Absher D. Whole-genome sequencing: a step closer to personalized medicine. JAMA. 2011;305(15):1596-1597. PMID: 21505140. doi: 10.1001/jama.2011.484. Exclude: X1

252. Payne K, Gavan SP, Wright SJ, Thompson AJ. Cost-effectiveness analyses of genetic and genomic diagnostic tests. Nat Rev Genet. 2018;19(4):235-246. PMID: 29353875. doi: 10.1038/nrg.2017.108. Exclude: X1

253. Pena LDM, Jiang YH, Schoch K, et al. Looking beyond the exome: a phenotype-first approach to molecular diagnostic resolution in rare and undiagnosed diseases. Genet Med. 2018;20(4):464-469. PMID: 28914269. doi: 10.1038/gim.2017.128. Exclude: X1

254. Pereira PC, Melo FM, De Marco LA, Oliveira EA, Miranda DM, Simoes e Silva AC. Whole-exome sequencing as a diagnostic tool for distal renal tubular acidosis. J Pediatr (Rio J). 2015;91(6):583-589. PMID: 26208211. doi: 10.1016/j.jped.2015.02.002. Exclude: X9

255. Peyron C, Pelissier A, Bejean S. Preference heterogeneity with respect to whole genome sequencing. A discrete choice experiment among parents of children with rare genetic diseases. Soc Sci Med. 2018;214:125-132. PMID: 30179780. doi: 10.1016/j.socscimed.2018.08.015. Exclude: X1

256. Pietraszkiewicz A, van Asten F, Kwong A, et al. Association of rare predicted loss-of-function variants in cellular pathways with sub-phenotypes in age-related macular degeneration. Ophthalmology. 2018;125(3):398-406. PMID: CN-01643197. doi: 10.1016/j.ophtha.2017.10.027. Exclude: X3

257. Poninska JK, Bilinska ZT, Franaszczyk M, et al. Next-generation sequencing for diagnosis of thoracic aortic aneurysms and dissections: diagnostic yield, novel mutations and genotype phenotype correlations. J Transl Med. 2016;14(1):115. PMID: 27146836. doi: 10.1186/s12967-016-0870-4. Exclude: X1

258. Posey JE, Harel T, Liu P, et al. Resolution of disease phenotypes resulting from multilocus genomic variation. N Engl J Med. 2017;376(1):21-31. PMID: 27959697. doi: 10.1056/NEJMoa1516767. Exclude: X4

259. Powis Z, Farwell Hagman KD, Speare V, et al. Exome sequencing in neonates: diagnostic rates, characteristics, and time to diagnosis. Genet Med. 2018;20(11):1468-1471. PMID: 29565416. doi: 10.1038/gim.2018.11. Exclude: X4

260. Prasad A, Sdano MA, Vanzo RJ, et al. Clinical utility of exome sequencing in individuals with large homozygous regions detected by chromosomal microarray analysis. BMC Med Genet. 2018;19(1):46. PMID: 29554876. doi: 10.1186/s12881-018-0555-3. Exclude: X2

261. Pronicka E, Piekutowska-Abramczuk D, Ciara E, et al. New perspective in diagnostics of mitochondrial disorders: two years' experience with whole-exome sequencing at a national paediatric centre. J Transl Med. 2016;14(1):174. PMID: 27290639. doi: 10.1186/s12967-016-0930-9. Exclude: X4

262. Punetha J, Kesari A, Uapinyoying P, et al. Targeted re-sequencing emulsion PCR panel for myopathies: results in 94 cases. J Neuromuscul Dis. 2016;3(2):209-225. PMID: 27854218. doi: 10.3233/jnd-160151. Exclude: X3

263. Pyle A, Smertenko T, Bargiela D, et al. Exome sequencing in undiagnosed inherited and sporadic ataxias. Brain. 2015;138(Pt 2):276-283. PMID: 25497598. doi: 10.1093/brain/awu348. Exclude: X4

264. Rady Pediatric Genomics. Perinatal precision medicine. https://ClinicalTrials.gov/show/NCT03211039. Published 2017. Updated June 29. Exclude: X7

265. Rajkovic A, Pangas S. Ovary as a biomarker of health and longevity: Insights from genetics. Semin Reprod Med. 2017;35(3):231-240. PMID. doi: 10.1055/s-0037-1603571. Exclude: X1

266. Reddy HM, Cho KA, Lek M, et al. The sensitivity of exome sequencing in identifying pathogenic mutations for LGMD in the United States. J Hum Genet. 2017;62(2):243-252. PMID: 27708273. doi: 10.1038/jhg.2016.116. Exclude: X4

267. Retterer K, Scuffins J, Schmidt D, et al. Assessing copy number from exome sequencing and exome array CGH based on CNV spectrum in a large clinical cohort. Genet Med. 2015;17(8):623-629. PMID: 25356966. doi: 10.1038/gim.2014.160. Exclude: X3

268. Reuter CM, Brimble E, DeFilippo C, et al. A new approach to rare diseases of children: the undiagnosed diseases network. J Pediatr. 2018;196:291-297.e292. PMID: 29331327. doi: 10.1016/j.jpeds.2017.12.029. Exclude: X1

269. Revel-Vilk S, Fischer U, Keller B, et al. Autoimmune lymphoproliferative syndrome-like disease in patients with LRBA mutation. Clin Immunol. 2015;159(1):84-92. PMID: 25931386. doi: 10.1016/j.clim.2015.04.007. Exclude: X1

270. Richardson R, Sowden J, Gerth-Kahlert C, Moore AT, Moosajee M. Clinical utility gene card for: Non-syndromic microphthalmia including next-generation sequencing-based approaches. Eur J Hum Genet. 2017;25(4). PMID: 28098148. doi: 10.1038/ejhg.2016.201. Exclude: X1

271. Rini C, Khan CM, Moore E, et al. The who, what, and why of research participants' intentions to request a broad range of secondary findings in a diagnostic genomic sequencing study. Genet Med. 2018;20(7):760-769. PMID: 29261173. doi: 10.1038/gim.2017.176. Exclude: X4

272. Roberts JS, Robinson JO, Diamond PM, et al. Patient understanding of, satisfaction with, and perceived utility of whole-genome sequencing: findings from the MedSeq Project. Genet Med. 2018;20(9):1069-1076. PMID: CN-01645006. doi: 10.1038/gim.2017.223. Exclude: X3

273. Robinson JO, Carroll TM, Feuerman LZ, et al. Participants and study decliners' perspectives about the risks of participating in a clinical trial of whole genome sequencing. J Empir Res Hum Res Ethics. 2016;11(1):21-30. PMID: 26928896. doi: 10.1177/1556264615624078. Exclude: X2

274. Robinson PN. Whole-exome sequencing for finding de novo mutations in sporadic mental retardation. Genome Biol. 2010;11(12):144. PMID: 21172032. doi: 10.1186/gb-2010-11-12-144. Exclude: X1

275. Rodriguez-Revenga L, Vallespin E, Madrigal I, et al. A parallel study of different array-CGH platforms in a set of Spanish patients with developmental delay and intellectual disability. Gene. 2013;521(1):82-86. PMID: 23524024. doi: 10.1016/j.gene.2013.02.043. Exclude: X3

276. Rohanizadegan M, Abdo SM, O'Donnell-Luria A, et al. Utility of rapid whole-exome sequencing in the diagnosis of Niemann-Pick disease type C presenting with fetal hydrops and acute liver failure. Cold Spring Harb Mol Case Stud. 2017;3(6). PMID: 28802248. doi: 10.1101/mcs.a002147. Exclude: X1

277. Rossi M, El-Khechen D, Black MH, Farwell Hagman KD, Tang S, Powis Z. Outcomes of diagnostic exome sequencing in patients with diagnosed or suspected autism spectrum disorders. Pediatr Neurol. 2017;70:34-43.e32. PMID: 28330790. doi: 10.1016/j.pediatrneurol.2017.01.033. Exclude: X4

278. Rump P, Jazayeri O, van Dijk-Bos KK, et al. Whole-exome sequencing is a powerful approach for establishing the etiological diagnosis in patients with intellectual disability and microcephaly. BMC Med Genomics. 2016;9:7. PMID: 26846091. doi: 10.1186/s12920-016-0167-8. Exclude: X4

279. Saes JL, Simons A, de Munnik SA, et al. Whole exome sequencing in the diagnostic workup of patients with a bleeding diathesis. Haemophilia. 2019;25(1):127-135. PMID: 30431218. doi: 10.1111/hae.13638. Exclude: X4

280. Salam A, Simpson MA, Stone KL, et al. Next generation diagnostics of heritable connective tissue disorders. Matrix Biol. 2014;33:35-40. PMID: 23896220. doi: 10.1016/j.matbio.2013.06.004. Exclude: X1

281. Sanchez Fernandez I, Loddenkemper T, Gainza-Lein M, Sheidley BR, Poduri A. Diagnostic yield of genetic tests in epilepsy: a meta-analysis and cost-effectiveness study. Neurology. 2019. PMID: 30610098. doi: 10.1212/wnl.0000000000006850. Exclude: X6

282. Saunders CJ, Miller NA, Soden SE, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. Sci Transl Med. 2012;4(154):154ra135. PMID: 23035047. doi: 10.1126/scitranslmed.3004041. Exclude: X3

283. Sawyer SL, Schwartzentruber J, Beaulieu CL, et al. Exome sequencing as a diagnostic tool for pediatric-onset ataxia. Hum Mutat. 2014;35(1):45-49. PMID: 24108619. doi: 10.1002/humu.22451. Exclude: X4

284. Scalais E, De Meurichy A, Amrom D, et al. Early onset epileptic encephalopathy: genetic analysis and further delineation of genotypephenotype correlation. Ann Neurol. 2017;82:S295-S296. PMID. Exclude: X1

285. Schabhuttl M, Wieland T, Senderek J, et al. Whole-exome sequencing in patients with inherited neuropathies: outcome and challenges. J Neurol. 2014;261(5):970-982. PMID: 24627108. doi: 10.1007/s00415-014-7289-8. Exclude: X4

286. Schilit SL, Schilit Nitenson A. My identical twin sequenced our genome. J Genet Couns. 2017;26(2):276-278. PMID: 27853911. doi: 10.1007/s10897-016-0046-7. Exclude: X1

287. Schrijver I, Galli SJ. Between hype and hope: whole-genome sequencing in clinical medicine. Per Med. 2012;9(3):243-246. PMID: 29758791. doi: 10.2217/pme.11.76. Exclude: X1

288. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med. 2018;20(10):1122-1130. PMID: 29446766. doi: 10.1038/gim.2017.247. Exclude: X6

289. Scocchia A, Wigby KM, Masser-Frye D, et al. Clinical whole genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico. NPJ Genom Med. 2019;4:5. PMID: 30792901. doi: 10.1038/s41525-018-0076-1. Exclude: X9

290. Seidelmann SB, Smith E, Subrahmanyan L, et al. Application of whole exome sequencing in the clinical diagnosis and management of inherited cardiovascular diseases in adults. Circ Cardiovasc Genet. 2017;10(1). PMID: 28087566. doi: 10.1161/circgenetics.116.001573. Exclude: X4

291. Seoul National University Hospital. WGS of Korean idiopathic bronchiectasis. https://ClinicalTrials.gov/show/NCT03809091. Published 2019. Updated January. Exclude: X7

292. Shakiba M, Keramatipour M. Effect of whole exome sequencing in diagnosis of inborn errors of metabolism and neurogenetic disorders. Iran J Child Neurol. 2018;12(1):7-15. PMID: 29379558. Exclude: X6

293. Shamseldin HE, Maddirevula S, Faqeih E, et al. Increasing the sensitivity of clinical exome sequencing through improved filtration strategy. Genet Med. 2017;19(5):593-598. PMID: 27711071. doi: 10.1038/gim.2016.155. Exclude: X3

294. Shapiro L, Chatterjee S, Ramadan DG, et al. Whole-exome sequencing gives additional benefits compared to candidate gene sequencing in the molecular diagnosis of children with growth hormone or IGF-1 insensitivity. Eur J Endocrinol. 2017;177(6):485-501. PMID: 28870985. doi: 10.1530/eje-17-0453. Exclude: X4

295. Shkedi-Rafid S, Dheensa S, Crawford G, Fenwick A, Lucassen A. Defining and managing incidental findings in genetic and genomic practice. J Med Genet. 2014;51(11):715-723. PMID: 25228303. doi: 10.1136/jmedgenet-2014-102435. Exclude: X6

296. Sitek JC, Kulseth MA, Rypdal KB, Skodje T, Sheng Y, Retterstol L. Whole-exome sequencing for diagnosis of hereditary ichthyosis. J Eur Acad Dermatol Venereol. 2018;32(6):1022-1027. PMID: 29444371. doi: 10.1111/jdv.14870. Exclude: X4

297. Skinner D, Raspberry KA, King M. The nuanced negative: meanings of a negative diagnostic result in clinical exome sequencing. Sociol Health Illn. 2016;38(8):1303-1317. PMID: 27538589. doi: 10.1111/1467-9566.12460. Exclude: X4

298. Solomon BD, Pineda-Alvarez DE, Hadley DW, et al. Personalized genomic medicine: lessons from the exome. Mol Genet Metab. 2011;104(1-2):189-191. PMID: 21767969. doi: 10.1016/j.ymgme.2011.06.022. Exclude: X1

299. Stalman SE, Solanky N, Ishida M, et al. Genetic analyses in small-for-gestational-age newborns. J Clin Endocrinol Metab. 2018;103(3):917-925. PMID: 29342293. doi: 10.1210/jc.2017-01843. Exclude: X1

300. Stals KL, Wakeling M, Baptista J, et al. Diagnosis of lethal or prenatal-onset autosomal recessive disorders by parental exome sequencing. Prenat Diagn. 2018;38(1):33-43. PMID: 29096039. doi: 10.1002/pd.5175. Exclude: X2

301. Stavropoulos DJ, Merico D, Jobling R, et al. Whole genome sequencing expands diagnostic utility and improves clinical management in pediatric medicine. NPJ Genom Med. 2016;1. PMID: 28567303. doi: 10.1038/npjgenmed.2015.12. Exclude: X3

302. Strande NT, Berg JS. Defining the clinical value of a genomic diagnosis in the era of next-generation sequencing. Annu Rev Genomics Hum Genet. 2016;17:303-332. PMID: 27362341. doi: 10.1146/annurev-genom-083115-022348. Exclude: X1

303. Stranneheim H, Engvall M, Naess K, et al. Rapid pulsed whole genome sequencing for comprehensive acute diagnostics of inborn errors of metabolism. BMC Genomics. 2014;15:1090. PMID: 25495354. doi: 10.1186/1471-2164-15-1090. Exclude: X3

304. Stranneheim H, Wedell A. Exome and genome sequencing: a revolution for the discovery and diagnosis of monogenic disorders. J Intern Med. 2016;279(1):3-15. PMID: 26250718. doi: 10.1111/joim.12399. Exclude: X1

305. Sun Y, Ruivenkamp CA, Hoffer MJ, et al. Next-generation diagnostics: gene panel, exome, or whole genome? Hum Mutat. 2015;36(6):648-655. PMID: 25772376. doi: 10.1002/humu.22783. Exclude: X1

306. Swaminathan R, Huang Y, Astbury C, et al. Clinical exome sequencing reports: current informatics practice and future opportunities. J Am Med Inform Assoc. 2017;24(6):1184-1191. PMID: 28535206. doi: 10.1093/jamia/ocx048. Exclude: X1

307. Takeichi T, Nanda A, Liu L, et al. Impact of next generation sequencing on diagnostics in a genetic skin disease clinic. Exp Dermatol. 2013;22(12):825-831. PMID: 24279917. doi: 10.1111/exd.12276. Exclude: X4

308. Tan NB, Tan TY, Martyn MM, et al. Diagnostic and service impact of genomic testing technologies in a neonatal intensive care unit. J Paediatr Child Health. 2019. PMID: 30756437. doi: 10.1111/jpc.14398. Exclude: X4

309. Tan R, Wang Y, Kleinstein SE, et al. An evaluation of copy number variation detection tools from whole-exome sequencing data. Hum Mutat. 2014;35(7):899-907. PMID: 24599517. doi: 10.1002/humu.22537. Exclude: X1

310. Tang CS, Dattani S, So MT, et al. Actionable secondary findings from whole-genome sequencing of 954 East Asians. Hum Genet. 2018;137(1):31-37. PMID: 29128982. doi: 10.1007/s00439-017-1852-1. Exclude: X9

311. Taylan F, Nilsson D, Asad S, et al. Whole-exome sequencing of Ethiopian patients with ichthyosis vulgaris and atopic dermatitis. J Allergy Clin Immunol. 2015;136(2):507-509.e519. PMID: 25819062. doi: 10.1016/j.jaci.2015.02.010. Exclude: X9

312. Taylor JC, Martin HC, Lise S, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet. 2015;47(7):717-726. PMID: 25985138. doi: 10.1038/ng.3304. Exclude: X3

313. Taylor RW, Pyle A, Griffin H, et al. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. JAMA. 2014;312(1):68-77. PMID: 25058219. doi: 10.1001/jama.2014.7184. Exclude: X4

314. Theunissen TEJ, Sallevelt S, Hellebrekers D, et al. Rapid resolution of blended or composite multigenic disease in infants by whole-exome sequencing. J Pediatr. 2017;182:371-374.e372. PMID: 28081892. doi: 10.1016/j.jpeds.2016.12.032. Exclude: X1

315. Thevenon J, Duffourd Y, Masurel-Paulet A, et al. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. Clin Genet. 2016;89(6):700-707. PMID: 26757139. doi: 10.1111/cge.12732. Exclude: X4

316. Toledo RA, Dahia PL. Next-generation sequencing for the diagnosis of hereditary pheochromocytoma and paraganglioma syndromes. Curr Opin Endocrinol Diabetes Obes. 2015;22(3):169-179. PMID: 25871962. doi: 10.1097/med.0000000000000150. Exclude: X1

317. Tomas Loges N, Raidt J, Hoben IM, et al. Mutations in C11ORF70 cause primary ciliary dyskinesia with randomization of left/right body asymmetry due to outer and inner dynein arm defects. Atemwegs- und lungenkrankheiten. 2018;44(2):71-. PMID: CN-01572764. doi: 10.5414/ATX02292. Exclude: X1

318. Tompson SWJ, Souma T, Siggs OM, et al. Mutations in a new gene cause glaucoma with variable onset. Investigative ophthalmology and visual science. Conference: 2016 annual meeting of the association for research in vision and ophthalmology, ARVO 2016. United states. 2016;57(12):799. PMID: CN-01377177. Exclude: X1

319. Tong W, Wang Y, Lu Y, et al. Whole-exome sequencing helps the diagnosis and treatment in children with neurodevelopmental delay accompanied unexplained dyspnea. Sci Rep. 2018;8(1):5214. PMID: 29581464. doi: 10.1038/s41598-018-23503-2. Exclude: X9

320. Trotta L, Norberg A, Taskinen M, et al. Diagnostics of rare disorders: whole-exome sequencing deciphering locus heterogeneity in telomere biology disorders. Orphanet J Rare Dis. 2018;13(1):139. PMID: 30115091. doi: 10.1186/s13023-018-0864-9. Exclude: X4

321. Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. Eur J Hum Genet. 2017;25(2):176-182. PMID: 27848944. doi: 10.1038/ejhg.2016.146. Exclude: X4

322. Tsuchida N, Nakashima M, Kato M, et al. Detection of copy number variations in epilepsy using exome data. Clin Genet. 2018;93(3):577-587. PMID: 28940419. doi: 10.1111/cge.13144. Exclude: X4

323. Tsurusaki Y, Kobayashi Y, Hisano M, et al. The diagnostic utility of exome sequencing in Joubert syndrome and related disorders. J Hum Genet. 2013;58(2):113-115. PMID: 23034536. doi: 10.1038/jhg.2012.117. Exclude: X8

324. Tufts Medical Center. Genomic medicine for ill neonates and infants (The GEMINI Study). https://ClinicalTrials.gov/show/NCT03890679. Published 2019. Updated March 21. Exclude: X7

325. Tumiene B, Maver A, Writzl K, et al. Diagnostic exome sequencing of syndromic epilepsy patients in clinical practice. Clin Genet. 2018;93(5):1057-1062. PMID: 29286531. doi: 10.1111/cge.13203. Exclude: X4

326. Turbitt E, Halliday JL, Amor DJ, Metcalfe SA. Preferences for results from genomic microarrays: comparing parents and health care providers. Clin Genet. 2015;87(1):21-29. PMID: 24773164. doi: 10.1111/cge.12398. Exclude: X2

327. University Hospital, Strasbourg, France. Various type of genetic events in patients with intellectual disability. https://ClinicalTrials.gov/show/NCT02881333. Published 2016. Updated September. Exclude: X7

328. University of California, San Francisco. Clinical utility of pediatric whole exome sequencing. https://ClinicalTrials.gov/show/NCT03525431. Published 2017. Updated August 1. Exclude: X7

329. University of Kentucky. Finding genes for rare diseases. https://ClinicalTrials.gov/show/NCT02724995. Published 2016. Updated February. Exclude: X7

330. University of North Carolina at Chapel Hill. North Carolina genomic evaluation by next-generation exome sequencing, 2. Published 2018. Updated September 28. Exclude: X7

331. University of Pittsburgh. Neurogenetics patient registry. https://ClinicalTrials.gov/show/NCT02995538. Published 2017. Updated January 30. Exclude: X7

332. Vairo FP, Boczek NJ, Cousin MA, et al. The prevalence of diseases caused by lysosome-related genes in a cohort of undiagnosed patients. Mol Genet Metab Rep. 2017;13:46-51. PMID: 28831385. doi: 10.1016/j.ymgmr.2017.08.001. Exclude: X4

333. Vallespin E, Palomares Bralo M, Mori MA, et al. Customized high resolution CGH-array for clinical diagnosis reveals additional genomic imbalances in previous well-defined pathological samples. Am J Med Genet A. 2013;161a(8):1950-1960. PMID: 23798500. doi: 10.1002/ajmg.a.35960. Exclude: X3

334. Van Cauwenbergh C, Coppieters F, Roels D, et al. Mutations in splicing factor genes are a major cause of autosomal dominant retinitis pigmentosa in Belgian families. PLoS One. 2017;12(1):e0170038. PMID: 28076437. doi: 10.1371/journal.pone.0170038. Exclude: X3

335. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid targeted genomics in critically ill newborns. Pediatrics. 2017;140(4). PMID: 28939701. doi: 10.1542/peds.2016-2854. Exclude: X3

336. van El CG, Cornel MC, Borry P, et al. Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2013;21(6):580-584. PMID: 23676617. doi: 10.1038/ejhg.2013.46. Exclude: X1

337. van Nimwegen KJ, Schieving JH, Willemsen MA, et al. The diagnostic pathway in complex paediatric neurology: a cost analysis. Eur J Paediatr Neurol. 2015;19(2):233-239. PMID: 25604808. doi: 10.1016/j.ejpn.2014.12.014. Exclude: X3

338. van Nimwegen KJ, van Soest RA, Veltman JA, et al. Is the $1000 genome as near as we think? A cost analysis of next-generation sequencing. Clin Chem. 2016;62(11):1458-1464. PMID: 27630156. doi: 10.1373/clinchem.2016.258632. Exclude: X4

339. Vanderver A, Helman G, Sherbini O, et al. Prospective whole genome sequencing in pediatric white matter disorders. Ann Neurol. 2018;84:S357-. PMID: CN-01654164. doi: 10.1002/ana.25305. Exclude: X1

340. Vassy JL, Christensen KD, Schonman EF, et al. The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: a pilot randomized trial. Ann Intern Med. 2017;167(3):159-169. PMID: 28654958. doi: 10.7326/m17-0188. Exclude: X2

341. Vassy JL, Christensen KD, Slashinski MJ, et al. 'Someday it will be the norm': physician perspectives on the utility of genome sequencing for patient care in the MedSeq Project. Per Med. 2015;12(1):23-32. PMID: 25642274. doi: 10.2217/pme.14.68. Exclude: X2

342. Vetro A, Goidin D, Lesende I, et al. Diagnostic application of a capture based NGS test for the concurrent detection of variants in sequence and copy number as well as LOH. Clin Genet. 2018;93(3):545-556. PMID: 28556904. doi: 10.1111/cge.13060. Exclude: X3

343. Vivante A, Hwang DY, Kohl S, et al. Exome sequencing discerns syndromes in patients from consanguineous families with congenital anomalies of the kidneys and urinary tract. J Am Soc Nephrol. 2017;28(1):69-75. PMID: 27151922. doi: 10.1681/asn.2015080962. Exclude: X9

344. Volk A, Conboy E, Wical B, Patterson M, Kirmani S. Whole-exome sequencing in the clinic: Lessons from six consecutive cases from the clinician's perspective. Mol Syndromol. 2015;6(1):23-31. PMID: 25852444. doi: 10.1159/000371598. Exclude: X4

345. Vyas V, Lambiase PD. The investigation of sudden arrhythmic death syndrome (SADS)-the current approach to family screening and the future role of genomics and stem cell technology. Front Physiol. 2013;4:199. PMID: 24062688. doi: 10.3389/fphys.2013.00199. Exclude: X1

346. Wall JD, Tang LF, Zerbe B, et al. Estimating genotype error rates from high-coverage next-generation sequence data. Genome Res. 2014;24(11):1734-1739. PMID: 25304867. doi: 10.1101/gr.168393.113. Exclude: X4

347. Wang E, Cho WCS, Wong SCC, Liu S. Disease biomarkers for precision medicine: challenges and future opportunities. Genom Proteom Bioinform. 2017;15(2):57-58. PMID. doi: 10.1016/j.gpb.2017.04.001. Exclude: X1

348. Wang L, Zhang J, Chen N, et al. Application of whole exome and targeted panel sequencing in the clinical molecular diagnosis of 319 Chinese families with inherited retinal dystrophy and comparison study. Genes (Basel). 2018;9(7). PMID: 30029497. doi: 10.3390/genes9070360. Exclude: X9

349. Warejko JK, Schueler M, Vivante A, et al. Whole exome sequencing reveals a monogenic cause of disease in approximately 43% of 35 families with midaortic syndrome. Hypertension. 2018;71(4):691-699. PMID: 29483232. doi: 10.1161/hypertensionaha.117.10296. Exclude: X4

350. Warman Chardon J, Beaulieu C, Hartley T, Boycott KM, Dyment DA. Axons to exons: the molecular diagnosis of rare neurological diseases by next-generation sequencing. Curr Neurol Neurosci Rep. 2015;15(9):64. PMID: 26289954. doi: 10.1007/s11910-015-0584-7. Exclude: X1

351. Weck KE. Interpretation of genomic sequencing: variants should be considered uncertain until proven guilty. Genet Med. 2018;20(3):291-293. PMID: 29388946. doi: 10.1038/gim.2017.269. Exclude: X1

352. Weiss K, Kurolap A, Paperna T, et al. Rare disease diagnostics: a single-center experience and lessons learnt. Rambam Maimonides Med J. 2018;9(3). PMID: 30089087. doi: 10.5041/rmmj.10341. Exclude: X4

353. Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. Genet Med. 2017;19(2):209-214. PMID: 27441994. doi: 10.1038/gim.2016.88. Exclude: X4

354. Willemsen MH, Kleefstra T. Making headway with genetic diagnostics of intellectual disabilities. Clin Genet. 2014;85(2):101-110. PMID: 23895455. doi: 10.1111/cge.12244. Exclude: X4

355. Williams JL, Rahm AK, Zallen DT, et al. Impact of a patient-facing enhanced genomic results report to improve understanding, engagement, and communication. J Genet Couns. 2018;27(2):358-369. PMID: 29204811. doi: 10.1007/s10897-017-0176-6. Exclude: X3

356. Wilson BJ, Miller FA, Rousseau F. Controversy and debate on clinical genomics sequencing-paper 1: genomics is not exceptional: rigorous evaluations are necessary for clinical applications of genomic sequencing. J Clin Epidemiol. 2017;92:4-6. PMID: 28870871. doi: 10.1016/j.jclinepi.2017.08.018. Exclude: X1

357. Wiszniewski W, Gawlinski P, Gambin T, et al. Comprehensive genomic analysis of patients with disorders of cerebral cortical development. Eur J Hum Genet. 2018;26(8):1121-1131. PMID: 29706646. doi: 10.1038/s41431-018-0137-z. Exclude: X4

358. Worst BC, Van Tilburg CM, Balasubramanian GP, et al. Personalized medicine for ALL? the pediatric INFORM project. Oncology Research and Treatment. 2016;39:16-17. PMID. doi: 10.1159/000449050. Exclude: X1

359. Worthey EA. Analysis and annotation of whole-genome or whole-exome sequencing-derived variants for clinical diagnosis. Curr Protoc Hum Genet. 2013;79:Unit 9.24. PMID: 24510652. doi: 10.1002/0471142905.hg0924s79. Exclude: X1

360. Worthey EA. Analysis and annotation of whole-genome or whole-exome sequencing derived variants for clinical diagnosis. Curr Protoc Hum Genet. 2017;95:9.24.21-29.24.28. PMID: 29044471. doi: 10.1002/cphg.49. Exclude: X1

361. Wouters RHP, Bijlsma RM, Frederix GWJ, et al. Is it our duty to hunt for pathogenic mutations? Trends Mol Med. 2018;24(1):3-6. PMID: 29246758. doi: 10.1016/j.molmed.2017.11.008. Exclude: X1

362. Wouters RHP, Cornelis C, Newson AJ, Bunnik EM, Bredenoord AL. Scanning the body, sequencing the genome: dealing with unsolicited findings. Bioethics. 2017;31(9):648-656. PMID: 28975656. doi: 10.1111/bioe.12375. Exclude: X1

363. Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet. 2015;385(9975):1305-1314. PMID: 25529582. doi: 10.1016/s0140-6736(14)61705-0. Exclude: X4

364. Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. Genet Med. 2018;20(10):1216-1223. PMID: 29323667. doi: 10.1038/gim.2017.246. Exclude: X4

365. Xiao B, Qiu W, Ji X, et al. Marked yield of re-evaluating phenotype and exome/target sequencing data in 33 individuals with intellectual disabilities. Am J Med Genet A. 2018;176(1):107-115. PMID: 29159939. doi: 10.1002/ajmg.a.38542. Exclude: X9

366. Xinhua Hospital SJTUSoM. Whole genome sequencing in the detection of rare undiagnosed genetic diseases in children in China. https://ClinicalTrials.gov/show/NCT03424772. Published 2018. Updated January 18. Exclude: X9

367. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med. 2013;369(16):1502-1511. PMID: 24088041. doi: 10.1056/NEJMoa1306555. Exclude: X8

368. Yao T, Udwan K, John R, et al. Integration of genetic testing and pathology for the diagnosis of adults with FSGS. Clin J Am Soc Nephrol. 2019. PMID: 30647093. doi: 10.2215/cjn.08750718. Exclude: X4

369. Yu TW, Chahrour MH, Coulter ME, et al. Using whole-exome sequencing to identify inherited causes of autism. Neuron. 2013;77(2):259-273. PMID: 23352163. doi: 10.1016/j.neuron.2012.11.002. Exclude: X1

370. Zazo Seco C, Wesdorp M, Feenstra I, et al. The diagnostic yield of whole-exome sequencing targeting a gene panel for hearing impairment in The Netherlands. Eur J Hum Genet. 2017;25(3):308-314. PMID: 28000701. doi: 10.1038/ejhg.2016.182. Exclude: X4

371. Zech M, Jech R, Wagner M, et al. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. Neurogenetics. 2017;18(4):195-205. PMID: 28849312. doi: 10.1007/s10048-017-0521-9. Exclude: X4

Appendix E. Individual Study Risk of Bias Assessments

Table E-1. Risk of Bias Assessment-Part 1

Author (Year)	Study Design	Was the study population described in adequate detail?	Was participant inclusion/exclusion criteria appropriate?	Could the way in which participants were selected introduce bias?	For RCTs, was the method of randomization and allocation concealment adequate and were baseline characteristics similar among groups?	For nonrandomized comparative studies, is the comparison group appropriate?
Balridge (2017)[43]	Single-arm observational cohort	Probably Yes	Probably Yes	Probably No	NA	NA
Bourchany (2017)[42]	Single-arm observational cohort	No	Probably Yes	Unclear	NA	NA
Cordoba (2018)[18]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Daga (2018)[41]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Dillon (2018)[17]	Modeling Study	Probably No	Unclear	Probably No	NA	NA
Ding (2014)[75]	Modeling Study	NA	NA	NA	NA	NA
Dragojlovic (2018)[23]	Modeling Study	No	Unclear	Unclear	NA	NA
Evers (2017)[52]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Ewans (2018)[21]	Single-arm observational cohort	Probably No	Unclear	Unclear	NA	NA
Hamilton (2016)[101]	Single-arm observational cohort	No	No	Yes	NA	Yes
Hauer (2017)[51]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Howell (2018)[28]	Single-arm observational cohort plus economic-modeling study	Yes	Yes	Probably No	NA	NA
Iglesias (2014)[46]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Jones (2018)[50]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Jurgens (2015)[65]	Single-arm observational cohort	Probably No	Probably Yes	Unclear	NA	NA
Lee (2015)[73]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Mann (2019)[48]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Matias (2019)[49]	Controlled (two or more groups) observational cohort	Yes	Yes	No	NA	Yes
McConkie-Rosell (2018)[69]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Meng (2017)[40]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Monies (2017)[61]	Single-arm observational cohort	Probably No	Probably No	Unclear	NA	NA
Monroe (2016)[80]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Muramatsu (2017)[70]	Single-arm observational cohort	Yes	Unclear	Unclear	NA	NA

Author (Year)	Study Design	Was the study population described in adequate detail?	Was participant inclusion/exclusion criteria appropriate?	Could the way in which participants were selected introduce bias?	For RCTs, was the method of randomization and allocation concealment adequate and were baseline characteristics similar among groups?	For nonrandomized comparative studies, is the comparison group appropriate?
Niguidula (2018)[39]	Single-arm observational cohort	Probably Yes	Probably Yes	Yes	NA	NA
Nolan (2016)[24]	Single-arm observational cohort	Probably Yes	Probably Yes	Unclear	NA	NA
Palmer (2018)[27]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Perucca (2017)[34]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Posey (2015)[63]	Single-arm observational cohort	Probably Yes	Yes	Probably No	NA	NA
Ream (2014)[58]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Retterer (2016)[64]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Roche (2019)[76]	Single-arm observational cohort	Probably Yes	Yes	Probably No	NA	NA
Sawyer (2016)[55]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Schofield (2017)[26]	Controlled (two or more groups) observational cohort	Probably Yes	Probably Yes	Unclear	NA	Probably Yes
Shamriz (2016)[53]	Case series	Yes	Yes	Yes	NA	NA
Shashi (2015)[74]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Snoeijen-Schouwenaars (2019)[32]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Soden (2014)[25]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Srivastava (2014)[57]	Single-arm observational cohort	Probably Yes	Yes	Probably No	NA	NA
Stark (2016, 2017, 2019)[13-16]	Single-arm observational cohort	Unclear	Probably Yes	Unclear	NA	NA
Stark (2018)[22]	Single-arm observational cohort	Probably No	Unclear	Unclear	NA	NA
Strauss (2017)[60]	Single-arm observational cohort	Probably Yes	Probably No	Probably Yes	NA	NA
Tammimies (2015)[72]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Tan (2017)[19]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Tarailo-Graovac (2016)[44]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Tsiplova (2017)[79]	Modeling Study	Probably No	NA	NA	NA	Probably Yes
Valencia (2015)[54]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Vanderver (2016)[71]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA

Author (Year)	Study Design	Was the study population described in adequate detail?	Was participant inclusion/exclusion criteria appropriate?	Could the way in which participants were selected introduce bias?	For RCTs, was the method of randomization and allocation concealment adequate and were baseline characteristics similar among groups?	For nonrandomized comparative studies, is the comparison group appropriate?
Vissers (2017)[20]	Single-arm trial	Yes	Yes	No	NA	Yes
Vrijenhoek (2018)[77]	Single-arm observational cohort	Probably No	NR	Unclear	NA	NA
Waldrop (2019)[47]	Single-arm observational cohort	Yes	Probably Yes	Probably No	NA	NA
Walsh (2017)[78]	Single-arm observational cohort	Probably Yes	Probably Yes	Probably No	NA	NA
Willing (2015)[56]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA
Yang (2014)[66]	Single-arm observational cohort	Yes	Yes	No	NA	NA
Zhu (2015)[45]	Single-arm observational cohort	Yes	Yes	Probably No	NA	NA

Abbreviations: NA = not applicable; NR = not reported

Table E-2. Risk of Bias Assessment-Part 2

Author (Year)	For nonrandomized comparative studies, does the analysis control for important baseline differences between groups or other known confounders?	Was the test and/or testing strategy described in adequate detail?	Were there important deviations from the intended tests or testing strategies used?	Were outcome assessors blinded?
Balridge (2017)[43]	NA	Probably Yes	Unclear	Unclear
Bourchany (2017)[42]	No	Yes	Probably No	Unclear
Cordoba (2018)[18]	NA	Probably Yes	No	Unclear
Daga (2018)[41]	NA	Yes	Probably No	Unclear
Dillon (2018)[17]	NA	No	Probably No	Unclear
Ding (2014)[75]	NA	No	NR	NA
Dragojlovic (2018)[23]	NA	Probably Yes	Unclear	Unclear
Evers (2017)[52]	NA	Yes	No	No
Ewans (2018)[21]	NA	Probably Yes	Unclear	Unclear
Hamilton (2016)[101]	Yes	Yes	Yes	No
Hauer (2017)[51]	NA	Probably Yes	Probably No	No
Howell (2018)[28]	NA	Probably Yes	Unclear	Probably No
Iglesias (2014)[46]	NA	Probably No	Probably No	Unclear
Jones (2018)[50]	NA	No	Unclear	No
Jurgens (2015)[65]	NA	Yes	No	NA
Lee (2015)[73]	NA	Yes	No	No
Mann (2019)[48]	NA	Yes	No	No
Matias (2019)[49]	Yes	Yes	No	Probably No
McConkie-Rosell (2018)[69]	NA	NA	NA	Yes
Meng (2017)[40]	NA	Yes	Probably No	Probably No
Monies (2017)[61]	NA	Probably Yes	Probably No	Unclear
Monroe (2016)[80]	NA	Probably Yes	Probably No	NR
Muramatsu (2017)[70]	NA	Yes	No	No
Niguidula (2018)[39]	NA	No	NR	No
Nolan (2016)[24]	NA	Probably No	Unclear	Unclear
Palmer (2018)[27]	NA	Probably No	Unclear	Unclear
Perucca (2017)[34]	NA	Yes	No	No
Posey (2015)[63]	NA	Yes	No	NA
Ream (2014)[58]	NA	Yes	No	No

Author (Year)	For nonrandomized comparative studies, does the analysis control for important baseline differences between groups or other known confounders?	Was the test and/or testing strategy described in adequate detail?	Were there important deviations from the intended tests or testing strategies used?	Were outcome assessors blinded?
Retterer (2016)[64]	NA	Yes	No	NA
Roche (2019)[76]	NA	No	Probably No	Unclear
Sawyer (2016)[55]	NA	Yes	No	No
Schofield (2017)[26]	NR	Probably No	Unclear	Unclear
Shamriz (2016)[53]	NA	Yes	No	No
Shashi (2015)[74]	NA	Yes	No	No
Snoeijen-Schouwenaars (2019)[32]	NA	Yes		No
Soden (2014)[25]	NA	Probably No	Probably No	Unclear
Srivastava (2014)[57]	NA	Yes	No	Probably No
Stark (2016, 2017, 2019)[13-16]	NA	No	Unclear	Unclear
Stark (2018)[22]	Probably No	Yes	Probably No	Unclear
Strauss (2017)[60]	NA	Yes	Probably No	Unclear
Tammimies (2015)[72]	NA	Yes	No	No
Tan (2017)[19]	NA	Probably No	Probably No	Unclear
Tarailo-Graovac (2016)[44]	NA	Yes	No	No
Tsiplova (2017)[79]	Probably Yes	Probably Yes	NA	NA
Valencia (2015)[54]	NA	Yes	Probably No	Unclear
Vanderver (2016)[71]	NA	Yes	Probably No	No
Vissers (2017)[20]	NA	Yes	No	No
Vrijenhoek (2018)[77]	NA	No	Probably No	Probably No
Waldrop (2019)[47]	NA	Probably No	Probably No	Unclear
Walsh (2017)[78]	NA	Probably No	Unclear	Unclear
Willing (2015)[56]	NA	Yes	No	No
Yang (2014)[66]	NA	Yes	Probably No	Unclear
Zhu (2015)[45]	NA	Yes	No	No

Abbreviations: NA = not applicable; NR = not reported

Table E-3. Risk of Bias Assessment-Part 3

Author (Year)	For clinical utility measures and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were clinical utility outcomes data available for at least 80% of participants that were enrolled without any evidence of differential attrition?	For health outcomes and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were health outcomes data available for at least 80% of participants that were enrolled? Any evidence of differential attrition?	For safety outcomes and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were safety outcomes data available for at least 80% of participants that were enrolled? Any evidence of differential attrition?
Balridge (2017)[43]	Probably No	Probably Yes	NA	NA	Probably Yes	Probably Yes
Bourchany (2017)[42]	NR	No	NA	NA	Probably Yes	Probably Yes
Cordoba (2018)[18]	No	Yes	NA	NA	NA	NA
Daga (2018)[41]	NR	Probably Yes	NA	NA	NA	NA
Dillon (2018)[17]	NA	NA	NA	NA	NA	NA
Ding (2014)[75]	NA	NA	NA	NA	Unclear	NA
Dragojlovic (2018)[23]	Unclear	NA	NR	NA	NA	NA
Evers (2017)[52]	Yes	Yes	NA	NA	NA	NA
Ewans (2018)[21]	NA	NA	NA	NA	NA	NA
Hamilton (2016)[101]	NA	NA	NA	NA	Probably No	No
Hauer (2017)[51]	Unclear	Yes	NA	NA	NA	NA
Howell (2018)[28]	No	Unclear	NA	NA	NA	NA
Iglesias (2014)[46]	Probably Yes	Probably Yes	NA	NA	NA	NA
Jones (2018)[50]	Probably Yes	Yes	Probably Yes	Yes	NA	NA
Jurgens (2015)[65]	NA	NA	NA	NA	Probably Yes	Yes
Lee (2015)[73]	NA	NA	NA	NA	Yes	Yes
Mann (2019)[48]	No	Yes	NA	NA	NA	NA
Matias (2019)[49]	Yes	Yes	NA	NA	NA	NA
McConkie-Rosell (2018)[69]	NA	NA	NA	NA	Yes	Yes

Author (Year)	For clinical utility measures and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were clinical utility outcomes data available for at least 80% of participants that were enrolled without any evidence of differential attrition?	For health outcomes and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were health outcomes data available for at least 80% of participants that were enrolled? Any evidence of differential attrition?	For safety outcomes and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were safety outcomes data available for at least 80% of participants that were enrolled? Any evidence of differential attrition?
Meng (2017)[40]	No	Probably Yes	Probably No	Yes	Probably Yes	Probably Yes
Monies (2017)[61]	NA	NA	NA	NA	Probably Yes	Probably Yes
Monroe (2016)[80]	NA	NA	NA	Unclear	NA	NA
Muramatsu (2017)[70]	NA	NA	NA	NA	Yes	Yes
Niguidula (2018)[39]	No	NA	NA	NA	NA	NA
Nolan (2016)[24]	Probably No	Yes	NA	Yes	Yes	Yes
Palmer (2018)[27]	No	Probably Yes	NA	NA	NA	NA
Perucca (2017)[34]	No	Yes	Probably No	Unclear	NA	NA
Posey (2015)[63]	NA	NA	NA	NA	Yes	Yes
Ream (2014)[58]	Probably Yes	Yes	No	Probably No	No	No
Retterer (2016)[64]	NA	NA	NA	NA	Yes	Yes
Roche (2019)[76]	NA	NA	NA	NA	Unclear	Probably Yes
Sawyer (2016)[55]	Unclear	Unclear	NA	NA	No	No
Schofield (2017)[26]	NA	NA	NA	NA	NA	NA
Shamriz (2016)[53]	Probably Yes	Yes	Probably Yes	Yes	NA	NA
Shashi (2015)[74]	NA	NA	NA	NA	Yes	Yes
Snoeijen-Schouwenaars (2019)[32]	No	Yes	Probably Yes	Yes	NA	NA
Soden (2014)[25]	No	Yes	NA	NA	NA	NA
Srivastava (2014)[57]	No	NR	NA	NA	NA	NA

Author (Year)	For clinical utility measures and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were clinical utility outcomes data available for at least 80% of participants that were enrolled without any evidence of differential attrition?	For health outcomes and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were health outcomes data available for at least 80% of participants that were enrolled? Any evidence of differential attrition?	For safety outcomes and analyses, are the measures and statistical methods used valid and appropriate (and similarly applied among groups for comparative studies)?	Were safety outcomes data available for at least 80% of participants that were enrolled? Any evidence of differential attrition?
Stark (2016, 2017, 2019)[13-16]	Probably No	Yes	Yes	Yes	Yes	Yes
Stark (2018)[22]	Probably No	Probably Yes	Probably Yes	Probably Yes	NA	NA
Strauss (2017)[60]	NA	NA	NA	NA	Yes	Yes
Tammimies (2015)[72]	NA	NA	NA	NA	Yes	Yes
Tan (2017)[19]	Probably Yes	Yes	NA	NA	NA	NA
Tarailo-Graovac (2016)[44]	Probably No	Yes	NA	NA	Yes	Yes
Tsiplova (2017)[79]	NA	NA	NA	NA	NA	NA
Valencia (2015)[54]	Probably No	Probably Yes	NA	NA	Yes	Probably Yes
Vanderver (2016)[71]	NA	NA	NA	NA	Yes	Yes
Vissers (2017)[20]	NA	NA	NA	NA	Yes	Yes
Vrijenhoek (2018)[77]	NA	NA	NA	NA	NA	NA
Waldrop (2019)[47]	NR	Probably Yes	NA	NA	NA	NA
Walsh (2017)[78]	NA	NA	NA	NA	NA	NA
Willing (2015)[56]	Probably No	Yes	Yes	Yes		
Yang (2014)[66]	NA	NA	NA	NA	Probably Yes	Yes
Zhu (2015)[45]	Probably No	Unclear	NA	NA	NA	NA

Abbreviations: NA = not applicable; NR = not reported

Table E-4. Quality of Health Economic Studies-Part 1

Author (Year)	Was the study objective presented in a clear, specific, and measurable manner?	Were the perspective of the analysis (societal, third-party payer, and so on) and reasons for its selection stated?	Were variable estimates used in the analysis from the best available source (i.e., Randomized Control Trial-Best, Expert Opinion-Worst)?	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	Was uncertainty handled by: (i) statistical analysis to address random events; (ii) sensitivity analysis to cover a range of assumptions?	Was incremental analysis performed between alternatives for resources and costs?	Was the methodology for data abstraction (including value health states and other benefits) stated?
Cordoba (2018)[18]	No	Yes	Unclear	NA	No	No	No
Dillon (2018)[17]	No	Unclear	Unclear	NA	No	No	No
Dragojlovic (2018)[23]	Yes	Yes	Yes	NA	Yes	No	Unclear
Ewans (2018)[21]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Howell (2018)[28]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Monroe (2016)[80]	Yes	Yes	Yes	NA	No	Unclear	Yes
Nolan (2016)(#6227)	No	No	Unclear	NA	No	NA	NA
Palmer (2018)[27]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Schofield (2017)[26]	Yes	Yes	Yes	NA	Yes	Yes	Unclear
Soden (2014)[25]	No	No	Unclear	NA	No	No	No
Stark (2018)[22]	Yes	Yes	Yes	NA	Yes	No	Yes
Stark (2016, 2017, 2019)[13-16]	Yes	Yes	Unclear	NA	Yes	Yes	Unclear
Tan (2017) [19]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Tsiplova (2017)[79]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Vissers (2017)[20]	Yes	Yes	Yes	NA	Yes	No	Yes
Vrijenhoek (2018)[77]	No	Yes	Yes	NA	No	No	Unclear
Walsh (2017)[78]	No	Yes	Unclear	NA	No	Yes	Unclear

Abbreviations: NA = not applicable; NR = not reported

Table E-5. Quality of Health Economic Studies-Part 2

Author (Year)	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3–5%) and justification given for the discount rate?	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	Was the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term and negative outcomes included?	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner?	Were the choice of economic model, main assumptions and limitations of the study stated and justified?
Cordoba (2018)[18]	NA	Unclear	No	NA	No	Unclear
Dillon (2018)[17]	NA	No	No	NA	No	Unclear
Dragojlovic (2018)[23]	NA	Yes	Unclear	NA	Unclear	No
Ewans (2018)[21]	NA	Yes	Unclear	NA	Yes	No
Howell (2018)[28]	NA	Yes	Yes	NA	Yes	Unclear
Monroe (2016)[80]	NA	Yes	Unclear	NA	Yes	Yes
Nolan (2016)(#6227)	Yes	No	No	NA	Yes	Yes
Palmer (2018)[27]	NA	Unclear	Yes	NA	Yes	Unclear
Schofield (2017)[26]	NA	Yes	Yes	NA	Yes	Yes
Soden (2014)[25]	NA	No	No	NA	No	Unclear
Stark (2018)[22]	NA	Yes	Unclear	NA	Yes	Unclear
Stark (2016, 2017, 2019)[13-16]	Yes	Unclear	Unclear	NA	Yes	Yes
Tan (2017) [19]	NA	Yes	No	NA	Yes	No
Tsiplova (2017)[79]	Yes	Yes	Unclear	NA	Yes	No
Vissers (2017)[20]	NA	Yes	Unclear	NA	Unclear	Unclear
Vrijenhoek (2018)[77]	NA	Yes	No	NA	No	Unclear
Walsh (2017)[78]	NA	Yes	No	NA	No	Unclear

Abbreviations: NA = not applicable; NR = not reported

Table E-6. Quality of Health Economic Studies - Part 3

Author (Year)	Did the author(s) explicitly discuss direction and magnitude of potential biases?	Were the conclusions/recommendations of the study justified and based on the study results?	Was there a statement disclosing the source of funding for the study?	Total Score[a]
Cordoba (2018)[18]	No	Unclear	Yes	26
Dillon (2018)[17]	No	Unclear	No	15
Dragojlovic (2018)[23]	Yes	Unclear	Yes	60
Ewans (2018)[21]	No	Unclear	Yes	73
Howell (2018)[28]	No	Yes	No	84
Monroe (2016)[80]	Yes	Yes	Yes	79
Nolan (2016)(#6227)	No	Unclear	Yes	40
Palmer (2018)[27]	No	Yes	Yes	79
Schofield (2017)[26]	Unclear	Yes	Yes	89
Soden (2014)[25]	No	Unclear	Yes	18
Stark (2018)[22]	No	Yes	Yes	75
Stark (2016, 2017, 2019)[13-16]	Yes	Yes	Yes	80
Tan (2017) [19]	Unclear	Unclear	Yes	73
Tsiplova (2017)[79]	Unclear	Unclear	Yes	80
Vissers (2017)[20]	Yes	Yes	Yes	73
Vrijenhoek (2018)[77]	No	Unclear	Yes	31
Walsh (2017)[78]	No	Yes	Yes	44

Notes: [a] Based on scale of 0 (worst quality) to 100 (best quality); studies <60 were assigned high risk of bias; studies between 60 to 89 were assigned some risk of bias, and studies >=90 were assigned low risk of bias.

Table E-7. Risk of Bias Assessment-Overall Summary

Author (Year)	Clinical Utility	Health Outcomes	Safety	Cost	Comments
Balridge (2017)[43]	Some risk of bias	NA	Some risk of bias	NA	Little information about how clinical utility measures were defined and abstracted from the medical record.
Bourchany (2017)[42]	High risk of bias	NA	Low risk of bias	NA	No information about how clinical utility measures collected; missing information for many participants regarding clinical utility measures.
Cordoba (2018)[18]	Some risk of bias	NA	NA	High risk of bias	No information about how clinical utility measures were specified and ascertained; very limited information about how costs were determined and specifically designation of expendable vs. nonexpendable costs.
Daga (2018)[41]	Some risk of bias	NA	NA	NA	No information about how clinical utility measures were collected.
Dillon (2018)[17]	NA	NA	NA	High risk of bias	Very little information about specific costs used and where obtained; includes costs from different years without indexing to a specific year.
Ding (2014)[75]	NA	NA	Some risk of bias	NA	This was a modeling study.
Dragojlovic (2018)[23]	NA	NA	NA	Some risk of bias	Missing data for a reasonable proportion of participants enrolled; cost analysis not well-described.
Evers (2017)[52]	Some risk of bias	NA	NA	NA	None
Ewans (2018)[21]	NA	NA	NA	Some risk of bias	Cost analysis based only on a subcohort of 14 participants with intellectual disability.
Hamilton (2016)[101]	NA	NA	High risk of bias	NA	Records or sequencing was not available for a large proportion of the cohort; excluded low coverage genes from analysis.
Hauer (2017)[51]	High risk of bias	NA	NA	NA	None
Howell (2018)[28]	High risk of bias	NA	NA	Some risk of bias	No information about how clinical utility was ascertained; finding is not similar to findings reported in other studies suggesting a problem in ascertainment. With respect to cost, main assumptions and limitations not well discussed; no statement disclosing funding.
Iglesias (2014)[46]	Some risk of bias	NA	NA	NA	No details regarding how medical record abstraction or test was conducted.
Jones (2018)[50]	High risk of bias	Some risk of bias	NA	NA	None

Author (Year)	Clinical Utility	Health Outcomes	Safety	Cost	Comments
Jurgens (2015)[65]	NA	NA	Some risk of bias	NA	None
Lee (2015)[73]	NA	NA	Low risk of bias	NA	None
Mann (2019)[48]	Some risk of bias	NA	NA	NA	None
Matias (2019)[49]	Some risk of bias	NA	NA	NA	Each patient is compared to themselves pre- and post - WES, then finding are compared between positive WES group and negative WES group.
McConkie-Rosell (2018)[69]	NA	NA	Low risk of bias	NA	None
Meng (2017)[40]	Some risk of bias	Some risk of bias	Some risk of bias	NA	None
Monies (2017)[61]	NA	NA	Some risk of bias	NA	Population tested was poorly described; conducted in a country known to have a higher degree of consanguinity.
Monroe (2016)[80]	NA	NA	NA	Some risk of bias	No sensitivity analysis or consideration of uncertainty in estimates; incremental analysis not entirely clear.
Muramatsu (2017)[70]	NA	NA	Low risk of bias	NA	None
Niguidula (2018)[39]	High risk of bias	NA	NA	NA	Clinical utility measures based on provider recall survey, no verification with medical records. Survey response rate was 2.2%, which could introduce very serious risk for selection bias.
Nolan (2016)[24]	Some risk of bias	NA	Some risk of bias	High risk of bias	For clinical utility and health outcomes, outcomes measured through review of medical record; unclear whether outcomes were defined a priori, outcome assessors likely not masked to testing intervention. For cost outcomes, details of costing methodology not provided, utilities established through clinician assessment of prognosis, currency year not specified, no sensitivity analyses for key parameters
Palmer (2018)[27]	Some risk of bias	NA	NA	Some risk of bias	Specification and method of ascertainment of clinical utility measures not well-described; unclear whether participants received all of the testing in first and second tier, or only some of the testing and the impact of this on cost analysis not discussed.
Perucca (2017)[34]	High risk of bias	High risk of bias	NA	NA	None
Posey (2015)[63]	NA	NA	Low risk of bias	NA	None

Author (Year)	Clinical Utility	Health Outcomes	Safety	Cost	Comments
Ream (2014)[58]	Some risk of bias	High risk of bias	High risk of bias	NA	Study only designed to measure potential changes in therapy. These were pre-defined, reducing risk of bias.
Retterer (2016)[64]	NA	NA	Low risk of bias	NA	None
Roche (2019)[76]	NA	NA	High risk of bias	NA	Focused on evaluation of nonmedically actionable results; reporting of medically actionable results was secondary; test used was not described; the specific variants considered medically actionable were not described; the variants considered nonmedically actionable appear to have overlap with what some would consider medically actionable.
Sawyer (2016)[55]	High risk of bias	NA	NA	NA	None
Schofield (2017)[26]	NA	NA	NA	Some risk of bias	Unclear what tests, out of the traditional pathway, participants in the WES or neuromuscular gene panel also received and at what time; those who got WES or NMD gene panel remained undiagnosed after traditional pathway, thus are likely not similar; several assumptions were made for cost analysis and costs of counseling in WES approach was not included, unclear whether all costs were captured from outside settings given duration of study (over 15 years).
Shamriz (2016)[53]	High risk of bias	High risk of bias	NA	NA	None
Shashi (2015)[74]	NA	NA	Low risk of bias	NA	ACMG list of medically actionable variants published during study; only 59 patients tested after publication.
Snoeijen-Schouwenaars (2019)[32]	High risk of bias	High risk of bias	NA	NA	None
Soden (2014)[25]	High risk of bias	NA	NA	High risk of bias	Ascertainment of clinical utility was partly through physician interview/recall, was not specified, and was only reported for those with diagnosis; multiple issues with cost analysis including no methods described, unknown year of currency, no incremental analysis, no sensitivity analysis, with results that are difficult to interpret.
Srivastava (2014)[57]	High risk of bias	NA	NA	NA	Management changes only reported for patients with diagnosis. Methods for determining management changes NR.

Author (Year)	Clinical Utility	Health Outcomes	Safety	Cost	Comments
Stark (2016, 2017, 2019)[13-16]	Some risk of bias	Some risk of bias	NA	Some risk of bias	For clinical utility and health outcomes, outcomes measured through review of medical record and unclear whether outcomes were defined a priori, outcome assessors likely not masked to testing intervention. For cost outcomes, details of costing methodology not provided, utilities established through clinician assessment of prognosis, currency year not specified, no sensitivity analyses for key parameters
Stark (2018)[22]	High risk of bias	Some risk of bias	NA	Some risk of bias	No information about how clinical utility measures were ascertained, and no reporting of measures for the standard WES cohort in this article. Cost analysis was not incremental, economic model and main assumptions not clear, magnitude and direction of biases regarding differences in complexity/severity not discussed. Unclear what differences in usual care existed between rapid and standard WES cohorts.
Strauss (2017)[60]	NA	NA	Some risk of bias	NA	Populations were predominantly old order Amish and Mennonite founder populations; thus some concern that the estimate could be biased.
Tammimies (2015)[72]	NA	NA	Low risk of bias	NA	None
Tan (2017)[19]	Some risk of bias	NA	NA	Some risk of bias	Only conducted sensitivity analysis for the cost of WES testing; assumed that no diagnoses would be made by standard diagnostic pathway, which seems unlikely.
Tarailo-Graovac (2016)[44]	Some risk of bias	NA	Low risk of bias	NA	None
Tsiplova (2017)[79]	NA	NA	NA	Some risk of bias	Modeling study, only considered costs of CMA and WES testing, not any other costs associated with the diagnostic trajectory; findings based on assumptions about number of tests conducted and diagnostic yields of 9.3% for CMA and 15.8% for CMA plus WES.
Valencia (2015)[54]	Some risk of bias	NA	Low risk of bias	NA	Retrospectively conducted study; methods for collecting and assessing alterations in management NR.
Vanderver (2016)[71]	NA	NA	Low risk of bias	NA	None
Vissers (2017)[20]	NA	NA	Some risk of bias	Some risk of bias	None
Vrijenhoek (2018)[77]	NA	NA	NA	High risk of bias	None

(Continued)

Author (Year)	Clinical Utility	Health Outcomes	Safety	Cost	Comments
Waldrop (2019)[47]	Some risk of bias	NA	NA	NA	No information about clinical utility measures were defined and collected.
Walsh (2017)[78]	NA	NA	NA	High risk of bias	Unable to clearly ascertain patient flow through testing strategies for accurate diagnostic yield estimates, comparator strategy based on hypothetical scenario based on several assumptions, no assessment of uncertainty to cover range of assumptions, other limitations present in the cost analysis.
Willing (2015)[56]	High risk of bias	High risk of bias	NA	NA	None
Yang (2014)[66]	NA	NA	Low risk of bias	NA	Enrollment of consecutive patients, > 90% did not opt out of receiving incidental findings and medically actionable variants.
Zhu (2015)[45]	High risk of bias	NA	NA	NA	None

Abbreviations: NA = not applicable; NR = not reported

Appendix F. Studies Reporting Diagnostic Yield

1. Alfares A, Alfadhel M, Wani T, et al. A multicenter clinical exome study in unselected cohorts from a consanguineous population of Saudi Arabia demonstrated a high diagnostic yield. *Mol Genet Metab.* 2017;121(2):91-95. PMID: 28454995. doi: 10.1016/j.ymgme.2017.04.002
2. Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med.* 2018;20(11):1328-1333. PMID: 29565419. doi: 10.1038/gim.2018.41
3. Al-Shamsi A, Hertecant JL, Souid AK, Al-Jasmi FA. Whole exome sequencing diagnosis of inborn errors of metabolism and other disorders in United Arab Emirates. *Orphanet J Rare Dis.* 2016;11(1):94. PMID: 27391121. doi: 10.1186/s13023-016-0474-3
4. Ammann S, Lehmberg K, Zur Stadt U, et al. Effective Immunological Guidance of Genetic Analyses Including Exome Sequencing in Patients Evaluated for Hemophagocytic Lymphohistiocytosis. *J Clin Immunol.* 2017;37(8):770-780. PMID: 28936583. doi: 10.1007/s10875-017-0443-1
5. Anderson JH, Tester DJ, Will ML, Ackerman MJ. Whole-Exome Molecular Autopsy After Exertion-Related Sudden Unexplained Death in the Young. *Circ Cardiovasc Genet.* 2016;9(3):259-265. PMID: 27114410. doi: 10.1161/circgenetics.115.001370
6. Angione K, Eschbach K, Smith G, Joshi C, Demarest S. Genetic testing in a cohort of patients with potential epilepsy with myoclonic-atonic seizures. *Epilepsy Res.* 2019;150:70-77. PMID: 30660939. doi: 10.1016/j.eplepsyres.2019.01.008
7. Balci TB, Hartley T, Xi Y, et al. Debunking Occam's razor: Diagnosing multiple genetic diseases in families by whole-exome sequencing. *Clin Genet.* 2017;92(3):281-289. PMID: 28170084. doi: 10.1111/cge.12987
8. Baldridge D, Heeley J, Vineyard M, et al. The Exome Clinic and the role of medical genetics expertise in the interpretation of exome sequencing results. *Genet Med.* 2017;19(9):1040-1048. PMID: 28252636. doi: 10.1038/gim.2016.224
9. Bardakjian TM, Helbig I, Quinn C, et al. Genetic test utilization and diagnostic yield in adult patients with neurological disorders. *Neurogenetics.* 2018;19(2):105-110. PMID: 29589152. doi: 10.1007/s10048-018-0544-x
10. Bourchany A, Thauvin-Robinet C, Lehalle D, et al. Reducing diagnostic turnaround times of exome sequencing for families requiring timely diagnoses. *Eur J Med Genet.* 2017;60(11):595-604. PMID: 28807864. doi: 10.1016/j.ejmg.2017.08.011
11. Chan LF, Campbell DC, Novoselova TV, Clark AJ, Metherell LA. Whole-Exome Sequencing in the Differential Diagnosis of Primary Adrenal Insufficiency in Children. *Front Endocrinol (Lausanne).* 2015;6:113. PMID: 26300845. doi: 10.3389/fendo.2015.00113
12. Charbit-Henrion F, Parlato M, Hanein S, et al. Diagnostic Yield of Next-Generation Sequencing in Very Early-Onset Inflammatory Bowel Diseases: A Multicenter Study. *J Crohns Colitis.* 2018. PMID: 29788237. doi: 10.1093/ecco-jcc/jjy068
13. Choi BO, Koo SK, Park MH, et al. Exome sequencing is an efficient tool for genetic screening of Charcot-Marie-Tooth disease. *Hum Mutat.* 2012;33(11):1610-1615. PMID: 22730194. doi: 10.1002/humu.22143
14. Cordoba M, Rodriguez-Quiroga SA, Vega PA, et al. Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. *PLoS One.* 2018;13(2):e0191228. PMID: 29389947. doi: 10.1371/journal.pone.0191228

15. Daga A, Majmundar AJ, Braun DA, et al. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. *Kidney Int.* 2018;93(1):204-213. PMID: 28893421. doi: 10.1016/j.kint.2017.06.025

16. de Castro-Miro M, Tonda R, Escudero-Ferruz P, et al. Novel Candidate Genes and a Wide Spectrum of Structural and Point Mutations Responsible for Inherited Retinal Dystrophies Revealed by Exome Sequencing. *PLoS One.* 2016;11(12):e0168966. PMID: 28005958. doi: 10.1371/journal.pone.0168966

17. Dillon OJ, Lunke S, Stark Z, et al. Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. *Eur J Hum Genet.* 2018;26(5):644-651. PMID: 29453417. doi: 10.1038/s41431-018-0099-1

18. Evers C, Staufner C, Granzow M, et al. Impact of clinical exomes in neurodevelopmental and neurometabolic disorders. *Mol Genet Metab.* 2017;121(4):297-307. PMID: 28688840. doi: 10.1016/j.ymgme.2017.06.014

19. Ewans LJ, Schofield D, Shrestha R, et al. Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. *Genet Med.* 2018;20(12):1564-1574. PMID: 29595814. doi: 10.1038/gim.2018.39

20. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med.* 2015;17(7):578-586. PMID: 25356970. doi: 10.1038/gim.2014.154

21. Fedida J, Fressart V, Charron P, et al. Contribution of exome sequencing for genetic diagnostic in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *PLoS One.* 2017;12(8):e0181840. PMID: 28767663. doi: 10.1371/journal.pone.0181840

22. Fichna JP, Macias A, Piechota M, et al. Whole-exome sequencing identifies novel pathogenic mutations and putative phenotype-influencing variants in Polish limb-girdle muscular dystrophy patients. *Hum Genomics.* 2018;12(1):34. PMID: 29970176. doi: 10.1186/s40246-018-0167-1

23. Fokstuen S, Makrythanasis P, Hammar E, et al. Experience of a multidisciplinary task force with exome sequencing for Mendelian disorders. *Hum Genomics.* 2016;10(1):24. PMID: 27353043. doi: 10.1186/s40246-016-0080-4

24. Gauthier-Vasserot A, Thauvin-Robinet C, Bruel AL, et al. Application of whole-exome sequencing to unravel the molecular basis of undiagnosed syndromic congenital neutropenia with intellectual disability. *Am J Med Genet A.* 2017;173(1):62-71. PMID: 27615324. doi: 10.1002/ajmg.a.37969

25. Ghaoui R, Cooper ST, Lek M, et al. Use of Whole-Exome Sequencing for Diagnosis of Limb-Girdle Muscular Dystrophy: Outcomes and Lessons Learned. *JAMA Neurol.* 2015;72(12):1424-1432. PMID: 26436962. doi: 10.1001/jamaneurol.2015.2274

26. Guo MH, Shen Y, Walvoord EC, et al. Whole exome sequencing to identify genetic causes of short stature. *Horm Res Paediatr.* 2014;82(1):44-52. PMID: 24970356. doi: 10.1159/000360857

27. Harris E, Topf A, Barresi R, et al. Exome sequences versus sequential gene testing in the UK highly specialised Service for Limb Girdle Muscular Dystrophy. *Orphanet J Rare Dis.* 2017;12(1):151. PMID: 28877744. doi: 10.1186/s13023-017-0699-9

28. Hartley T, Wagner JD, Warman-Chardon J, et al. Whole-exome sequencing is a valuable diagnostic tool for inherited peripheral neuropathies: Outcomes from a cohort of 50 families. *Clin Genet.* 2018;93(2):301-309. PMID: 28708278. doi: 10.1111/cge.13101

29. Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. *Genet Med.* 2018;20(6):630-638. PMID: 29758562. doi: 10.1038/gim.2017.159

30. Howell KB, Eggers S, Dalziel K, et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. *Epilepsia.* 2018;59(6):1177-1187. PMID: 29750358. doi: 10.1111/epi.14087

31. Iglesias A, Anyane-Yeboa K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* 2014;16(12):922-931. PMID: 24901346. doi: 10.1038/gim.2014.58

32. Iwama K, Mizuguchi T, Takeshita E, et al. Genetic landscape of Rett syndrome-like phenotypes revealed by whole exome sequencing. *J Med Genet.* 2019. PMID: 30842224. doi: 10.1136/jmedgenet-2018-105775

33. Keogh MJ, Steele H, Douroudis K, et al. Frequency of rare recessive mutations in unexplained late onset cerebellar ataxia. *J Neurol.* 2015;262(8):1822-1827. PMID: 25976027. doi: 10.1007/s00415-015-7772-x

34. Lazaridis KN, Schahl KA, Cousin MA, et al. Outcome of Whole Exome Sequencing for Diagnostic Odyssey Cases of an Individualized Medicine Clinic: The Mayo Clinic Experience. *Mayo Clin Proc.* 2016;91(3):297-307. PMID: 26944241. doi: 10.1016/j.mayocp.2015.12.018

35. Lee K, Berg JS, Milko L, et al. High Diagnostic Yield of Whole Exome Sequencing in Participants With Retinal Dystrophies in a Clinical Ophthalmology Setting. *Am J Ophthalmol.* 2015;160(2):354-363.e359. PMID: 25910913. doi: 10.1016/j.ajo.2015.04.026

36. Long PA, Evans JM, Olson TM. Diagnostic Yield of Whole Exome Sequencing in Pediatric Dilated Cardiomyopathy. *J Cardiovasc Dev Dis.* 2017;4(3). PMID: 29367541. doi: 10.3390/jcdd4030011

37. Mann N, Braun DA, Amann K, et al. Whole-Exome Sequencing Enables a Precision Medicine Approach for Kidney Transplant Recipients. *J Am Soc Nephrol.* 2019;30(2):201-215. PMID: 30655312. doi: 10.1681/asn.2018060575

38. Matias M, Wusik K, Neilson D, Zhang X, Valencia CA, Collins K. Comparison of medical management and genetic counseling options pre- and post-whole exome sequencing for patients with positive and negative results. *J Genet Couns.* 2019. PMID: 30648779. doi: 10.1002/jgc4.1054

39. McInerney-Leo AM, Harris JE, Leo PJ, et al. Whole exome sequencing is an efficient, sensitive and specific method for determining the genetic cause of short-rib thoracic dystrophies. *Clin Genet.* 2015;88(6):550-557. PMID: 25492405. doi: 10.1111/cge.12550

40. Meng L, Pammi M, Saronwala A, et al. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. *JAMA Pediatr.* 2017;171(12):e173438. PMID: 28973083. doi: 10.1001/jamapediatrics.2017.3438

41. Miller KA, Twigg SR, McGowan SJ, et al. Diagnostic value of exome and whole genome sequencing in craniosynostosis. *J Med Genet.* 2017;54(4):260-268. PMID: 27884935. doi: 10.1136/jmedgenet-2016-104215

42. Moccia A, Srivastava A, Skidmore JM, et al. Genetic analysis of CHARGE syndrome identifies overlapping molecular biology. *Genet Med.* 2018;20(9):1022-1029. PMID: 29300383. doi: 10.1038/gim.2017.233

43. Mu W, Schiess N, Orthmann-Murphy JL, El-Hattab AW. The utility of whole exome sequencing in diagnosing neurological disorders in adults from a highly consanguineous population. *J Neurogenet.* 2019:1-6. PMID: 30724636. doi: 10.1080/01677063.2018.1555249

44. Nambot S, Thevenon J, Kuentz P, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: substantial interest of prospective annual reanalysis. *Genet Med.* 2018;20(6):645-654. PMID: 29095811. doi: 10.1038/gim.2017.162

45. Need AC, Shashi V, Hitomi Y, et al. Clinical application of exome sequencing in undiagnosed genetic conditions. *J Med Genet.* 2012;49(6):353-361. PMID: 22581936. doi: 10.1136/jmedgenet-2012-100819

46. Need AC, Shashi V, Schoch K, Petrovski S, Goldstein DB. The importance of dynamic re-analysis in diagnostic whole exome sequencing. *J Med Genet.* 2017;54(3):155-156. PMID: 27899421. doi: 10.1136/jmedgenet-2016-104306

47. Nolan D, Carlson M. Whole Exome Sequencing in Pediatric Neurology Patients: Clinical Implications and Estimated Cost Analysis. *J Child Neurol.* 2016;31(7):887-894. PMID: 26863999. doi: 10.1177/0883073815627880

48. Ohba C, Osaka H, Iai M, et al. Diagnostic utility of whole exome sequencing in patients showing cerebellar and/or vermis atrophy in childhood. *Neurogenetics.* 2013;14(3-4):225-232. PMID: 24091540. doi: 10.1007/s10048-013-0375-8

49. Olson HE, Tambunan D, LaCoursiere C, et al. Mutations in epilepsy and intellectual disability genes in patients with features of Rett syndrome. *Am J Med Genet A.* 2015;167a(9):2017-2025. PMID: 25914188. doi: 10.1002/ajmg.a.37132

50. Palmer EE, Schofield D, Shrestha R, et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness. *Mol Genet Genomic Med.* 2018;6(2):186-199. PMID: 29314763. doi: 10.1002/mgg3.355

51. Perucca P, Scheffer IE, Harvey AS, et al. Real-world utility of whole exome sequencing with targeted gene analysis for focal epilepsy. *Epilepsy Res.* 2017;131:1-8. PMID: 28199897. doi: 10.1016/j.eplepsyres.2017.02.001

52. Posey JE, Harel T, Liu P, et al. Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation. *N Engl J Med.* 2017;376(1):21-31. PMID: 27959697. doi: 10.1056/NEJMoa1516767

53. Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. *Genet Med.* 2016;18(7):678-685. PMID: 26633545. doi: 10.1038/gim.2015.142

54. Powis Z, Farwell Hagman KD, Speare V, et al. Exome sequencing in neonates: diagnostic rates, characteristics, and time to diagnosis. *Genet Med.* 2018;20(11):1468-1471. PMID: 29565416. doi: 10.1038/gim.2018.11

55. Pyle A, Smertenko T, Bargiela D, et al. Exome sequencing in undiagnosed inherited and sporadic ataxias. *Brain.* 2015;138(Pt 2):276-283. PMID: 25497598. doi: 10.1093/brain/awu348

56. Ream MA, Mikati MA. Clinical utility of genetic testing in pediatric drug-resistant epilepsy: a pilot study. *Epilepsy Behav.* 2014;37:241-248. PMID: 25108116. doi: 10.1016/j.yebeh.2014.06.018

57. Reddy HM, Cho KA, Lek M, et al. The sensitivity of exome sequencing in identifying pathogenic mutations for LGMD in the United States. *J Hum Genet.* 2017;62(2):243-252. PMID: 27708273. doi: 10.1038/jhg.2016.116

58. Rossi M, El-Khechen D, Black MH, Farwell Hagman KD, Tang S, Powis Z. Outcomes of Diagnostic Exome Sequencing in Patients With Diagnosed or Suspected Autism Spectrum Disorders. *Pediatr Neurol.* 2017;70:34-43.e32. PMID: 28330790. doi: 10.1016/j.pediatrneurol.2017.01.033

59. Sawyer SL, Schwartzentruber J, Beaulieu CL, et al. Exome sequencing as a diagnostic tool for pediatric-onset ataxia. *Hum Mutat.* 2014;35(1):45-49. PMID: 24108619. doi: 10.1002/humu.22451

60. Schabhuttl M, Wieland T, Senderek J, et al. Whole-exome sequencing in patients with inherited neuropathies: outcome and challenges. *J Neurol.* 2014;261(5):970-982. PMID: 24627108. doi: 10.1007/s00415-014-7289-8

61. Schofield D, Alam K, Douglas L, et al. Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases. *NPJ Genom Med.* 2017;2. PMID: 29152331. doi: 10.1038/s41525-017-0006-7

62. Seidelmann SB, Smith E, Subrahmanyan L, et al. Application of Whole Exome Sequencing in the Clinical Diagnosis and Management of Inherited Cardiovascular Diseases in Adults. *Circ Cardiovasc Genet.* 2017;10(1). PMID: 28087566. doi: 10.1161/circgenetics.116.001573

63. Shapiro L, Chatterjee S, Ramadan DG, et al. Whole-exome sequencing gives additional benefits compared to candidate gene sequencing in the molecular diagnosis of children with growth hormone or IGF-1 insensitivity. *Eur J Endocrinol.* 2017;177(6):485-501. PMID: 28870985. doi: 10.1530/eje-17-0453

64. Shashi V, McConkie-Rosell A, Schoch K, et al. Practical considerations in the clinical application of whole-exome sequencing. *Clin Genet.* 2016;89(2):173-181. PMID: 25678066. doi: 10.1111/cge.12569

65. Sitek JC, Kulseth MA, Rypdal KB, Skodje T, Sheng Y, Retterstol L. Whole-exome sequencing for diagnosis of hereditary ichthyosis. *J Eur Acad Dermatol Venereol.* 2018;32(6):1022-1027. PMID: 29444371. doi: 10.1111/jdv.14870

66. Snoeijen-Schouwenaars FM, van Ool JS, Verhoeven JS, et al. Diagnostic exome sequencing in 100 consecutive patients with both epilepsy and intellectual disability. *Epilepsia.* 2019;60(1):155-164. PMID: 30525188. doi: 10.1111/epi.14618

67. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med.* 2014;6(265):265ra168. PMID: 25473036. doi: 10.1126/scitranslmed.3010076

68. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol.* 2014;76(4):473-483. PMID: 25131622. doi: 10.1002/ana.24251

69. Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. *Genet Med.* 2018;20(12):1554-1563. PMID: 29543227. doi: 10.1038/gim.2018.37

70. Stark Z, Schofield D, Alam K, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. *Genet Med.* 2017;19(8):867-874. PMID: 28125081. doi: 10.1038/gim.2016.221

71. Stark Z, Schofield D, Martyn M, et al. Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. *Genet Med.* 2019;21(1):173-180. PMID: 29765138. doi: 10.1038/s41436-018-0006-8

72. Strauss KA, Gonzaga-Jauregui C, Brigatti KW, et al. Genomic diagnostics within a medically underserved population: efficacy and implications. *Genet Med.* 2018;20(1):31-41. PMID: 28726809. doi: 10.1038/gim.2017.76

73. Takeichi T, Nanda A, Liu L, et al. Impact of next generation sequencing on diagnostics in a genetic skin disease clinic. *Exp Dermatol.* 2013;22(12):825-831. PMID: 24279917. doi: 10.1111/exd.12276

74. Tammimies K, Marshall CR, Walker S, et al. Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder. *JAMA.* 2015;314(9):895-903. PMID: 26325558. doi: 10.1001/jama.2015.10078

75. Tan NB, Tan TY, Martyn MM, et al. Diagnostic and service impact of genomic testing technologies in a neonatal intensive care unit. *J Paediatr Child Health.* 2019. PMID: 30756437. doi: 10.1111/jpc.14398

76. Tan TY, Dillon OJ, Stark Z, et al. Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. *JAMA Pediatr.* 2017;171(9):855-862. PMID: 28759686. doi: 10.1001/jamapediatrics.2017.1755

77. Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome Sequencing and the Management of Neurometabolic Disorders. *N Engl J Med.* 2016;374(23):2246-2255. PMID: 27276562. doi: 10.1056/NEJMoa1515792

78. Taylor RW, Pyle A, Griffin H, et al. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. *JAMA.* 2014;312(1):68-77. PMID: 25058219. doi: 10.1001/jama.2014.7184

79. Thevenon J, Duffourd Y, Masurel-Paulet A, et al. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. *Clin Genet.* 2016;89(6):700-707. PMID: 26757139. doi: 10.1111/cge.12732

80. Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. *Eur J Hum Genet.* 2017;25(2):176-182. PMID: 27848944. doi: 10.1038/ejhg.2016.146

81. Tsuchida N, Nakashima M, Kato M, et al. Detection of copy number variations in epilepsy using exome data. *Clin Genet.* 2018;93(3):577-587. PMID: 28940419. doi: 10.1111/cge.13144

82. Vairo FP, Boczek NJ, Cousin MA, et al. The prevalence of diseases caused by lysosome-related genes in a cohort of undiagnosed patients. *Mol Genet Metab Rep.* 2017;13:46-51. PMID: 28831385. doi: 10.1016/j.ymgmr.2017.08.001

83. Valencia CA, Husami A, Holle J, et al. Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. *Front Pediatr.* 2015;3:67. PMID: 26284228. doi: 10.3389/fped.2015.00067

84. Vanderver A, Simons C, Helman G, et al. Whole exome sequencing in patients with white matter abnormalities. *Ann Neurol.* 2016;79(6):1031-1037. PMID: 27159321. doi: 10.1002/ana.24650

85. Vissers L, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med.* 2017;19(9):1055-1063. PMID: 28333917. doi: 10.1038/gim.2017.1

86. Volk A, Conboy E, Wical B, Patterson M, Kirmani S. Whole-Exome Sequencing in the Clinic: Lessons from Six Consecutive Cases from the Clinician's Perspective. *Mol Syndromol.* 2015;6(1):23-31. PMID: 25852444. doi: 10.1159/000371598

87. Vrijenhoek T, Middelburg EM, Monroe GR, et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. *Eur J Hum Genet.* 2018;26(11):1566-1571. PMID: 29959382. doi: 10.1038/s41431-018-0203-6

88. Waldrop MA, Pastore M, Schrader R, et al. Diagnostic Utility of Whole Exome Sequencing in the Neuromuscular Clinic. *Neuropediatrics.* 2019. PMID: 30665247. doi: 10.1055/s-0039-1677734

89. Walsh M, Bell KM, Chong B, et al. Diagnostic and cost utility of whole exome sequencing in peripheral neuropathy. *Ann Clin Transl Neurol.* 2017;4(5):318-325. PMID: 28491899. doi: 10.1002/acn3.409

90. Warejko JK, Schueler M, Vivante A, et al. Whole Exome Sequencing Reveals a Monogenic Cause of Disease in approximately 43% of 35 Families With Midaortic Syndrome. *Hypertension.* 2018;71(4):691-699. PMID: 29483232. doi: 10.1161/hypertensionaha.117.10296

91. Weiss K, Kurolap A, Paperna T, et al. Rare Disease Diagnostics: A Single-center Experience and Lessons Learnt. *Rambam Maimonides Med J.* 2018;9(3). PMID: 30089087. doi: 10.5041/rmmj.10341

92. Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. *Genet Med.* 2017;19(2):209-214. PMID: 27441994. doi: 10.1038/gim.2016.88

93. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med.* 2015;3(5):377-387. PMID: 25937001. doi: 10.1016/s2213-2600(15)00139-3

94. Wiszniewski W, Gawlinski P, Gambin T, et al. Comprehensive genomic analysis of patients with disorders of cerebral cortical development. *Eur J Hum Genet.* 2018;26(8):1121-1131. PMID: 29706646. doi: 10.1038/s41431-018-0137-z

95. Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. *Genet Med.* 2018;20(10):1216-1223. PMID: 29323667. doi: 10.1038/gim.2017.246

96. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA.* 2014;312(18):1870-1879. PMID: 25326635. doi: 10.1001/jama.2014.14601

97. Yao T, Udwan K, John R, et al. Integration of Genetic Testing and Pathology for the Diagnosis of Adults with FSGS. *Clin J Am Soc Nephrol.* 2019. PMID: 30647093. doi: 10.2215/cjn.08750718

98. Zazo Seco C, Wesdorp M, Feenstra I, et al. The diagnostic yield of whole-exome sequencing targeting a gene panel for hearing impairment in The Netherlands. *Eur J Hum Genet.* 2017;25(3):308-314. PMID: 28000701. doi: 10.1038/ejhg.2016.182

99. Zech M, Jech R, Wagner M, et al. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. *Neurogenetics.* 2017;18(4):195-205. PMID: 28849312. doi: 10.1007/s10048-017-0521-9

Appendix G. Detailed GRADE Assessments

№ of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Summary of Findings	Certainty
Clinical Utility-Actual Changes in Management						
1 cohort with modeling; 1 case series; 1 controlled cohort; 28 single-arm observational cohort	Some to High	Serious	Not serious	Serious	Among populations that included diverse phenotypes, medical management changed in 12% to 100% of those who received a molecular diagnosis. Medication changed for 5% to 25% of those who received a diagnosis. Among populations with epilepsy, medical management changed for 0% to 31.3% of patients who received a diagnosis from WES	⊕◯◯◯ VERY LOW
Health Outcomes						
1 case series; 1 controlled observational cohort; 5 single-arm observational cohorts	High	Serious	Not Serious	Serious	Difference in study designs and ascertainment limit the ability to draw any conclusions about the impact of WES testing on any health outcomes	Unable to determine
Safety Outcomes-ACMG-defined medically actionable variants						
21 single-arm observational cohorts; 1 modeling study	Some to High	Not serious	Not serious	Not serious	Across 13 studies with data available for pooling, the pooled result was 3.9% (95% CI, 2.4% to 5.3%). The range across the other studies was reported as 0% to 10%.	⊕⊕◯◯ LOW
Cost outcomes-Cost per Diagnosis						
8 cost studies	Some to High	Serious	Not serious	Serious	In single-phenotype populations: cost per diagnosis was less in WES pathways compared to the standard diagnostic pathways, and costs were less in early WES pathways compared to WES as a last resort. In diverse phenotype populations: cost per diagnosis was less in early WES pathways compared to WES as a last resort	⊕◯◯◯ VERY LOW

№ of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Summary of Findings	Certainty
Cost Outcomes-Cost per Additional Diagnosis						
7 cost studies	Some to High	Serious	Not serious	Serious	For single-phenotype populations: WES was cost-effective when compared to the standard pathway. Early WES cost less and identified more diagnosis in most studies while WES later in the pathway identified additional diagnoses but at an additional cost ($1,775 to $8,550 per additional diagnosis). In diverse phenotypes, early WES cost less and identified more diagnoses when compared to a standard pathway; WES used after some initial evaluation or as a last resort strategy is likely cost-effective (range of estimates suggest cost savings or an additional cost of up to AU$8,112	⊕◯◯◯ VERY LOW
Cost-effectiveness						
1 cost study	High	Unable to assess, single study body of evidence	Not serious	Serious	Cost per QALY gained over median 473 days follow-up AU$ -1,578 (95% CI, -205,450 to AU$ 19,780) considering only changes in proband management. Cost per QALY gained AU$ 8,119 (95% CI, AU$ 1,062 to AU$ 38,944) when also considering cascade testing and reproductive counseling in first-degree relatives Modeled over 20 years: Cost per QALY $31,144 for changes in proband management. Cost per QALY gained $14,235 when also considering cascade testing and reproductive outcomes	⊕◯◯◯ VERY LOW

Abbreviations: AU = Australian; CI = confidence interval; QALY = quality-adjusted life year; WES = whole exome sequencing