Washington State Health Care Authority

Genomic microarray and whole exome sequencing

Final evidence report

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Health Technology Assessment Program (HTA)

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The information in this report is intended to help the Washington HCA make well-informed coverage determinations and thereby improve the quality of health care services. 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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Contents

List of Appendices

List of Figures

List of Tables

List of Abbreviations

ASD	autism spectrum disorder
CGH	comparative genomic hybridization
CMA	chromosomal microarray (also called genomic microarray)
CNV	copy number variant
DD	developmental disability
FISH	fluorescent in situ hybridization
GDD	global developmental delay
HTA	health technology assessment
ID	intellectual disability
MCA	multiple congenital anomalies
UK	United Kingdom
U.S.	United States
WES	whole exome sequencing

Structured Abstract

Purpose: To review the safety, efficacy, and cost of chromosomal microarrays and whole exome sequencing when used for the diagnosis and management of chromosomal abnormalities among children with developmental and intellectual disabilities, autism spectrum disorder, or multiple congenital anomalies.

Data Sources: PubMed from January 2000 through September 2017; clinical trial registry, payor coverage databases, websites for the United States Food and Drug Administration, professional societies, and organizations that conduct health technology assessments, and bibliographies of relevant articles.

Study Selection: We selected English-language studies using a priori criteria. We included studies that evaluated chromosomal microarray or whole exome sequencing if they addressed the safety, diagnostic yield, impact on management or health outcomes, or cost or cost-effectiveness when used to diagnose chromosomal abnormalities in children with developmental and intellectual disabilities, autism spectrum disorder, or multiple congenital anomalies. Studies focused on prenatal use, analytic validity, or ethics of testing were excluded. Diagnostic yield studies were excluded if the testing was performed prior to 2009 or used obsolete testing platforms, or the studies were conducted outside of the United States.

Data Extraction: One research team member extracted data and a second checked for accuracy. Two investigators independently assessed risk of bias of included studies.

Data Synthesis: We included a total of 18 studies. One study provided evidence on a safety issue; specifically, discrimination resulting from abnormal chromosomal microarray results. Five primary research studies and one health technology assessment provided evidence related to diagnostic yield of chromosomal microarray and the types of clinical conditions for which it is most useful. The pooled summary estimate of diagnostic yield from the five primary research studies was 8.8% (95% CI, 8.4% to 9.3%). The diagnostic yield of copy number variants in the one primary research study that reported on whole exome sequencing was 1.6%; the total diagnostic yield was 27% (95% CI not reported).

Seven studies evaluated the impact of chromosomal microarray testing on the clinical management of children. Between 27.1% to 93.8% of children with a pathogenic variant on testing, which was 3.6% and 6.7% of all cases tested, had a change in management prompted by their results. We did not identify any studies that reported the impact of testing on health outcomes. We identified five eligible studies reporting cost outcomes, all specific to chromosomal microarray testing and diagnostic yield. Costs per array ranged from $271 to $1,575 (in 2010 U.S. dollars). No studies reported cost-effectiveness with respect to health outcomes. The cost per additional diagnosis for chromosomal microarray testing as a first-line diagnostic test compared to testing without CMA varied between $-88,819 and $12,296 (in 2010 U.S. dollars).

We graded the strength of evidence as *very low* for safety, impact on clinical management, and cost and cost-effectiveness, and as *low* for diagnostic yield. These grades were resulted from observational study designs and depending on the outcome (safety, efficacy, or cost) serious

concerns in one or more domains including risk of bias, inconsistency, indirectness, or imprecision.

Limitations: The risk of bias of individual studies varied, and study reporting limited our ability to assess risk of bias for some included studies. Studies assessing diagnostic yield and impact on management, and cost were clinically and methodologically heterogenous. The evidence base was very limited for assessing safety, and none of the cost studies we identified evaluated cost-effectiveness related to health outcomes or were conducted in the United States.

Conclusions: Chromosomal microarray identifies a pathogenic or likely pathogenic variant in nearly 9% of all children referred for testing and in 5% of those referred because of autism spectrum disorders; these findings are based on a low strength of evidence. The results of chromosomal microarray tests generate changes in management in over half of children identified as having a pathogenic or likely pathogenic variant; this finding is based on very low strength of evidence. The evidence is very limited with respect to the safety of testing and we identified no evidence related to the impact of testing on health outcomes, or cost-effectiveness. The cost per additional diagnosis for chromosomal microarray testing as a first-line diagnostic test compared to testing without CMA varied.

Executive Summary

Background

Condition Description

Chromosomes, the genetic structures of a cell, are constructed of deoxyribose nucleic acid (DNA) and the proteins and other elements that protect, regulate, and package the DNA. Humans normally have 23 pairs of chromosomes, with half inherited from each parent. During cell replication, chromosomes are sometimes lost or broken and rearranged. Rearrangements vary in size and complexity, and may be balanced, with no loss of DNA, or unbalanced with loss or gain of DNA.

Disease Burden

Unbalanced chromosomal rearrangements that are present at conception or that occur during fetal development have profound consequences for the developing fetus, resulting in fetal death, structural defects, genetic diseases, or intellectual impairment.[1] Chromosomal abnormalities occur in 43.8 per 10,000 births that survive to 20 weeks gestation or later.[2] Trisomies 21 (Down syndrome), 18, and 13; 45, X (Turner syndrome), and other sex chromosome abnormalities account for most abnormalities. Excluding these, the prevalence of more rare abnormalities is 7.4 per 10,000 births.[2] Small pathogenic duplications or deletions, called copy number changes or variants (CNV), occur in 1 of 270 pregnancies.[3] The consequences of CNVs depend on the size and location within the genome.

Approximately 3% of infants born in the United States have a major structural defect,[4] and almost 6% of children in the United States have an intellectual disability (ID), developmental delay (DD), or autism spectrum disorder (ASD).[5] These conditions are expensive to manage: in 2004, U.S. hospitalization costs for birth defects totaled $2.6 billion.[6] In Washington, 10.3% of adults living in the state in 2014 had a cognitive disability.[7] State expenditures in caring for residents with an ID included over $600 million in Medicaid expenditures for long-term care and over $1 billion on special education programs.

Technology Description

The quest of genetics laboratories over the last 60 years has been to increase the resolution of genetic tests and to reduce the level of targeting required. This report discusses chromosomal microarray (CMA) and whole exome sequencing (WES), untargeted genome-wide tests that detect changes across the genome. CMA can detect unbalanced changes as small as 30,000 base pairs, and WES can detect changes as small as a single base pair.

Chromosomal Microarrays (CMA)

In the early 2000s, genome-wide microarrays for chromosomal analysis, commonly known as CMA, were introduced as an adjunct to karyotype and fluorescent in situ hybridization (FISH) testing for chromosome abnormalities. Comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays are used to evaluate the number of copies of portions of the chromosomes. In CGH, patient and control DNA samples are tagged with fluorescent

markers and hybridized to probes.[8] Computer analysis determines the number of copies of each chromosomal region present based on the intensity and color of fluorescence. The first genome-wide platforms used bacterial artificial chromosome (BAC) probes that could detect deletions or duplications of approximately 1,000,000 base pairs (1 Mb).[8] Around 2007, oligonucleotide arrays ('oligo') began replacing BAC arrays. Oligonucleotide probes are smaller, and oligo-based arrays have many more probes, enabling detection of smaller CNVs.[9] SNP arrays tag individual base pairs throughout the genome that vary within the normal population with different fluorescent dyes. The number of alleles and whether the individual has the same allele on both chromosome or different alleles can be determined by analysis of the color and intensity of the bound fluorescent dyes.[8] Many current CMA testing platforms use a combination of labeled SNPs and oligo-based probes to assess genetic bases or sequences throughout the genome.

CMA can identify rearrangements as small as 150,000 base pairs, whereas karyotyping can detect approximately 5,000,000 base pairs. For this reason, professional societies now recommend that CMA be the first test used to diagnose chromosomal abnormalities in children with multiple congenital anomalies (MCAs) or DD/IDs (***Table ES-1***).[10-15] However, CMA cannot identify balanced rearrangements or low-level mosaicism so karyotyping may still be required in some cases.[16]

Whole Exome Sequencing

WES provides the base pair sequence for all the protein coding regions in the genome, the exons.[17] Multiple large regions of the genome are sequenced simultaneously. WES allows the detection of single nucleotide changes within any gene; it is used clinically to detect pathogenic single nucleotide changes or small insertions or deletions when the clinical presentation does not point to a specific genetic disorder.

Although WES is usually used to detect single base pair substitutions or duplications or deletions of a few base pairs, it can identify CNVs that contain three or more protein coding regions with the sensitivity of medium-resolution CMAs.[18] WES has a lower sensitivity for the identification of CNVs than whole genome sequencing or high-resolution CMAs due to limitations of exon capture methods and a lack of standard bioinformatics for this purpose.[19,20]

Table ES-1. Resolution and Detection of Chromosomal Microarray and Whole Exome Sequencing

	Chromosomal Microarray	Whole Exome Sequencing
Types of genetic disease	Chromosomal abnormality syndromes	Single gene disorders
Types of genetic defect	Microduplications, microdeletions, unbalanced rearrangements	Base pair insertions, deletions, or substitutions,
Minimum resolution (no. of base pairs)	≥ 30,000	≥1

Test Interpretation

The determination of whether variants are pathogenic or benign is made by the laboratory using public databases of pathogenic and benign variants, the laboratory's internal database of prior

test results, published literature, and consultation with other laboratories. The American College of Medical Genetics (ACMG) and the Association of Molecular Pathology published guidelines for the interpretation of sequence variants,[21] and tools have been developed to aid in their use.[22]

Genome-wide testing can result in secondary or incidental findings. The ACMG recommends that laboratories conducting clinical exome or genome sequencing actively seek and report a list of specific, clinically actionable variants within 24 genes or classes of genes,[23] regardless of the indication for testing. Approximately 2% of patients sequenced are expected have a reportable variant. The ACMG recommendations do not address copy number variants (CNVs) or structural abnormalities, but the apply to CNVs that delete or disable listed genes with autosomal dominant inheritance. Incidental findings from CMA have been studied less than those from sequencing; the studies that have examined them have found less than 1% of individuals tested have an incidental finding.[24]

Policy Context

The State of Washington Health Care Authority selected testing with CMA and WES as a topic based on medium, high, and high concerns for safety, efficacy, and cost, respectively. Several practice guidelines have been issued that call for CMA to replace G-banded karyotype as the first-tier test for diagnosis of individuals with DD, ID, or MCA, and for the clinical evaluation of ASD.[13,25] These guidelines, combined with the increasing prevalence of autism,[26] could greatly increase orders for CMA. The increased diagnostic yield of chromosomal abnormalities by CMA compared to karyotype underlies these guidelines.[13,25] The degree of DD or ID for which CMA is most likely to yield a diagnosis is unclear, however, as is the effect of the testing results on the medical and educational management and health outcomes of affected children.

Regulatory Status

CMA and WES are considered laboratory-developed tests and are not regulated by the United States (U.S.) Food and Drug Administration (FDA). Clinical laboratories that conduct these tests must comply with regulatory standards for high complexity testing within the Clinical Laboratory Improvement Act (CLIA). Thus, these tests are generally only available through commercial diagnostic testing laboratories or hospital-based laboratories.

FDA approval is required when a company markets and sells a kit for CMA or WES testing. The FDA has approved two CMA kits for marketing in the United States: the Affymetrix CytoScan® Dx assay (Affymetrix, Inc., Santa Clara, CA), approved as a Class II test on January 21, 2014[27] and the Agilent GenetiSure Dx Postnatal Assay (Agilent Technologies, Inc., Santa Clara, CA),[28] approved under a substantial equivalence determination on August 14, 2017. The FDA-approved indications for the kits include postnatal detection of CNVs associated with DD, ID, MCA, or dysmorphic features.

Practice Guidelines and Payer Coverage

Several practice guidelines or policy statements (***Table ES-2***) endorse the use of CMA in place of karyotype as a first-line test in the evaluation of children with DD, ID, ASD, or MCA, particularly when dysmorphic features are present or signs, symptoms and initial nongenetic testing are not consistent with a single gene disorder.

Table ES-2. Practice Guidelines Endorsing or Providing Guidance on Chromosomal Microarray Testing

Organization	Year
International Standard Cytogenomic Consortium[25]	2010
National Institute for Health and Care Excellence (UK)[12]	2011
American College of Medical Genetics and Genomics[13]	2013
American Academy of Pediatrics[15]	2014
American Academy of Neurology[14]	2015

The Centers for Medicare and Medicaid Services (CMS) has no national coverage determination for the use of CMA or WES. ***Table ES-3*** summarizes selected payer coverage determinations for CMA and WES testing. Among payers, good alignment exists for the criteria under which CMA is covered. Typically, it is covered as first-line diagnostic for DD, ID, and ASD when relevant biochemical and metabolic diseases have been ruled out, the clinical presentation is not specific to a well-delineated genetic syndrome, and the results of CMA could impact the clinical management of the child.

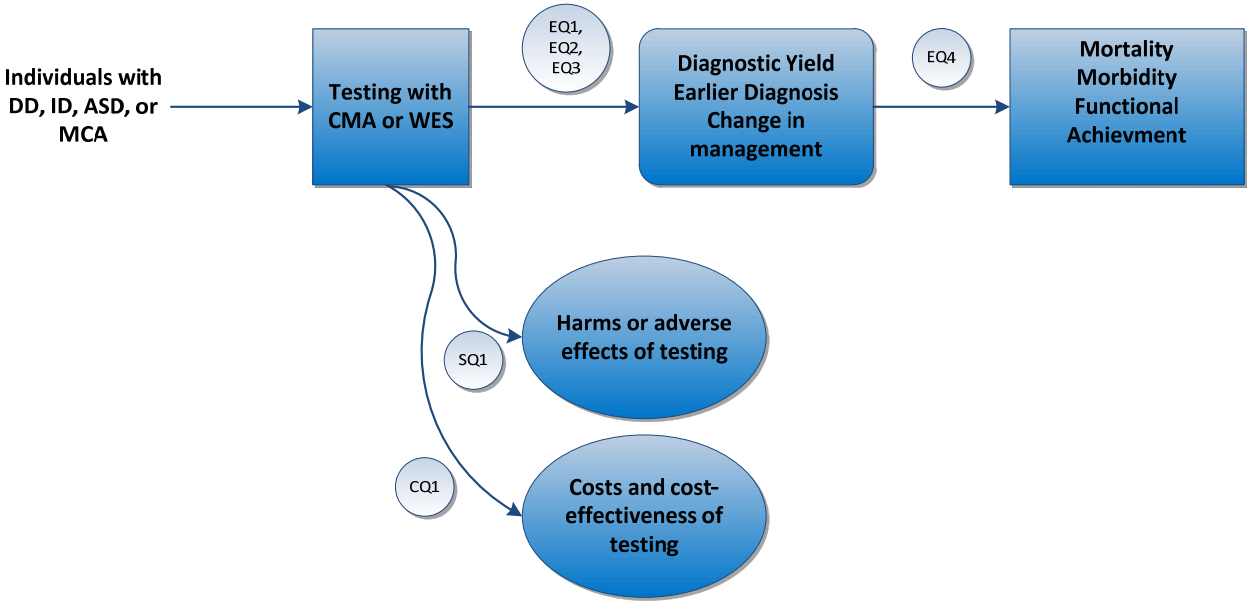
Table ES-3. Payer Coverage for CMA and WES Testing

Payer	CMA Testing	WES Testing
Aetna[29]	Covered for specific indications	Not covered
Blue Cross (Premera)[30]	Covered for specific indications	Covered for specific indications
Regence Blue Shield Regence[31,32]	Covered for specific indications	Not covered
Cigna[33,34]	Covered for specific indications	Covered for specific indications
Humana[35]	Covered for specific indications	Not covered
Kaiser Permanente[36]	Covered for specific indications	Not covered
Medicare Fee for Service	None	None
Medicaid[15,37,38]	Not all states have policies; those that do typically cover for specific indications	Unknown
UnitedHealthcare[39]	Covered for specific indications	Covered for specific indications

Research Questions

Figure ES-1 provides the analytic framework and ***Table ES-4*** provides the final research questions and study selection criteria related to the population, intervention, comparator, outcomes, time period, and setting used to conduct this health technology assessment (HTA).

Figure ES-1. Analytic Framework for Chromosomal Microarray and Whole Exome Sequencing in Children with Developmental or Intellectual Disability, Autism, or Multiple Congenital Anomalies



Abbreviations: ASD=autism spectrum disorder; CMA=chromosomal microarray; CQ=cost question; DD=developmental disability; EQ=efficacy question; ID=intellectual disability; MCA=multiple congenital anomalies; SQ=safety question; WES=whole exome sequencing

Table ES-4. Research Questions and Scoping Parameters for Chromosomal Microarray or Whole Exome Sequencing in Children with Intellectual Disability, Autism, or Birth Defects

Research Questions	
Safety	SQ1. What, if any, safety issues do CMA and WES pose beyond those associated with phlebotomy?
Efficacy	EQ1. How often do CMA or WES return an informative result (i.e., diagnostic yield)? EQ2. For what types of conditions is CMA or WES most useful? EQ3. Does the diagnosis of a chromosomal disorder change the child's management? EQ4. Do children with congenital defects, autism, ID, or DD tested with CMA or WES have better health outcomes?
Cost	CQ1. What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with CMA or WES?
Populations; Interventions; Comparators, Outcomes; Time Period; Setting	
Populations	Children diagnosed with congenital defects, autism, ID/DD without known syndrome or specific genetic abnormality.
Intervention	1. CMA testing with currently available platforms, obsolete and superseded platforms will be excluded. 2. WES
Comparator	EQ1, EQ2, SQ1: Descriptive and may not have comparator groups. EQ3: Management before and after diagnosis; management of similarly affected undiagnosed children EQ4 and CQ1: No genetic diagnostic testing or genetic diagnostic testing did not include CMA or WES.
Safety Outcomes	SQ1. Harms reported as related to testing other than those associated with phlebotomy
Efficacy Outcomes	EQ1 and EQ2. Diagnostic yield or earlier diagnosis EQ3. Change in medical or educational interventions EQ4. Mortality during infancy or childhood EQ4. Development of comorbidities EQ4. Functional achievement
Cost Outcomes	CQ1: Cost of assay, cost per diagnosis, cost per additional diagnosis, cost per quality-adjusted life year, cost per disability-adjusted life year
Time Period	2009 to 2017 for EQ1 and EQ2, 2000-2017 for all others
Setting	Clinical genetic laboratories, medical genetic clinics, general and specialty pediatric clinics; non-U.S. studies were excluded for EQ1 and EQ2.

Abbreviations: CMA=chromosomal/genomic microarray; CQ=cost question; DD=developmental disability; EQ=efficacy question; ID=intellectual disability; SQ=safety question; U.S.=United States; WES=whole exome sequencing.

What is Excluded from This HTA

This HTA does not address the analytic validity of CMA or WES, because this testing is available within CLIA-licensed laboratories as a laboratory-developed test and analytic validity is assumed based on meeting those standards.[40] This review is focused on the diagnosis of chromosomal abnormalities; therefore, we do not address single gene testing for these disorders, including the use of WES to identify mutations within single genes. The review does not assess either the ethical issues or the clinical utility of incidental findings not related to the health conditions for which the tests were ordered. Because of the large volume of studies on diagnostic yield (EQ1) and the rapidly evolving technology in use for CMA testing, we limited the studies considered for EQ1 to those conducted in the United States in 2009 or later that used current testing platforms.

Methods

Data Sources and Search

We searched MEDLINE® (via PubMed) and a clinical trials registry (clinicaltrials.gov) for relevant English-language studies published in 2000 or later. We searched the FDA website, selected payer and health care professional society websites, and other organizations that conduct and disseminate HTAs. In addition, we reviewed the reference lists of relevant studies, practice guidelines, and other HTAs on this topic to identify any relevant articles not found through the electronic search. The detailed search strategy is provided in ***Appendix A*** of the Full Report.

Study Selection

We screened titles and abstracts and full-text articles based on the study selection criteria listed in ***Table ES-3***. We included all study designs except case reports. A single team member screened titles/abstracts following an initial set of 20 independent, dual reviews with the entire team to assess interrater reliability. The principal investigator reviewed all abstracts excluded for "ineligible intervention" and a sample of titles/abstracts excluded for other reasons to ensure continued consistency in application of study selection criteria. One senior team member screened each full-text article for inclusion, and the principal investigator confirmed the decisions.

Data Abstraction and Quality Assessment

One team member extracted relevant study data into a structured abstraction form. The principal investigator reviewed the abstractions for accuracy and consistency. Two senior team members conducted an independent risk of bias assessment on all included studies and met to reconcile any disagreements, in consultation with the principal investigator if needed. Because of the diverse types of studies included in this HTA, we adapted signaling questions from the QUADAS-2 instrument, a risk of bias assessment for diagnostics test studies, and items from the RTI item bank for observational studies.[41,42] The signaling questions assessed the major sources of bias including selection bias (both how study population was selected and attrition/missing data), confounding, and measurement/information bias. We used the ROBIS instrument to assess the risk of bias for systematic reviews.[43]

Data Synthesis and Analysis

Study characteristics and results were qualitatively synthesized for each research question in tabular and narrative formats. For cost outcomes, we adjusted all reported outcomes to 2010 U.S. dollars (***Appendix B***).[44,45] To determine whether quantitative synthesis was appropriate, we assessed the number of studies and the clinical and methodological heterogeneity present based on established guidance.[46,47] We required three or more publications with similar approach and the same outcome measure to calculate a summary estimate. We estimated summary effects using a fixed effects model if the test for heterogeneity was nonsignificant and a random effects model if the test for heterogeneity was significant using OpenMetaAnalyst (for Windows 8, 64-bit) and the method of Hedges and Olkin to estimate between-study variance.[48] We graded the strength of evidence for each research question using GRADE, which assesses the strength of evidence based on domains relating to risk of bias, inconsistency, imprecision, indirectness, and other considerations, such as reporting bias.[49] Under GRADE, the strength of evidence can be graded as very low, low, moderate, or high.

Results

Literature Search

We identified and screened 2,717 unique citations. We excluded 2,375 after title and abstract review. We reviewed the full-text of 348 articles, and excluded 330 for the reasons listed in ***Figure 2*** of the Full Report. We included 18 studies. One provided evidence on safety issues (SQ1), seven provided evidence on diagnostic yield (EQ1 and EQ2), seven on changes in management (EQ3), and five on costs (CQ1). No studies provided information on health outcomes (EQ4). Individual study characteristics for all included studies are summarized in Full Report ***Appendix C, Table C-1***. The list of studies we screened at the full-text stage, but which were excluded from the review, is provided in ***Appendix D***. Note that studies may have been excluded based on more than one reason but we report only one reason. Individual risk of bias assessments for all included studies are reported in ***Appendix E***.

Safety

SQ1. What, if any, safety issues do CMA and WES pose beyond those associated with phlebotomy?

One study[50] provided evidence on safety issues that arise in CMA testing. ***Table ES-5*** summarizes the study characteristics and key outcomes related to discrimination resulting from testing. We graded the strength of evidence for this research question as very low (***Table ES-6***). We did not identify any studies reporting on safety outcomes related to WES testing.

Table ES-5. Summary of Findings for the Safety of Testing with Chromosomal Microarray or Whole Exome Sequencing

Author (Year)	Study Population; Sample Size	Primary Outcomes	Key Results	Risk of Bias
Hamilton (2015)[50]	Children referred for CMA testing noted as being in foster care; N=6	Adoption request for child in foster care withdrawn after report of CNV associated with autism	1 of 4 cases with abnormal results experienced discrimination	High

Abbreviations: CMA=chromosomal microarray; CNV=copy number variant.

Table ES-6. Strength of Evidence for Findings Related to the Safety of Testing with Chromosomal Microarray or Whole Exome Sequencing

No. of Studies; Subjects	Study Design	Risk of Bias	Inconsistency	Indirectness	Precision	Reporting Bias	Strength of Evidence Grade
1;6	Observational	Serious[a]	Unable to assess	Not serious	Unable to assess	Not serious	Very low

[a] Enrollment in foster care not routinely collected, only available if noted on test requisition. High risk of selection bias.

Efficacy

EQ1. How often do CMA or WES return an informative result (i.e., diagnostic yield)?

Five primary studies[51-55] and one HTA[40] provided evidence related to diagnostic yield (EQ1) and the types of clinical conditions for which CMA is most useful (EQ2). One study provided evidence related to diagnostic yield of WES testing.[56] ***Table ES-7*** summarizes the study characteristics and findings of included studies. The pooled summary estimate of diagnostic yield from the five primary research studies we identified was 8.8% (95% CI, 8.4% to 9.3%). The individual study estimates of diagnostic yield in these studies ranged from 7.3%[51] to 14.9%.[54] The median diagnostic yield for CMA testing among patients with global DD with or without ID in the HTA conducted by Grant et al. was 13.6% [interquartile range, 9.5% to 17.2%] across 55 applicable studies in this HTA, and was 19% among the 21 studies published in 2012 or later.[40] This difference was due to higher diagnostic yield among studies conducted outside of the United States than studies conducted in the United States, and lower diagnostic yield among studies published in 2010 or 2011 than ones published in 2012 or later.

Table ES-7. Summary of Findings for the Diagnostic Yield of Testing with Chromosomal Microarray or Whole Exome Sequencing

Author (Year)	Study Population; Sample Size; Test	Diagnostic Yield [Detection of A Pathogenic Variant] N (%)	Risk of Bias
Bowling (2017)[56]	Clinic-based family recruitment of children with mild to severe ID, age ≥ 2; N=365; WES	CNV only: 2 (1.6%) Total: 100 (27%)	Low
Coulter (2011)[51]	Patients of children's hospital; N =1,792, CMA	131 (7.3%)	Unclear
Henderson (2014)[52]	Laboratory-based series of patients; N= 1,780; CMA	227 (12.7%)	Low
Ho (2016)[53]	Laboratory-based series of patients with neurodevelopmental disorders; N=10,351; CMA	890 (8.6%)	Low
Roberts (2014)[54]	Laboratory-based series of patients with mixed phenotypes of ID/MCA; N=215; CMA	32 (14.9%)	Low
Stobbe (2014)[55]	Clinic-based study of adults with autism; N=25; CMA	2 (12.0%)	Low

Abbreviations: CMA=chromosomal microarray; CNV= copy number variant; ID= intellectual disability; MCA=multiple congenital anomalies; VUS=variant of undetermined significance; WES=whole exome sequencing.

The diagnostic yield in the one study that reported on WES testing was 1.6% for CNVs, and 27% (95% CI, NR) overall.[56] Many of the probands in the study had had CMA prior to WES. We graded the strength of evidence for this research question as low (***Table ES-8***).

Table ES-8. Strength of Evidence for Findings Related to the Diagnostic Yield (EQ1) of Testing with Chromosomal Microarray or Whole Exome Sequencing

Outcome	Number of Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirectness	Precision	Other considerations	Strength of Evidence Grade
Diagnostic yield of CMA Range 7.3% to 14.9% Grant et al. 19%	5; 14,163; Obser-vational 21; 6,662 Observational	Not serious	Not serious	Not serious	Not serious	Definition of outcome	Low
Diagnostic yield of WES 27%	1; 632; Obser-vational	Not serious	NA, single study	Not serious	Serious[a]	None	Very low

Abbreviations: CMA=chromosomal microarray; NA= not applicable; WES=whole exome sequencing.

[a] No confidence intervals or other estimates of precision provided.

EQ2. For what types of conditions is CMA or WES most useful?

Few studies reported diagnostic yield by patient characteristics or specific diagnosis. However, three studies, Stobbe et al.,[55] Ho et al.,[53] and Roberts et al.,[54] reported the diagnostic yield of CMA among patients whose indication for testing was ASD. The pooled summary estimate of diagnostic yield among these children was 5.4% (95% CI, 4.8% to 6.0%).

EQ3. Does the diagnosis of a chromosomal disorder change the child's management?

Seven studies[51,52,57-61] evaluated the impact of CMA testing on the clinical management of children with ASD, DD, ID, or MCA. These studies varied in design and outcomes measured. ***Table ES-9*** summarizes study characteristics and findings. Across this body of evidence, in 27.1% to 93.8% of children with a pathogenic variant on CMA testing, a management change occurred because of the new information provided by the CMA results. This finding represents between 3.6% and 6.7% of all cases tested. Hayeems et al.[58] found that patients with a pathogenic variant were 36% more likely (RR, 1.36 [95% CI, 1.21 to 1.53]) to have changes in management than patients with a benign variant on CMA testing. We graded the strength of evidence for this research question as very low (***Table ES-10***). We identified no studies reporting on the impact of clinical management resulting from WES testing.

Table ES-9. Summary of Findings for the Impact of Chromosomal Microarray Testing on Clinical Management

Author (Year)	Study Population; Sample Size	Outcome Definition	Result[1]	Risk of Bias
Coulter (2011)[51]	Retrospective clinic-based cohort of all children with CMA Total tested: 1,792 Total with pathogenic or VUS: 235 Eligible for follow-up study: 194	At least one management change (surveillance start/stopped, referral, diagnostic testing) due to pathogenic CNV.	65 patients with management change (53.7% of follow-up study; 3.6% of all tested)	Cannot determine
Ellison (2012)[57]	Retrospective laboratory-based cohort. Total tested: 46,298 Clinically actionable CNV: 1,996	Patients with clinically actionable CNV (known microdeletion or duplication syndrome, increased cancer susceptibility, deleted genes associated with genetic disease requiring follow-up).	1,996 cases with clinically actionable CNV (4.3%)	High
	Patients whose physicians were surveyed: 122 Responses received: 81	At least one guideline-recommended management change (not specified) due to pathogenic CNV	74 patients whose physicians reported at least one recommended clinical action taken (93.8%)	High
Hayeems (2015)[58]	Retrospective clinic-based cohort of all children with CMA testing	Average number of recommendations	Mean 2.35 recommend-ations per patient	Low

Author (Year)	Study Population; Sample Size	Outcome Definition	Result[1]	Risk of Bias
	followed at tertiary pediatric hospital; N=752	(surveillance, referral, diagnostic testing, medication indication/contraindication, family testing) due to pathogenic CNV		
Henderson (2014)[52]	Retrospective laboratory-based cohort of all children with CMA testing Tested: N=1,780 Pathogenic CNV: 227 Follow-up available: 187	At least one management change (surveillance, referral, diagnostic testing, medical/surgical procedure, medication indication, contraindication) due to pathogenic CNV	102 cases with management change (54.5% of follow-up study; 5.7% of total tested)	Low
Riggs (2014)[59]	Retrospective case series of syndromes diagnosable by CMA; N=28,526 Pathogenic and likely pathogenic: 4,125	At least one management change (referral, diagnostic testing, surgical/intervention procedures, surveillances, medication, contraindication, lifestyle changes) recommended for pathogenic CNV	1,908 (46.3% of cases with recommended change in management; 6.7% of all tested)	High

Table ES-9. Summary of Findings for the Impact of Chromosomal Microarray Testing on Clinical Management (continued)

Author (Year)	Study Population; Sample Size	Outcome Definition	Result[1]	Risk of Bias
Saam (2008)[60]	Retrospective case series of patients with abnormal CNV; N=48	At least one management change (referral, screening, stop screening) due to pathogenic CNV	13 cases with change in management (27.1%)	Cannot determine
Tao (2014)[61]	Retrospective case series of children with ID/DD, ASD, or MCA; N=327	At least one management change (surveillance, referral, diagnostic testing, medical/surgical procedure, medication indication, contraindication, lifestyle recommendation) due to pathogenic CNV	28 cases with recom-mended change in management (75.7%)	Low

Abbreviations: CMA=chromosomal microarray; CNV= copy number variant; DD=developmental disability; ID= intellectual disability; MCA=multiple congenital anomalies; VUS=variant of undetermined significance

[1] Confidence intervals were not reported by study authors unless specified.

Table ES-10. Strength of Evidence for Findings Related to the Impact of Testing with Chromosomal Microarray on Clinical Management (EQ3)

Outcome	Number of Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirectness	Precision	Other Consider-ations	Strength of Evidence Grade
Percentage of patients with abnormal results that have a change in management range 27.1 to 93.8%	7; 658; Obser-vational	Serious[a]	Serious[b]	Serious[c]	Serious[d]	None	Very low

[a] Potential for recall bias when changes in management are collected by physician interview, lack of detail in determining clinical actionability by retrospective review, potential conflict of interest due to goal of promoting reimbursement for CMA.

[b] Wide range of findings among studies.

[c] Three studies measured actionability based on published guidelines and recommendations, not actual changes in management for tested patients.

[d] None of the studies provided confidence intervals or other measures of precision. Sample sizes were small to moderate.

EQ4. Do children with congenital defects, autism, intellectual disability, or developmental disability tested with CMA or WES have better health outcomes?

We did not identify any studies that reported on health outcomes among children tested with CMA or WES, either as single-arm studies or compared to patients not tested or tested with other platforms.

Cost and Cost-Effectiveness

CQ1. What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with CMA or WES?

We identified five eligible studies reporting cost, cost per patient, cost per diagnosis, or cost per additional diagnosis.[62-66] All identified studies were specific to CMA testing; no studies evaluated WES testing or reported cost effectiveness based on cost per quality-adjusted or disability-adjusted life year. Study findings are summarized in ***Table ES-11*** by phenotype. Costs per array varied across studies and by testing platforms; these costs ranged from $271 to $1,575 (in 2010 U.S. dollars). These costs reflect the cost per array, which was only one of several costs used to estimate overall costs of CMA testing compared to no CMA testing. The cost per additional diagnosis varied widely. We graded the strength of evidence for this research question as very low (***Table ES-12)***.

Table ES-11. Summary of Findings of Studies Evaluating Cost Outcomes of Chromosomal Microarray Testing, Outcomes Reported in 2010 U.S. Dollars

Phenotype	No. of Studies (No. of Participants)	Cost Per Patient or Diagnosis (95% CI)			Difference in Cost (95% CI)	Cost per additional diagnosis (95% CI)
		Outcome	CMA Testing	No CMA Testing		
Intellectual Disability	2 (NA[a])	Cost per diagnosis[65]	$2,919[b] (2,671 to $3,188)	$2,707 (2,448 to 2,990)	$213 (168 to 256)	$2,592 ($1,586 to $5,188)
		Cost per diagnosis[66]	$6,269[c] (NR)	Range $4,280 to $9,966[d]	Range -$3,697 to $1,988[d]	Range[e] -$370 to $199
Developmental Delay	1 (114)[63]	Cost per patient	NR	NR	-$101 (98% CI, -$186 to $-16)[f] $402 (98% CI, $227 to $577)[g]	NA
		Cost per diagnosis	NR	NR	NR	$1,317 (NR)[f]; $12,296 (NR)[g]
Intellectual disability or developmental delay or both	2(1,636)	Cost per patient	$2,536 (NR)[62] $415 (range $271 to $1,792)[64]	$3,223 (NR)[62] $759 (range $556 to $2,029)[64]	-$687 (NR, p=0.34)[62] -$344 (95% CI, -$366 to -$322)[64]	NA
		Cost per diagnosis	Range $4,381 to $7,757[62] $3,625 (NR)[64]	NR[62] $6,866 (NR)[64]	NR[62] $-3,241 (95% CI NR)[64]	$4,381 (NR)[62] $-88,819 (NR)[64]

Abbreviations: CMA=chromosomal microarray; CI=confidence interval; NA=not applicable; NR=not reported.
[a] Both studies were conducted using decision analyses using hypothetical cohorts; thus, sample size is not applicable.
[b] Assumes that CMA testing increases diagnostic yield from 19.2% to 27.5%.
[c] Assumes that CMA testing increases diagnostic yield from 8% to 18%, cost per diagnosis is 2440 with a 15% absolute increase in diagnostic yield.
[d] Depending on which kinds of follow-up testing after karyotype used.
[e] Calculated based on data provided in the study.
[f] When using local hospital laboratory for testing.
[g] When using commercial laboratory for testing.

Table ES-12. Strength of Evidence for Findings Related to the Cost-Effectiveness of Chromosomal Microarray Testing Compared to No Testing (CQ1)

Outcome	Number of Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirect-ness	Imprecision	Other Consider-ations	Strength of Evidence Grade
Cost per additional diagnosis range $-88,919 to $12,296	5; 1,750[a] Obser-vational and decision analyses	Not serious	Serious[b]	Serious[c]	Very serious[d]	None	Very low

[a] Total sample size from three retrospective cohort studies; two additional studies generated outcomes based on decision analyses among hypothetical cohorts.

[b] Clinical and methodological heterogeneity likely explains most of inconsistency in results, though it is unclear to what extent these factors can explain the degree of inconsistency noted.

[c] Cost per additional diagnosis is a surrogate outcome; this outcome presumes that additional diagnoses would leave to changes in management that ultimately would lead to improved health outcomes.

[d] Few studies provided confidence intervals around estimates; optimal information size criteria likely not met by any included studies.

Discussion

Summary of the Evidence

The strength of the evidence for all included research questions was very low (safety, impact on management, and costs) or low (diagnostic yield). We identified no eligible studies addressing the impact of CMA or WES testing on patient health outcomes (EQ4). Key findings include:

- Safety: The only safety concern that we identified based on one included study is discrimination because of the test results. The body of evidence was not sufficient to determine the frequency with which these issues may arise in CMA testing compared to other types of genetic tests. We graded the strength of the evidence related to safety as very low. We identified no studies that reported safety outcomes related to WES testing.
- Diagnostic yield: In studies that conducted testing in the United States in 2009 or later, CMA testing identified pathogenic or likely pathogenic variants in 8.8% (95% CI, 8.4% to 9.3%) of children tested for any reason, and 5.4% (95% CI, 4.8% to 6.0%) of children referred for ASD. A previous HTA by Grant et al. that included U.S. and non-U.S. studies found that among studies published in 2012 or later, the diagnostic yield averaged 19% for global DD or ID and 12% for ASD.[40] We graded the strength of the evidence related to diagnostic yield of CMA testing as low. One primary research study of WES

reported a diagnostic yield of 27% (95% CI, NR) and we graded the strength of this evidence as very low.

- Impact on clinical management: CMA results prompted changes in clinical management in 27% to 94% of patients with a pathogenic variant, which was 3.6% to 6.7% of all patients tested. We graded the strength of this evidence as very low. We identified no studies reported on change in management related to WES testing.
- Costs: The cost *per additional* diagnosis across this body of evidence ranged in 2010 U.S. dollars from $-88,819 to $12,296. No studies reported on cost per quality-adjusted or disability-adjusted life year. We graded the strength of the evidence on costs as very low.

Contextual Information

Our review revealed information related to CMA and WES that was not formally evaluated in our systematic review, but may add to the interpretation of our results.

CNVs in General Population

CMA testing on samples and phenotype information from the general population of Estonia found 0.7% had a DECIPHER-listed pathogenic variant, and 70% of individuals with a pathogenic variant reported clinical features consistent with their genetic findings.[67]

Analytic Validity

Compared to sequencing, the Affymetrix® CytoScan® Dx Assay identified 98.8% (95% CI: 93.5%, 99.8%) of duplications and 97.3% (92.3%, 99.1%) of deletions of 1000 base pairs or more, with a false positive rate of 1.2% (0.2%, 6.5%) for duplications and 2.7% (0.9%, 7.7%) for deletions.[28] The Agilent GenetiSure Dx Postnatal Assay identified 97.6% (94.0%, 99.1%) of duplications and 96.9% (93.4%, 98.6%) of deletions of 10,000 base pairs or larger, with false positive rates of 2.4% (0.9%, 6.0%) and 3.1% (1.4%, 6.6%), respectively.[28]

Limitations and Applicability of the Evidence Base

Almost all studies we included focused on CMA. Clinical use of WES is still new, and the body of evidence regarding its impact is limited. Across the body of evidence for all research questions, study design, study population, and outcome measurement details were often sparse, resulting in our inability to assess the risk of bias for some studies. Most of the studies reporting on diagnostic yield included some cases for indications other than our population of interest. In addition, prior diagnostic testing received by the cases varied. The differences among studies likely increase the inconsistency between studies and the lack of precision in study estimates. Diagnostic yield among more homogenous case series may be more consistent within the same types of cases, but differ from our results.

Financial or intellectual conflicts of interest of the study authors were not addressed in the existing instruments we used; thus, we did not evaluate that aspect of the risk of bias. Authors of several included studies stated that a goal of the research was to provide evidence of clinical utility to get CMA covered by payors, potentially providing a strong incentive for analytic decisions that would increase the estimate of diagnostic yield or impact on management. Studies

evaluating the impact of testing on management were small, so each included only a small portion of known microduplication or microdeletion syndromes. The clinical features of these syndromes and the appropriate management actions vary accordingly, and are likely an explanation for the large heterogeneity of estimates on impact on management.

The body of evidence related to cost and cost-effectiveness is limited by the lack of studies conducted in the United States, the absence of a societal perspective in any of the analyses, and the absence of cost per quality-adjusted or disability-adjusted life year outcomes. Further, this body of evidence is limited by extreme clinical and methodological heterogeneity, which most likely explains the inconsistency in cost per additional diagnosis. The precise role of these tests in the overall sequence and approach to diagnostic evaluation in children with DD, ID, and ASD has also evolved; thus, the cost of the diagnostic journey with or without CMA testing reflected in the included studies may no longer be relevant to current clinical practice.

Limitations of this HTA

We did not include studies published in languages other than English and only searched two U.S.-based electronic databases. We used a single reviewer to screen most titles/abstracts, which may have led to studies inappropriately excluded. For the research question related to diagnostic yield (EQ1), we restricted eligibility to studies with CMA conducted in the United States in 2009 or later that used current testing platforms to reduce heterogeneity and provide results more applicable to what is in current clinical use. We did not assess analytic validity or reproducibility or conduct an in-depth analysis or synthesis of the cases, breakpoints, or other information related to CNV findings that were presented by study authors. In addition, our review was limited to the use of WES to detect chromosomal abnormalities. WES studies may have been more likely to be missed or inappropriately excluded because the distinction between test validation and clinical studies was unclear, and because we did not identify any systematic reviews or HTAs of this test.

Conclusion

CMA identifies a pathogenic or likely pathogenic variant in nearly 9% of all children referred for testing and in 5% of those referred because of ASDs; these findings are based on a low strength of evidence. The results of CMA tests generate changes in management in over half of children identified as having a pathogenic or likely pathogenic variant; this finding is based on very low strength of evidence. The evidence is very limited with respect to the safety of testing and we identified no evidence related to the impact of testing on health outcomes or cost-effectiveness. The cost per additional diagnosis for CMA testing as a first-line diagnostic test compared to no testing with CMA varied.

Full Technical Report

Background

Purpose

This health technology assessment (HTA) will review the efficacy, cost, and potential harms in the use of chromosomal microarray (CMA) or whole exome sequencing (WES) to identify chromosomal abnormalities, including aneuploidies, rearrangements, and copy number variants (CNVs) for the diagnosis and management of children with autism, intellectual disability, birth defects, or undiagnosed genetic disease. CMAs or WES can identify smaller rearrangements and CNVs than karyotype or fluorescent in-situ hybridization (FISH) analysis.[8] When present at conception or acquired during prenatal development, chromosomal abnormalities can cause genetic diseases, congenital structural defects, or developmental disabilities.[13,25]

Condition Description

Chromosomes, the genetic structures of a cell, are constructed of deoxyribose nucleic acid (DNA) and the proteins and other elements that protect, regulate, and package the DNA. Humans normally have 23 pairs of chromosomes, with half inherited from each parent. During cell replication, chromosomes are sometimes lost or gained, or broken and rearranged. Rearrangements vary in size and complexity, and may be balanced, with no loss of genetic material, or unbalanced with loss or gain of DNA.

Unbalanced chromosomal rearrangements that are present at conception or that occur during fetal development can have profound consequences for the developing fetus or infant, including fetal or neonatal death.[1] Chromosomal abnormalities account are a significant cause of congenital anomalies, intellectual disability (ID), developmental delay (DD), and autism. Among one cohort of 4-year old children with ID, the disability was due to a genetic cause in 20% (31 of 151) of the children. Twelve children (8%)[68] had a specific chromosomal abnormality, 7 (4,6%) had a single gene disorder, and the remainder had a multifactorial condition.

Disease Burden

Chromosomal abnormalities occur in 43.8 per 10,000 births that survive to 20 weeks gestation or later.[2] Trisomies 21, 18, and 13; 45, X, and other sex chromosome abnormalities account for most abnormalities. Excluding these, the prevalence of more rare abnormalities is 7.4 per 10,000 births.[2] Small pathogenic duplications or deletions, called copy number changes or variants (CNVs), occur in 1 of 270 pregnancies.[3] The consequences of CNVs depend on the size and location within the genome. The number of living children or adults with a chromosomal abnormality is unknown. Studies examining the prevalence of chromosomal abnormalities have focused on the prenatal period,[2] the prevalence at birth,[69] or the prevalence among individuals with specific structural defects[70] or developmental disabilities.[71] The life expectancy for individuals with a chromosomal abnormality may be significantly shortened by birth defects and other conditions, but for some such defects, life expectancy has increased in recent years.[72]

Approximately 3% of infants born in the United States have a major structural defect,[4] and almost 6% of children in the United States have an ID, DD, or autism spectrum disorder (ASD).[5] These conditions are expensive to manage: in 2004, U.S. hospitalization costs for birth defects totaled $2.6 billion dollars.[6] In Washington, 10.3% of adults living in the state in 2014 had a cognitive disability.[7] State expenditures in caring for residents with an ID included over $600 million in Medicaid expenditures for long-term care and over $1 billion on special education programs.

Technology Description

History

The diagnosis of genetic disease began approximately 60 years ago, with the development of tests at the extremes of resolution and targeting. Karyotype, developed in 1959, initially only detected the largest of genomic changes, changes in the number of chromosomes, but is completely untargeted: a single test could detect changes in any chromosome. The Guthrie test for phenylketonuria, on the other hand, detected the results of a single base pair change, but only for one genetic disease. The quest of genetics laboratories over the last 60 years has been to increase the resolution of genetic tests and to reduce the level of targeting needed. This report discusses two recent developments in untargeted testing. CMA and WES detect changes across the genome. CMA can detect unbalanced changes as small as 30,000 base pairs and WES can detect changes as small as a single base pair.

Chromosomal Microarrays (CMA)

Karyotyping and FISH have traditionally been used to identify unbalanced chromosomal rearrangements. In the early 2000s, genome-wide microarrays for chromosomal analysis, commonly known as CMA, which use comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays to evaluate the number of copies of portions of the chromosomes, were introduced as an adjunct to karyotype and FISH testing for chromosome abnormalities. CGH uses probes fixed to glass plates.[8] Patient and control DNA samples are tagged with fluorescent markers and hybridized to the probes. Computer analysis uses the intensity and color of fluorescence to determine how many copies of each chromosomal region are present. For SNP arrays, individual base pairs throughout the genome that vary within the normal population are tagged with different fluorescent dyes. The number of alleles and whether the individual has the same allele on both chromosome or different alleles can be determined by analysis of the color and intensity of the bound fluorescent dyes.[8]

Although CMA can identify aneuploidies and large rearrangements, its strength lies in identifying small deletions and duplications.[8] CMA can identify rearrangements as small as 30,000 base pairs, whereas karyotyping can detect approximately 5,000,000 base pairs. For this reason, professional societies now recommend CMA be the first test used to diagnose chromosomal abnormalities in children with multiple congenital anomalies (MCAs) or DD/IDs (***Table 1***).[10-15] As a result, CMA has increasingly replaced karyotyping and FISH as the initial test for postnatal diagnosis of chromosomal abnormalities. However, CMA cannot identify balanced rearrangements or low-level mosaicism so karyotyping may still be required in some cases.[16]

The platforms used for CGH have changed since their introduction. The first genome-wide platforms used bacterial artificial chromosome (BAC) probes that could detect deletions or duplications of approximately 1,000,000 base pairs (1 Mb).[8] Around 2007, arrays based on small synthesized oligonucleotides ('oligo') began replacing BAC arrays. Oligonucleotide probes are smaller, and oligo-based arrays have many more probes, enabling detection of smaller CNVs.[9] Although some early platforms used SNP arrays, the probes were widely spaced, limiting the size of the CNVs that could be detected. Newer SNP arrays include probes for many more base pairs, and target the probes to gene-rich regions where CNVs are most likely to be detrimental. Many current CMA testing platforms use a combination of labeled SNPs and oligo-based probes to assess genetic bases or sequences throughout the genome.

CMA is more expensive than karyotyping. Greenwood Genetics Center, a nonprofit organization that provides clinical genetic services and diagnostic testing, charges $602 for routine resolution karyotyping, $794 for high-resolution karyotyping,[73] and $1,950 for chromosomal analysis by CMA.[74] The laboratory recommends karyotyping in conjunction with the CMA (charge $620) if not completed previously. A hospital-based genetics laboratory located in a midwestern academic medical center charges $1,905 for CMA testing.[75] Several commercial diagnostic laboratories also provide this testing, but prices are not publicly available.

Whole Exome Sequencing

WES is the provides the base pair sequence for all the protein coding regions in the genome, the exons.[17] Multiple large regions of the genome are sequenced simultaneously. WES allows the detection of single nucleotide changes within any gene; it is used clinically to detect pathogenic single nucleotide changes or small insertions or deletions when the clinical presentation does not point to a specific genetic disorder. Defects in several genes may result in similar clinical presentations. In these cases, WES may be more efficient than sequential testing for single gene disorders.

Although WES is usually used for the detection of single base pair substitutions or duplications or deletions of a few base pairs, it can identify CNVs that contain three or more protein coding regions with the sensitivity of medium resolution chromosomal microarrays.[18] WES has a lower sensitivity for the identification of CNVs than whole genome sequencing or high-resolution CMAs due to limitations of exon capture methods and a lack of standard bioinformatics for this purpose.[19,20]

Table 1. Resolution and Detection of Chromosomal Microarray and Whole Exome Sequencing

	Chromosomal Microarray	Whole Exome Sequencing
Types of genetic disease	Chromosomal abnormality syndromes	Single gene disorders
Types of genetic defect	Microduplications, microdeletions, unbalanced rearrangements	Base pair insertions, deletions, or substitutions,
Minimum resolution (no. of base pairs)	≥ 30,000	≥1

Test Interpretation

After any genetic changes are identified, the laboratory determines if the variant is pathogenic, i.e., it is the likely cause of the patient's symptoms or, if it is not the cause of the patient's symptoms, it may have other clinical consequences, a secondary or incidental finding. These determinations are made through examining public databases of known pathogenic and benign variants, the laboratory's internal database of prior test results, published literature, and consultation with other laboratories. The American College of Medical Genetics (ACMG) and the Association of Molecular Pathology published guidelines for the interpretation of sequence variants,[21] and tools have been developed to aid in their use.[22,76]

Any genome-wide genetic testing can have secondary or incidental findings. What to do with these findings has been hotly debated. The ACMG recommended that laboratories conducting clinical exome or genome sequencing actively seek and report a list of specific, clinically actionable variants within 24 genes or classes of genes,[23] regardless of the indication for testing. They estimated that approximately 2% of patients sequenced would have a reportable variant, and this number has been confirmed in clinical studies.[56] The ACMG recommendations did not address CNVs or structural abnormalities, but they apply to CNVs that deleted or disabled listed genes with autosomal dominant inheritance. Incidental findings from CMA have been studied less than those from sequencing and studies have been limited to specific types of disease or genes. One study found 14 patients with a single gene CNV that were likely to cause adult-onset disease and 27 patients with a multi-gene CNV unrelated to their presenting symptoms that included a cancer predisposition gene among a total of 9,005 tested patients, a prevalence of 0.4%.[24]

Policy Context

The State of Washington Health Care Authority selected testing with CMA and WES as a topic based on medium, high, and high concerns for safety, efficacy, and cost, respectively. Several practice guidelines have been issued that call for CMA to replace G-banded karyotype as the first-tier test for diagnosis of individuals with DD, ID, MCA, and for the clinical evaluation of ASD.[13,25] These guidelines, combined with the increasing prevalence of autism,[26] could greatly increase orders for CMA. The increased diagnostic yield of chromosomal abnormalities by CMA compared to karyotype underlies these guidelines (***Table 2***).[13,25] The degree of DD or ID for which CMA is most likely to yield a diagnosis is unclear, however, as is the effect of the testing results on the medical and educational management and health outcomes of affected children.

Table 2. Practice Guidelines Endorsing or Providing Guidance on Chromosomal Microarray Testing

Organization	Year
International Standard Cytogenomic Consortium[25]	2010
National Institute for Health and Care Excellence (UK)[12]	2011
American College of Medical Genetics and Genomics[13]	2013
American Academy of Pediatrics[15]	2014
American Academy of Neurology[14]	2015

Washington State Agency Utilization Data

The State of Washington Health Care Authority provided the information and data in this section.

Populations

The *Genomic Micro-array and Single Exome Sequencing* analysis includes member utilization and cost data from the following agencies: PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan) and HCA Medicaid (formerly Fee-for-Service) and the Managed Care (MCO) Medicaid programs. Neither the Department of Labor and Industries (LNI) workers' compensation plan, nor PEBB Medicare experienced any paid claim activity during the four years examined.

The analysis period was four (4) calendar years, 2013 to 2016. Primary population inclusion criteria included experiencing at least one of the Current Procedural Terminology/ Healthcare Common Procedure Coding System (CPT/HCPCS) codes from ***Table 3***. Individuals with denied claims were excluded from the analysis.

Methods

Lab services/units were calculated based on an individual experiencing a paid provider-patient face-to-face, on a specific date *and* including at least one of the CPT codes from Table 3. Data evaluation included examining utilization by member; and by average claims' cost incurred by a member.

Total claims were not analyzed for all services provided on the date of lab service. A high level of cost variability, based on site of service (inpatient/outpatient), and simultaneous or subsequent procedures including births, would have skewed the findings. ***Table 5*** provides the findings from this analysis.

Table 3. CPT Descriptions

CPT	
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
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)

Table 4. Definitions for Utilization and Cost Tables

Unique Patients	Nonduplicated members seen as patients by year, reported by agency
Encounters	Defined as a single patient-provider face-to-face on a specific date.
Average Encounters/Patient	Total encounters/total unique members
Total Dollars Paid	Paid dollars for all specified CPT codes
Dollars Paid by Encounter-Mean	Paid dollars for services received on the date of the treatment
Mean	Sum of all values, divided by the number of observations

Table 5. Utilization Analysis – Genomic Micro-array and single exome sequencing

	2013	2014	2015	2016	Overall
PEBB/ UMP					
Unique patients	1	1	6	17	25
Encounters	1	1	6	17	25
Average encounters/ Patient	1	1122	1	1	1
Total dollars paid	$540	$492	$12,080	$28,054	$41,166
Dollars paid by encounter - Mean	$540	$492	$2,013	$1,650	$1,647

	2013	2014	2015	2016	Overall
Medicaid MCO[1] and Medicaid					
Unique patients	122	314	574	685	1677
Encounters	134	335	599	749	1817
Average encounters/ Patient	1	1	1	1	1
Total dollars paid	$14,683	$169,085	$257,922	$302,643	$744,333
Dollars paid by encounter - Mean	$110	$505	$431	$404	$410

[1] *Medicaid MCO accounts for 95% of all Paid Dollars and 93% of all Services.*

	2013	2014	2015	2016
Medicaid MCO and Medicaid HCA Detail				
MCO Max of Paid Dollars per CPT	$1,537	$5,842	$2,775	$7,500
MCO Median of Paid Dollars	$711	$424	$105	$21
LNI	**No encounters**			
Medicare/ PEBB	No encounters			

Regulatory Status

At the current time, CMA and WES are considered laboratory-developed tests and are not regulated by the United States (U.S.) Food and Drug Administration (FDA). Clinical laboratories that conduct these tests must comply with regulatory standards for high complexity testing within the Clinical Laboratory Improvement Act (CLIA). Thus, these tests are generally only available through commercial diagnostic testing laboratories (e.g., LabCorp, Ambry Genetics, Lineagen, CombiMatrix) or hospital-based laboratories.

FDA approval is required when a company markets and sells a kit for CMA or WES testing. The FDA has approved two CMA kits for marketing in the United States, the Affymetrix CytoScan® Dx assay (Affymetrix, Inc., Santa Clara, CA), approved as a Class II test on January 21, 2014[27] and the Agilent GenetiSure Dx Postnatal Assay (Agilent Technologies, Inc., Santa Clara, CA),[28] approved under a substantial equivalence determination on August 14, 2017. The FDA-approved indications for the kits include postnatal detection of CNVs associated with DD, ID, MCA, or dysmorphic features.

Practice Guidelines

In 2010, the International Standard Cytogenomic Array (ISCA) Consortium released a consensus statement that CMA should replace G-banded karyotype as a first-tier test for the diagnosis of individuals with DD/IDs or MCAs.[25]

In 2011, the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued a clinical guideline related to ASD in children recommending that CMA testing should not be routinely done on all children with autism, but only in those with dysmorphic features or ID.[12]

In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended that CMA replace G-band karyotype for the clinical evaluation of ASDs.[13]

In a 2014 Clinical Report from the American Academy of Pediatrics (AAP) Committee on Genetics, CMA is considered the first-tier diagnostic test in all children with global DD/ID for whom the causal diagnosis is not known.[77] The AAP also considers CMA as a standard for diagnosis of patients with ASDs and MCAs. The AAP Committee on Genetics considers WES an emerging technology for the future and has no current practice guideline related to its use.[77]

In a 2015 medical coverage policy, the American Academy of Neurology (AAN) considers CMA to be reasonable and medically necessary for diagnosing children with DD/ID or ASD when relevant biochemical and metabolic testing is negative, relevant targeted genetic testing is negative, the results of testing could impact the clinical management of the patient, and face-to-face genetic counseling with a trained and experienced health care professional has been provided.[78] The AAN's practice guideline for evaluation of children with global DD (2003) is currently being updated.[79] In a 2016 statement, the AAN acknowledges the rapidly changing landscape of WES testing and costs, yet indicates the following may be indications for WES: undiagnosed neurologic disorder with nonspecific or clinically heterogenous phenotype; expert evaluation with detailed clinical history, comprehensive neurological examination, and complete family history, complete evaluation for common causes not requiring genetic testing, and

negative initial genetic testing (e.g., high-yield single gene or multigene testing, CMA testing) based on clinical evaluation as appropriate.[14]

Other Related HTAs

Sun F, Oristaglio J, Levy SE, Hakonarson H, Sullivan N, Fontanarosa J, Schoelles KM. *Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder* [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Jun. Available from: http://www.ncbi.nlm.nih.gov/books/NBK304462/PubMed PMID: 26158183.

Grant M, Chopra R. TEC Special Report: Chromosomal Microarray for the Genetic Evaluation of Patients with Global Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder. BlueCross BlueShield Association. Technology Evaluation Center. 2015. Available from: http://www.bcbs.com/blueresources/tec/vols/

Selected Payer Coverage Determinations

Table 6 summarizes the Centers for Medicare and Medicaid Services (CMS) and selected other payer coverage determinations for CMA and WES. Among payers, good alignment exists for the criteria under which CMA is covered. Typically, it is covered as first-line diagnostic for global DD/ID or ASD when relevant biochemical and metabolic diseases have been ruled out and the clinical presentation is not specific to a well-delineated genetic syndrome and the results of CMA could impact the clinical management of the child.

Table 6. Payer Coverage for CMA and WES Testing

Payer	CMA Testing	WES Testing
Aetna	Covered for specific indications	Not covered
Blue Cross (Premera)	Covered for specific indications	Covered for specific indications
Regence Blue Shield	Covered for specific indications	Not covered
Cigna	Covered for specific indications	Covered for specific indications
Humana	Covered for specific indications	Not covered
Kaiser Permanente	Covered for specific indications	Not covered
Medicare Fee for Service	None	None
Medicaid	Not all states have coverage policies; those that do typically cover for specific indications	
United Healthcare	Covered for specific indications	Covered for specific indications

CMS

Medicare has no national coverage determination for the use of CMA or WES. Local coverage determinations vary.

Aetna

Aetna considers CMA medically necessary and covered for diagnosing genetic abnormalities in children with MCAs, DD/ID, or ASD when relevant biochemical testing for metabolic diseases is negative; when targeted genetic testing if or when indicated by clinical and family history is negative; when the clinical presentation is not specific to a well-delineated genetic syndrome, and when the results of testing could impact the clinical management of the child.[29] This coverage policy was last affirmed September 22, 2017.

Aetna considers WES testing to be experimental and investigational and, thus, not a covered benefit. This coverage policy was last affirmed on August 8, 2017.

Blue Cross (Premera)

Premera considers CMA medically necessary as first-line testing of individuals with nonsyndromic DD/ID or ASD or two or more congenital anomalies not specific to a well-delineated genetic syndrome.[30] Premera considers testing using next-generation sequencing to be investigational. This coverage policy was effective August 25, 2017.

Premera considers WES medically necessary for (1) the evaluation of unexplained congenital or neurodevelopmental disorders in children when the patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing, (2) there is a potential for change in management and clinical outcome as a result of testing, and (3) a genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing or when prior genetic testing failed to yield a diagnosis and the individual is faced with invasive procedures or testing as the next diagnostic step.[30] This coverage policy was effective February 1, 2017.

Blue Shield (Regence)

Regence considers CMA medically necessary in children as first- or second-line assessment in children with apparent nonsyndromic cognitive DD/ID, ASD, or MCAs not specific to a well-delineated genetic syndrome.[31] Further, Regence considers testing using next-generation sequencing to be investigational and not a covered benefit. This policy was last affirmed April 2017.

Regence considers all applications of WES to be investigational and not a covered benefit.[31] This coverage policy was last effective August 1, 2017.

Cigna

Cigna considers CMA medically necessary when phenotypic characteristics of a specific genetic disorder are absent for patients with ASD and nonsyndromic global DD/ID. Testing is also considered medically necessary when MCAs are present and cannot be ascribed to a specific genetic syndrome.[33] In addition to these indications, testing must be recommended by independent board-certified or eligible medical geneticists, certified genetic counselors, or certified genetic nurses. The health professionals recommending testing (1) cannot be employed by a commercial genetic testing laboratory, (2) must have evaluated the individual, including a

three-generation pedigree, and (3) must intend to engage in post-test follow-up counseling. This coverage policy was effective November 15, 2016.

Cigna considers WES medically necessary when a genetic etiology is the most likely explanation for the phenotype demonstrated, no other cause can explain symptoms, and the clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available; and the differential diagnosis and/or phenotype would require testing of multiple genes such that WES testing would be more practical than separate genetic tests or preclude the need for multiple and/or invasive procedures. In addition, the individual must have been evaluated by a board-certified medical geneticist or other physician specialist with expertise in the conditions and relevant genes for which testing is being considered, and WES results are expected to directly impact clinical decision-making and clinical outcome for the individual being tested.[34] Pre- and post-test genetic counseling is required. This coverage policy was effective November 15, 2016.

Humana

Humana covers CMA for the evaluation of children diagnosed with ASD, unexplained global DD/ID and the absence of a clinically identifiable single gene disorder, clinical syndrome, and no family history of chromosomal rearrangement or multiple miscarriages. Humana also covers CMA for the evaluation of multiple anomalies, the combination of which are not suggestive of a specific syndrome.[35] This coverage policy was effective July 27, 2017.

Humana considers WES experimental/investigational, and this testing is not covered. This coverage policy was effective August 18, 2017.[35]

Kaiser Permanente

Kaiser considers CMA medically necessary for the evaluation of ID for individuals with significant dysmorphic features or congenital anomalies, when results are expected to affect clinical management, and when genetic counseling by a health care professional with appropriate genetic training and experience has been conducted.[36] The source documentation did not include an effective date for this coverage policy.

Kaiser does not cover WES.[36] The source documentation did not include an effective date for this coverage policy.

Medicaid

Some states have Medicaid coverage policies related to CMA testing. In Indiana, CMA testing is covered as a first-line test in postnatal evaluation of children with unexplained intellectual disability, development delay, or ASD.[37] Similarly, CMA testing is also covered in North Carolina. In Massachusetts, testing is covered with prior authorization.[15,38]

United

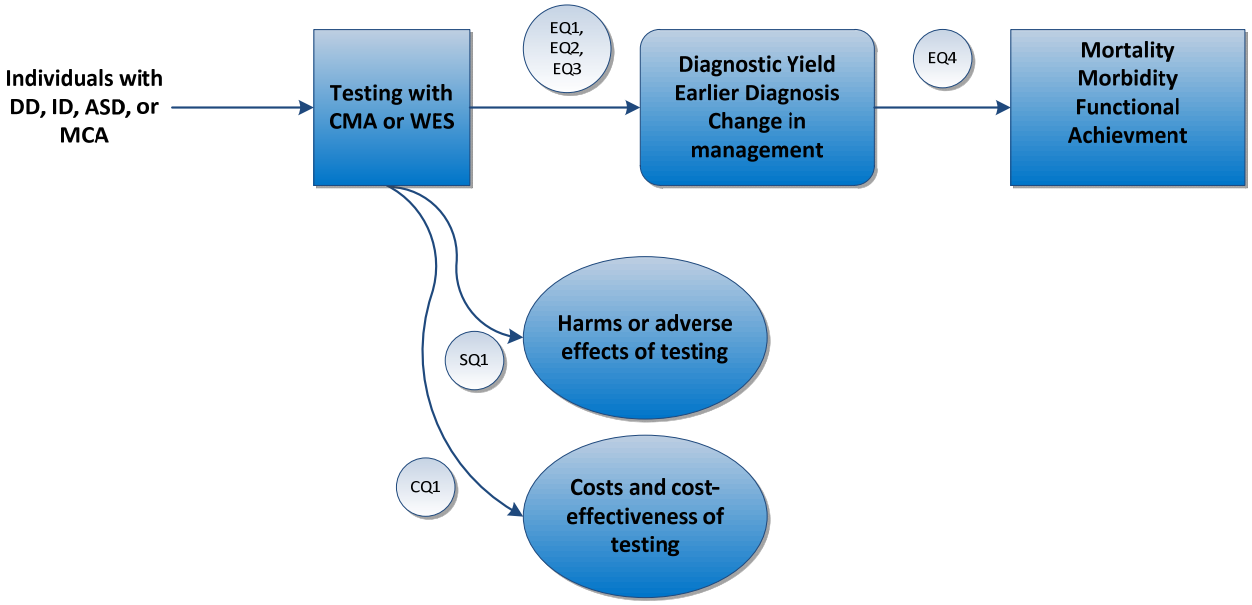
United Healthcare considers CMA medically necessary for evaluating patients with multiple anomalies not specific to a well-delineated genetic syndrome and that cannot be identified by a clinical evaluation alone, nonsyndromic DD/ID, and ASDs.[39] This coverage determination was effective August 1, 1017.

United Healthcare considers WES medically necessary when the patient's clinical presentation is nonspecific, does not fit a well-defined syndrome for which a targeted gene test exists, and testing has been recommended by a board-certified medical geneticist, neonatological, neurologist, or developmental pediatrician with specific expertise in the conditions for which testing is being considered, and the results are expected to directly influence management and clinical outcome. Additional medically necessary conditions are: the patient's clinical presentation and family history strongly suggest a genetic cause; the patient has a confident clinical diagnosis of a genetic condition where there is significant genetic heterogeneity, and WES would be more practical approach than multiple individual genetic tests; or the patient likely has a genetic disorder and has had multiple targeted gene tests that failed to identify the underlying cause.[80] This coverage determination was effective November 1, 2017.

Research Questions and Analytic Framework

The draft research questions for this Health Technology Assessment (HTA) were posted from August 16, 2017 to August 29, 2017 and received one public comment requesting inclusion of fragile X testing along with consideration of chromosomal microarray (CMA) and whole exome sequencing (WES) testing. This item was not added to the scope to keep the HTA focused on CMA and WES testing for the diagnosis of chromosomal abnormalities. ***Figure 1*** provides the analytic framework and ***Table 7*** provides the final research questions and study selection criteria related to the population, intervention, comparator, outcomes, time period, and setting.

Figure 2. Analytic Framework for the Detection of Chromosomal Abnormalities Chromosomal Microarray and Whole Exome Sequencing in Children with Intellectual Disability, Autism, or Birth Defects



Abbreviations: ASD=autism spectrum disorder; CD=congenital defects; CMA=chromosomal microarray; CQ=cost question; DD=developmental disability; EQ=efficacy question; ID=intellectual disability; MCA= multiple congenital anomalies; SQ=safety question; WES=whole exome sequencing.

Table 7. Research Questions and Scoping Parameters for the Detection of Chromosomal Abnormalities by Chromosomal Microarray or Whole Exome Sequencing in Children with Intellectual Disability, Autism, or Birth Defects

Research Questions	
Safety	SQ1. What, if any, safety issues do CMA and WES pose beyond those associated with phlebotomy?
Efficacy	EQ1. How often do CMA or WES return an informative result (i.e., diagnostic yield)? EQ2. For what types of conditions is CMA or WES most useful? EQ3. Does the diagnosis of a chromosomal disorder change the child's management? EQ4. Do children with congenital defects, autism, ID, or DD tested with CMA or WES have better health outcomes?
Cost	CQ1. What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with CMA or WES?
Populations; Interventions; Comparators, Outcomes; Time Period; Setting	
Populations	Children diagnosed with congenital defects, autism, ID/DD without known syndrome or specific genetic abnormality.
Intervention	1. CMA testing with currently available platforms, obsolete and superseded platforms will be excluded. 2. WES
Comparator	EQ1, EQ2, SQ1: Descriptive and may not have comparator groups. EQ3: Management before and after diagnosis; management of similarly affected undiagnosed children EQ4 and CQ1: No genetic diagnostic testing or genetic diagnostic testing did not include CMA or WES.
Safety Outcomes	SQ1. Harms reported as related to testing other than those associated with phlebotomy
Efficacy Outcomes	EQ1 and EQ2. Diagnostic yield or earlier diagnosis EQ3. Change in medical or educational interventions EQ4. Mortality during infancy or childhood EQ4. Development of comorbidities EQ4. Functional achievement
Cost Outcomes	CQ1: Cost of assay, cost per diagnosis, cost per additional diagnosis, cost per quality-adjusted life year, cost per disability-adjusted life year
Time Period	2009 to 2017 for EQ1 and EQ2, 2000-2017 for all others
Setting	Clinical genetic laboratories, medical genetic clinics, general and specialty pediatric clinics; non-U.S. studies were excluded for EQ1 and EQ2.

Abbreviations: CMA=chromosomal/genomic microarray; CQ=cost question; DD=developmental disability; EQ=efficacy question; ID=intellectual disability; SQ=safety question; U.S.=United States; WES=whole exome sequencing.

What is Excluded from This HTA

This HTA does not address the analytic validity of CMA or WES because this testing is available within Clinical Laboratory Improvement Act (CLIA)-licensed laboratories as a laboratory-developed test and analytic validity is assumed based on meeting CLIA standards.[40] It also does not address the use of CMA or WES to identify or monitor chromosomal changes in tumor cells or its use for prenatal testing. This review is focused on the diagnosis of chromosomal abnormalities; therefore, we do not address single gene testing for these disorders, including the use of WES to identify mutations within single genes. The review does not assess either the ethical issues or the clinical utility of incidental findings not related to the health conditions for which the tests were ordered. Because of the large volume of studies on diagnostic yield (EQ1) and the rapidly evolving technology in use for CMA testing, we limited the studies considered for EQ 1 to studies that were conducted in the United States in 2009 or later and that used current testing platforms.

Methods

Data Sources and Searches

We searched MEDLINE® (via PubMed) and a clinical trials registry (clinicaltrials.gov) for relevant English-language studies published in 2000 or later. We searched the FDA website, selected payer and health care professional society websites, the U.S. Agency for Healthcare Research and Quality, and other organizations that conduct and disseminate HTAs. In addition, we reviewed the reference lists of relevant studies, practice guidelines, and other HTAs on this topic to identify any relevant articles not identified through the electronic search. The detailed search strategy is provided in ***Appendix A***.

Study Selection

Study selection criteria for this HTA were as follows:

Population

For all research questions, we included studies that reporting testing individuals (children or adults) with autism, cerebral palsy, global developmental delay (GDD), developmental disability(DD), intellectual disability (ID), autism spectrum disorder (ASD), including Asperger's syndrome, mental retardation, mental deficiency, congenital defects, or birth defects. We excluded studies focused on testing among populations with syndromes known to be associated with single gene disorders or among populations with single, specific birth defects.

Intervention and Comparator

For all research questions, we included studies that reported on the use of chromosomal microarray (CMA) testing (including the specific terms such as genome-wide array, genomic array, chromosomal array, chromosomal microarray, comparative genomic hybridization, deoxyribose nucleic acid (DNA) sequencing, or molecular karyotype) or whole exome sequencing (WES testing). Further, we required studies to be using these tests to identify imbalanced rearrangements, translocations, duplications, deletions, copy number variants (CNVs), or chromosomal aberrations and limited study selection for diagnostic yield (EQs1 and

2) to studies using current testing platforms. Studies that focused on fragile X testing, mutations in a single gene or a single gene panel or single gene sequencing, epigenetic testing, or whole genomic sequencing were excluded. Further, studies that used CMA or WES to identify mutations, trinucleotide repeats, or aneuploidy were excluded. For the research questions on comparative efficacy related to management and health outcomes (EQ3 and EQ4), we selected studies with comparison groups that were historical (management before/after testing) or concurrent controls (no CMA or WES testing or testing that did not include CMA or WES).

Outcomes

For the research question on safety (SQ1), we included studies that reported on harms or adverse effects of testing with CMA or WES. We excluded studies solely reporting harms associated with phlebotomy, and did not include harms or adverse effects associated with incidental findings or ethical issues associated with this testing. For the research questions on diagnostic yield (EQ1 and EQ2), we included studies that reported on the proportion of CMA and WES testing that identified a known or likely pathogenic variant among all tested children or among children or adults with the conditions of interest. For EQ3, we included studies that reported on time to diagnosis and medical or educational interventions resulting from the results of testing. For EQ4, we included studies that reported mortality, morbidity, or functional achievement. For the research question on cost (CQ1), we included studies that reported on the cost of testing, cost per patient, cost per diagnosis, cost per additional diagnosis, or cost per quality-adjusted life year or disability-adjusted life year measures from either a payer or societal perspective. Studies that did not report at least one eligible outcome were excluded.

Time Period

For EQ1 and EQ2 we selected studies that conducted testing in 2009 or later. Studies published in 2000 or later were eligible for all other research questions.

Settings

We included studies conducted in clinical settings or where the CMA or WES was being evaluated as a clinical test; we excluded studies focused on test development or that occurred strictly within a research setting without any connection to clinical practice. For EQ1 and EQ2, we excluded studies conducted outside of the U.S.

Study Design

We included all study designs except case reports.

We screened titles and abstracts and full-text articles based on these study selection criteria. Team members were trained on study selection criteria, and all team members independently screened an initial set of 20 titles and abstracts. Because we had excellent concordance among screeners on the initial set, a single team member screened the remaining titles/abstracts. The principal investigator reviewed all abstracts excluded for "ineligible intervention" and a sample of titles/abstracts excluded for other reasons to ensure continued consistency in application of study selection criteria by team members. A senior team member screened each full-text article for inclusion, and the principal investigator confirmed the decisions.

Data Abstraction and Quality Assessment

One team member extracted relevant study data into a structured abstraction form. The principal investigator reviewed the abstractions for accuracy and consistency. Two senior team members conducted independent risk of bias assessment on all included studies and met to reconcile any disagreements, in consultation with the principal investigator if needed. Because of the diverse types of studies included in this HTA, we adapted signaling questions from the QUADAS-2 instrument, a risk of bias assessment for diagnostics test studies, and items from the RTI item bank for observational studies.[41,42] The signaling questions assessed the major sources of bias including selection bias (both how study population was selected and attrition/missing data), confounding, and measurement/information bias. We used the ROBIS instrument to assess the risk of bias for systematic reviews.[43]

Data Synthesis and Analysis

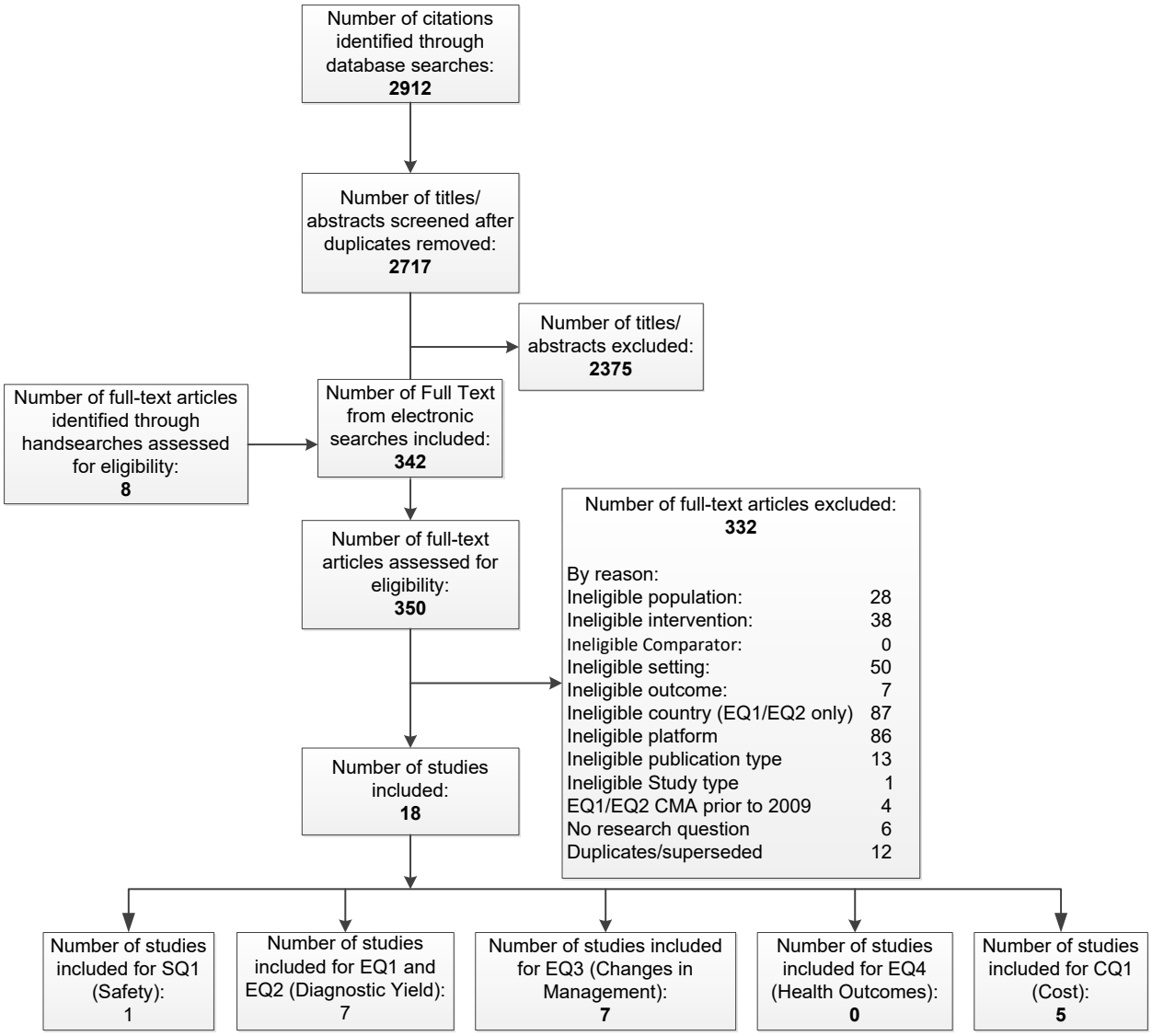
Study characteristics and results were qualitatively synthesized for each research question in tabular and narrative formats. For cost outcomes, we adjusted all reported outcomes in foreign currency to U.S. dollars based on the U.S. Department of Treasury mid-year exchange rate for the year reported by study authors and then used the chain-weighted consumer price index (CPI) to adjust to 2010 U.S. dollars (***Appendix B***).[44,45] To determine whether quantitative synthesis was appropriate, we assessed the number of studies and the clinical and methodological heterogeneity present based on established guidance.[46,47] We required three or more publications with similar approach and the same outcome measure to calculate a summary estimate. We estimated summary effects using a fixed effects model if the test for heterogeneity was nonsignificant and a random effects model if the test for heterogeneity was significant using OpenMetaAnalyst (For Windows 8, 64-bit) using the method of Hedges and Olkin to estimate between-study variance.[48] We graded the strength of evidence for each research question using GRADE, which assesses the strength of evidence based on domains relating to risk of bias, inconsistency, imprecision, indirectness, and other considerations, such as reporting bias.[49] Under GRADE, the strength of evidence can be graded as very low, low, moderate, or high.

Results

Literature Search

Figure 2 depicts the study flow diagram. We identified and screened 2,717 unique citations. We excluded 2,375 after title and abstract review. We reviewed the full-text of 348 articles, and excluded 330 for the reasons listed in ***Figure 2***. We included a total of 18 studies. One provided evidence on safety issues (SQ1), seven provided evidence on diagnostic yield (EQ1 and EQ2), seven on changes in management (EQ3), and five on costs (CQ1). No studies provided information on health outcomes (EQ4). Individual study characteristics for all included studies are summarized in ***Appendix C, Table C-1***. The list of studies we screened at the full text stage, but which were excluded from the review, is provided in ***Appendix D***. Note that studies may have been excluded based on more than one reason but we report only one reason. Individual risk of bias assessments for all included studies are reported in ***Appendix E***.

Figure 3. Study Flow Diagram



Safety

SQ1. What, if any, safety issues do CMA and WES pose beyond those associated with phlebotomy?

One study[50] provided evidence on safety issues that arise in chromosomal microarray (CMA) testing. Individual study characteristics and findings are included in ***Appendix C, Table C-1*** and ***C-2*** respectively; individual study risk of bias assessments are in ***Appendix E, Table E-1***. We did not identify any studies reporting on safety outcomes related to whole exome sequencing (WES) testing.

Study Characteristics

The sole study[50] that reported on a safety issues was related to CMA testing. Hamilton et al.[50] reported on a study of six children in the United Kingdom that evaluated the consequences of CMA testing among children in foster care.

Findings

Discrimination and social consequences. Of six children whose referral for CMA testing noted that they were in foster care, four had abnormal or ambiguous results.[50] In one of the cases of abnormal results, the application to adopt the child from foster care was withdrawn by the prospective adopters because of the chromosome abnormality that was identified with CMA testing. The 18-month-old boy had mild speech and motor delay, but showed no evidence of social disability. CMA testing detected a microduplication at 15.11.2, a variant suspected to cause behavioral difficulties and/or autism. The authors caution that data from untargeted genetic testing such as CMA or WES may be considered in ways detrimental to tested children.

Summary and Strength of Evidence: Safety

The findings are summarized in ***Table 8*** and the strength of evidence is summarized in ***Table 9***. The one included study has a very small sample and a high probability of selection bias, since four of six children identified as being in foster care had an abnormal CMA result. The study demonstrates that there are safety issues to be considered in CMA or WES testing, but the body of evidence is insufficient to estimate the frequency with which these issues arise or to compare the frequency to other types of genetic testing. We graded the strength of this body of evidence as very low because of serious study limitations in the study and the inability to evaluate inconsistency and imprecision domains.

Table 8. Summary of Findings for the Safety of Testing with Chromosomal Microarray or Whole Exome Sequencing

Author (Year)	Study Population; Sample Size	Primary Outcomes	Key Results	Risk of Bias
Hamilton (2015)[50]	Children referred for CMA testing noted as being in foster care; N=6	Adoption request for child in foster care withdrawn after report of CNV associated with autism	1 of 4 cases with abnormal results experienced discrimination	High

Abbreviations: CMA=chromosomal microarray; CNV=copy number variant.

Table 9. Strength of Evidence for Findings Related to the Safety of Testing with Chromosomal Microarray or Whole Exome Sequencing

No. of Studies; Subjects	Study Design	Risk of Bias	Inconsistency	Indirectness	Precision	Reporting Bias	Strength of Evidence Grade
1; 6	Observational	Serious[a]	Unable to assess	Not serious	Unable to assess	Not serious	Very Low

[a] Enrollment in foster care not routinely collected, only available if noted on test requisition. High risk of selection bias.

Efficacy

EQ1. How often do CMA or WES return an informative result (i.e., diagnostic yield)?

Five primary studies[51-55] and one health technology assessment (HTA)[40] provided evidence related to diagnostic yield (EQ1) and the types of clinical conditions for which CMA is most useful (EQ2). One study provided evidence related to diagnostic yield of WES testing.[56] Study characteristics and findings are summarized in ***Table 10***. ***Appendix C, Tables C-1*** and ***C-3*** provide detailed individual study characteristics and findings, respectively; individual study risk of bias assessments are provided in ***Appendix E***, ***Table 1***.

Study Characteristics

Grant et al. conducted an HTA of CMA testing that was published in 2015 and included a thorough review on the diagnostic yield of CMA in patients with global developmental delay (GDD), intellectual disability (ID), or autism spectrum disorders (ASDs).[40] This review included 67 studies published prior to June 24, 2015 that provided evidence on the diagnostic yield of CMA or its impact on clinical management decisions or patient outcomes. They included case series or cohorts of at least 20 patients with GDD with or without ID, or ASD with or without negative karyotype results. We assessed this risk of bias of this HTA as "unclear", primarily because it did not assess the risk of bias for studies included in its synthesis.

In addition to the Grant et al. HTA[40], we included four primary research studies[51,52,54,55] published from 2010 to 2015 that were included in the Grant et al. HTA, and one study[53] published in 2016, for a total of five primary research studies that provided evidence on the diagnostic yield of CMA. We also included one study of the diagnostic yield of WES.[56] Three[52,54,55] studies used oligonucleotide CMA, two[61,81] used SNP-oligo CMA, and two studies[53,81] used high-resolution SNP CMA. The patient populations of the studies were mixed. Four studies[51-54] of CMA testing reported findings for patients with congenital anomalies, DD, ID, or both DD and ID. Stobbe et al.[55] reported on CMA results among adults with ASD. The single study reporting on diagnostic yield of WES testing[56] reported findings for children with ID.

The methods for classifying a variant as pathogenic or likely pathogenic varied across studies. Coulter et al.[51] classified a variant as pathologic if it was 1) associated with a known microduplication or deletion syndrome, 2) a deletion of genes that are known to cause disease when haploinsufficient, 3) or a large (size unspecified) duplication or deletion. A variant was classified as possibly pathogenetic if it overlapped a known syndromic region, or contained genes suspected of causing disease, with the potential unmasking of recessive alleles. Henderson et al.[52] defined variants as pathologic if they were 1) associated with a known microduplication or deletion syndrome, 2) encompassed or interrupted genes associated with disease, 3) included numerous genes and were not found in healthy individuals, or 4) were a region of homozygosity greater than 10 Mb. Ho et al.[53] classified variants as pathologic if they were found in less than 1% of the general population and there were at least two independent peer-reviewed reports that haploinsufficiency or triplosensitivity of the region or gene(s) caused clinical symptoms similar to those of the patient. Roberts et al. [54]classified variants as pathologic if they had previously been associated with ASD or learning disability. They evaluated variants using the University of California at Santa Cruz (UCSC) Genome Browser,[82] Database of Genomic Variants (DGV),[83]

Online Mendelian Inheritance in Man (OMIM),[84] (DECIPHER),[85] dbVar,[86] and CombiTrak, an internal database. Strobbe classified variants as likely pathogenic if a prior case report including well-defined breakpoints and well-specified phenotype linked the variant to autism or if the duplication or deletion included a gene for which there was compelling and specific evidence that it was associated with autism. Bowling et al. [56] defined variants or mutations as pathogenic if they resulted in loss-of-function (LOF) of genes where LOF is a known disease mechanism; if the mutation was a missense mutation known or computationally predicted to cause disease; if the mutation or variant was de novo and predicted to be damaging or to cause LOF in a gene known to cause dominantly inherited disease; if the individual had compound heterozygotes for two recessive alleles in a gene associated with recessive genetic disease, both alleles were predicted to be damaging, and the population frequency of each is low enough to plausible given the incidence of disease. We rated Coulter et al. [51] as having an unclear risk of bias, primary because of incomplete reporting on their microarray platform. The other five studies were rated as having a low risk of bias.

Our exclusion of diagnostic yield studies conducted outside of the United States substantially reduced the number of studies we included compared to the number included in the Grant et al. HTA[40] Of the 31 studies published in 2010 or later that were included in the Grant et al. HTA, 24 were not conducted in the U.S., and five studies were excluded from our review because of obsolete platforms or testing was conducted prior to 2009 (***Appendix D***).

Findings

Diagnostic Yield of CMA Testing. The median diagnostic yield for CMA testing among patients with GDD with or without ID in the Grant et al. HTA was 13.6% [interquartile range (IQR), 9.5 to 17.2%] across 55 applicable studies in this HTA, and was 19% among the 21 studies published in 2012 or later.[40] Diagnostic yield of CMA among patients with GDD increased by 1% per year on average. For patients with ASD, the median diagnostic yield among 12 relevant studies was 8.4% (IQR,7.2% to 17.3%) and was 12.3% among the four studies published in 2012 or later.

Table 10 summarizes the study characteristics and findings related to diagnostic yield among the five primary research studies on CMA testing that we included. The pooled summary estimate of diagnostic yield, from these studies including known and likely pathogenic variants, was 8.8% (95% CI, 8.4% to 9.3%) (***Figure 3***). The individual study estimates ranged from 7.3%[51] to 14.9%.[54] The studies were heterogeneous ($p < 0.001$), so a random effects model was used to calculate the pooled summary estimate.

Table 10. Summary of Findings for the Diagnostic Yield of Testing with Chromosomal Microarray or Whole Exome Sequencing

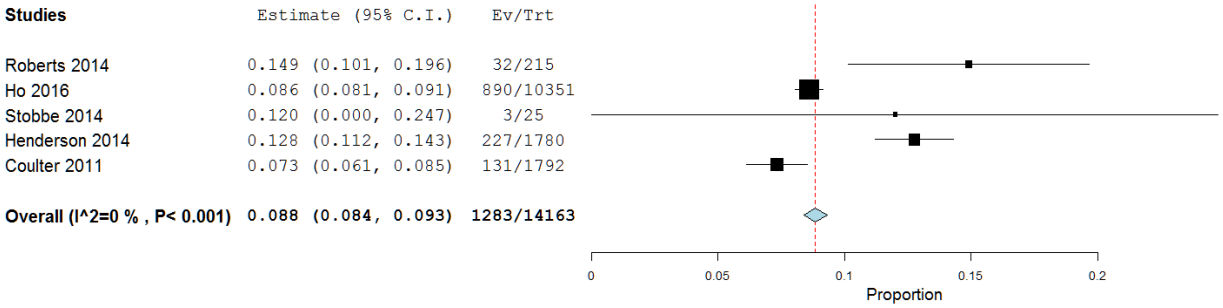
Author (Year)	Study Population; Sample Size, Test	Diagnostic Yield [Detection of A Pathogenic Variant] N (%)	Risk of Bias
Bowling (2017)[56]	Clinic-based family recruitment of children with mild to severe ID, age ≥ 2; N=365, WES	CNV only: 2 (1.6%) Total: 100 (27%)	Low
Coulter (2011)[51]	Patients of children's hospital; N =1,792, CMA	131 (7.3%)	Unclear
Henderson (2014)[52]	Laboratory-based series of patients; N= 1780, CMA	227 (12.7%)	Low

Author (Year)	Study Population; Sample Size, Test	Diagnostic Yield [Detection of A Pathogenic Variant] N (%)	Risk of Bias
Ho (2016)[53]	Laboratory-based series of patients with neurodevelopmental disorders; N=10,351, CMA	890 (8.6%)	Low
Roberts (2014)[54]	Laboratory-based series of patients with mixed phenotypes of ID/MCA; N=215, CMA	32 (14.9%)	Low
Stobbe (2014)[55]	Clinic-based study of adults with autism; N=25, CMA	2 (12.0%)	Low

Abbreviations: CMA=chromosomal microarray; CNV= copy number variant; ID= intellectual disability; MCA=multiple congenital anomalies; VUS=variant of undetermined significance; WES=whole exome sequencing.

Figure 4. Summary Pooled Estimate for Diagnostic Yield of Chromosomal Microarray for All Included Phenotype

Diagnostic Yield of WES Testing. One study (Bowling et al.[56]) examined the diagnostic yield



Bowling et al.[56] evaluated use of WES among 371 cases with DD or ID aged 2 years or older. A pathogenic or likely pathogenic mutation or CNV was identified in 100 (27.1%) cases, of which 92 (24.8% of all cases) were single gene mutations and eight (2.2% of all cases) were CNVs.

Summary and Strength of Evidence: Efficacy of Diagnostic Yield

The pooled average diagnostic yield from the five primary research studies we included was 8.8% (95% CI, 8.4% to 9.3%), lower than the diagnostic yield reported by the Grant et al. HTA (19% for GDD [with or without ID] among studies published in 2012 or later. This difference was due to two factors. Diagnostic yield averaged five percentage points higher among studies conducted outside of the United States than studies conducted in the United States, and averaged four percentage points lower among studies published in 2010 or 2011 than ones published in 2012 or later.

The studies included in this body of evidence are predominantly consecutive case series from individual clinical laboratories. Most studies included a mix of phenotypes, including DD, ID, and ASD, and multiple congenital anomalies (MCAs). The definition of pathogenic variant used in the studies varied, partially because the tools for assessing pathogenicity have evolved. Although all the definitions used are valid, the differing definitions may account for some of the variability in the findings. These studies are likely applicable to diagnostic yield in clinical practice; however, they may have included some patients with indications that did not fit our inclusion criteria. Although most of these studies have a low risk of bias, because of

observational study designs the strength of evidence cannot be graded any higher than low (***Table 11***).

Only one study[56] provided evidence on the diagnostic yield of WES testing. They identified 2 copy number variants, a diagnostic yield of 1.6%. Most probands had been previously tested with chromosomal microarray. The total diagnostic yield, including single nucleotide variants and indels, was 27.1%. No confidence intervals were provided for this observational study, thus we graded the strength of evidence for WES testing as very low.

Table 11. Strength of Evidence for Findings Related to the Diagnostic Yield (EQ1) of Testing with Chromosomal Microarray or Whole Exome Sequencing

Outcome	Number of Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirectness	Precision	Other consider-ations	Strength of Evidence Grade
Diagnostic yield of CMA Range 7.3% to 14.9%	5; 14,795; Obser-vational	Not serious	Not serious	Not serious	Not serious	Definition of outcome	Low
Grant et al. 19%	21; 6,662 Obser-vational						
Diagnostic yield of WES CNV only: 1.6%	1; 632; Obser-vational	Not serious	NA, single study	Not serious	Serious[a]	None	Very low

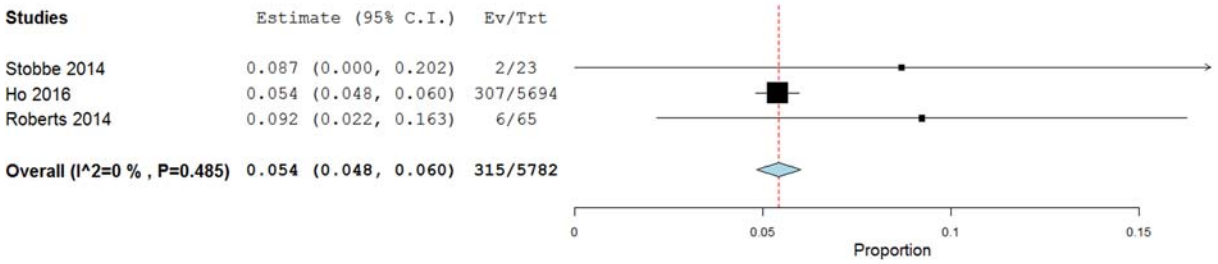
Abbreviations: CMA=chromosomal microarray; NA= not applicable; WES=whole exome sequencing.

[a] No confidence intervals or other estimates of precision provided.

EQ2. For what types of conditions is CMA or WES most useful?

Although some studies reported on diagnostic yield by patient characteristics or specific diagnosis, most factors were only examined in a single study. Thus, we were unable to evaluate the diagnostic yield for most individual phenotypes. However, three studies, Stobbe et al.,[55] Ho et al.,[53] and Roberts et al.[54] reported the diagnostic yield of CMA among patients whose indication for testing was ASD. The summary estimate of diagnostic yield was 5.4% (95% CI, 4.8% to 6.0%) as depicted in ***Figure 4***. We used a fixed effects model to calculate the summary estimate because the test for heterogeneity was nonsignificant ($p > 0.05$). As with the estimate for all phenotypes, our estimated diagnostic yield is lower than that of Grant et al. who found an average diagnostic yield of 12.3% for ASD among studies published after 2012.[40]

Figure 5. Evidence on Diagnostic Yield of Chromosomal Microarray for Autism Spectrum Disorders



EQ3. Does the diagnosis of a chromosomal disorder change the child's management?

Seven studies[51,52,57-61] evaluated the impact of CMA testing on the management of children with ASD, DD, ID, or MCA.[51,52,57-61] Study characteristics and findings are summarized in ***Table 12, Appendix C, Table C-1*** and ***Table C-4***, provide detailed individual study characteristics and results, respectively; ***Appendix E***, ***Table 1*** provides individual study risk of bias assessments.

Study Characteristics

Included studies used two different approaches to addressing this research question. Two studies[57,59]evaluated queried databases to identify CMA-tested cases with abnormal variants that had implications for medical management.[57,59] Ellison[57] and five additional studies[51,52,58,60,61] measured actual actions taken as a result of the CMA results, four[51,52,58,61] by medical record review and two[57,59] by physician survey. Five[51,52,57,59,60] of the studies were conducted in the U.S., although the databases that Riggs et al.[59] and Ellison et al.[57] used could have contained cases from other countries. Hayeems et al.[58] was conducted in Canada, and Tao et al.[61] in Hong Kong. The studies were conducted between 2008 and 2013, and included patients tested between 2004 and 2013. Three[52,58,61] of the studies were rated as low risk of bias, two as unclear risk of bias,[51,60] and two as high risk of bias.[57,59] The reasons for the ratings were lack of detail on testing methodology[51] or variant classification[51,57,59] or potential recall bias.[57,60] We did not identify any studies that evaluated the impact of WES testing on clinical management.

Except for Hayeems et al.,[58] these studies limited their population to patients diagnosed with a pathogenic or likely pathogenic variant and only counted management changes attributable to the CMA results. Hayeems et al.[58] included all patients with detected CNV, and compared management changes, in total and the number attributable to the CMA results, for patients with pathogenic or likely pathogenic variants to management changes for patients with benign variants.

The methods for classifying a variant as pathogenic varied among the studies. Hayeems et al.[58] and Saam et al.[60] relied primarily on the clinical laboratory report. If the laboratory report did not classify the variant, Hayeems classified it according to the American College of Medical Genetics (ACMG) guidelines.[13] Tao et al. also used the ACMG guidelines to classify variants, referring to internal and public databases of variants to aid in the classification. Coulter et al.[51] and Henderson et al.[52] classified as pathogenic known microduplication or microdeletion syndromes, large duplications or deletions, and deletions that encompassed genes known to

cause disease when haploinsufficient[51] or associated with genetic disease.[52] Henderson et al. also classified as pathogenic large (>10 Mb) regions of homozygosity.[52]

Ellison et al.[57] reviewed the results of all patients with CMA testing in Signature Genetics' laboratory database to identify those with abnormal results that were clinically actionable. They defined a clinically actionable variant as one that was associated with a microduplication or microdeletion syndrome with features that require specific follow-up (40 variants), that were associated with increased cancer susceptibility (27 variants), or that involved known dosage sensitive genes that cause genetic disease requiring specific follow-up (38 variants).[57]

Riggs et al. identified genes covered by the International Standards for Cytogenomic Arrays (ISCA) Consortium 180k array design that were associated with a syndrome described in Gene Reviews, DECIPHER (https://decipher.sanger.ac.uk/syndromes), or the ISCA Consortium's known pathogenic list (http://www.ncbi.nlm.nih.gov/dbvar/studies/nstd45/), a total of 205 syndromes for a total of 235 phenotypes.[59] They excluded 49 phenotypes as not diagnosable by CMA. Of the 186 phenotypes diagnosable by CMA, 146 (79%) had specific medical management recommendations based on professional guidelines (level 1) or peer-reviewed publications (level 2) and were classified as clinically actionable.

All studies defined management change to include specialist referrals, diagnostic testing, changes in medical surveillance or screening, surgical or intervention procedures, and prescribed or contraindicated medications specifically related to the CMA results. Riggs et al.[59] and Tao et al.[61] also included recommendations for lifestyle changes. Saam et al.[60] included changes in counseling on recurrence risk and improved access to services.

Findings

In 27.1% to 93.8% of children with a pathogenic variant on CMA testing, a management change occurred because of the new information provided by the CMA results. ***Table 12*** summarizes the findings related to the impact on clinical management of CMA testing for the seven primary research studies we included**.** Among the three studies that measured management changes using medical record review, in 53.7% to 75.7% of cases with a pathogenic variant at least one management change occurred because of the new information provided by the CMA results. The cases with management changes represented 3.6% to 6.7% of all cases tested, which is similar to the proportion of clinically actionable variants identified by Ellison et al.[57] and Riggs et al.[59] Of the 46,298 patients with CMA results in their laboratory database, 1,996 (4.3%) had variants defined by Ellison et al. as clinically actionable.[57] Of 28,526 cases in the ISCA database, 1,908 (6.8%), were clinically actionable.[59] Almost half, 48% of the pathogenic variants in the ISCA database were clinically actionable. Hayeems et al.[58] found that patients with a pathogenic variant received an average of 2.4 medical management recommendations directly related to their CMA results and were 36% (RR, 1.36 [95% CI, 1.21 to 1.53]) more likely to have changes in management than patients with a benign variant on CMA testing.

Table 12. Summary of Findings for the Impact of Chromosomal Microarray Testing on Clinical Management

Author (Year)	Study Population; Sample Size	Outcome Definition	Result[a]	Risk of Bias
Coulter (2011)[51]	Retrospective clinic-based cohort of all children with CMA Total tested: 1,792 Total with pathogenic or VUS: 235 Eligible for follow-up study: 194	At least one management change (surveillance start/stopped, referral, diagnostic testing) due to pathogenic CNV.	65 (53.7% of follow-up study; 3.6% of all tested)	Cannot determine
Ellison (2012)[57]	Retrospective laboratory-based cohort. Total tested: 46,298 Clinically actionable CNV: 1,996	Patients with clinically actionable CNV (known microdeletion or duplication syndrome, increased cancer susceptibility, deleted genes associated with genetic disease requiring follow-up).	1,996 (4.3%)	High
	Patients whose physicians were surveyed: 122 Responses received: 81	At least one guideline-recommended management change (not specified) due to pathogenic CNV	74 (93.8%)	
Hayeems (2015)[58]	Retrospective clinic-based cohort. of all children with CMA testing followed at tertiary pediatric hospital; N=752	Average number of recommendations (surveillance, referral, diagnostic testing, medication indication/contraindication, family testing) due to pathogenic CNV	Mean 2.35 recommend-ations per patient	Low
Henderson (2014)[52]	Retrospective laboratory-based cohort of all children with CMA testing Tested: N=1,780 Pathogenic CNV: 227 Follow-up available: 187	At least one management change (surveillance, referral, diagnostic testing, medical/surgical procedure, medication indication, contraindication) due to pathogenic CNV	102 (54.5% of follow-up study; 5.7% of total tested)	Low
Riggs (2014)[59]	Retrospective case series of syndromes diagnosable by CMA; N=28,526 Pathogenic and likely pathogenic: 4,125	At least one management change (referral, diagnostic testing, surgical/intervention procedures, surveillances, medication, contraindication, lifestyle changes) due to pathogenic CNV	1,908 (46.3% of pathogenic; 6.7% of all tested)	High
Saam (2008)[60]	Retrospective case series of patients with abnormal CNV; N=48	At least one management change (referral, screening, stop screening) due to pathogenic CNV	13 (27.1%)	Cannot determine
Tao (2014)[61]	Retrospective case series of children with ID/DD, ASD, or MCA; N=327	At least one management change (surveillance, referral, diagnostic testing, medical/surgical procedure, medication indication, contraindication, lifestyle recommendation) due to pathogenic CNV	28 (75.7%)	Low risk of bias

Abbreviations: CMA=chromosomal microarray; CNV= copy number variant; DD=developmental disability; ID= intellectual disability; MCA=multiple congenital anomalies; VUS=variant of undetermined significance.

[a] Confidence intervals were not reported by study authors unless specified.

Recommended changes to medical surveillance for cancer or other conditions resulted from CMA test results in up to 50% of cases. CMA may identify an increased risk of cancer susceptibility among the population of children with ID, DD, MCA, or ASD in three ways: 1) increased cancer susceptibility that is a known feature of the syndrome that also causes the phenotype for which they were tested (i.e., Beckwith-Widermann or Rubinstein-Taybi syndrome), CNVs that involve a cancer susceptibility gene as well as other genes that are likely to cause the phenotype, and 3) CNVs that are unlikely to have produced the observed clinical phenotype that involve a cancer susceptibility gene (secondary finding). CMA may also find that a presumed diagnosis that indicates an increased risk of cancer is incorrect, negating the need for frequent cancer screening.

Except for Saam et al.,[60] the studies reviewed here limited their consideration of the impact of CMA testing to short-term clinical management of the proband. Saam et al. considered two additional applications of CMA testing results to management: increased access to services and more accurate estimation of recurrence risk. CMA diagnosis provided easier access to services for 25% of the cases and more accurate estimation of recurrence risk for family counseling in 35% of the cases.

Summary and Strength of Evidence: Efficacy for Impact of Testing on Clinical Management

The proportion of cases with a pathogenic variant that had a change in management prompted by CMA testing ranged from 27.1% to 93.8%. However, the body of evidence comprised exclusively of observational study designs also had serious concerns in all four domains, and we graded the strength of the evidence as very low (***Table 13***). As discussed above, four of seven studies were rated as having an unclear or high risk of bias due to unreported study information or potential recall bias. Only three studies measured impact directly by documented management changes in the medical record. The estimates of impact were inconsistent.

Table 13. Strength of Evidence for Findings Related to the Impact of Testing with Chromosomal Microarray on Clinical Management (EQ3)

Outcome	Number of Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirect-ness	Precision	Other Consider-ations	Strength of Evidence Grade
Percentage of patients with abnormal results that have a change in management range 27.1 to 93.8%	7; 658; Obser-vational	Serious[a]	Serious[b]	Serious[c]	Serious[d]	None	Very low

[a] Potential for recall bias when changes in management collected by physician interview, lack of detail in determining clinical actionability by retrospective review, potential conflict of interest due to goal of promoting reimbursement for CMA.

[b] Wide range of findings among studies.

[c] Three studies measured actionability based on published guidelines and recommendations, not actual changes in management for tested patients.

[d] None of the studies provided confidence intervals or other measures of precision. Sample sizes were small to moderate.

EQ4. Do children with congenital defects, autism, intellectual disability, or developmental disability tested with CMA or WES have better health outcomes?

We did not identify any studies that reported on health outcomes among children tested with CMA or WES, either as single-arm studies or compared to patients not tested or tested with other platforms.

Cost and Cost-Effectiveness

CQ1. What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with CMA or WES?

We identified five eligible studies reporting cost, cost per patient, cost per diagnosis, or cost per additional diagnosis.[62-66] All identified studies were specific to CMA testing; no studies evaluated WES testing or reported cost-effectiveness based on cost per quality-adjusted or disability-adjusted life year. Study characteristics and findings are summarized in ***Table 9***. ***Appendix C, Tables C-1*** and ***C-5A,*** provide individual study characteristics and findings respectively. ***Appendix E***, ***Tables E-1 and E-2,*** provide individual study risk of bias assessments.

Study Characteristics

The populations included across the five studies varied; two focused exclusively on children with ID[65,66] one focused exclusively on children with DD,[63] and two included a mixed population of children with ID, DD, or both.[62,64] Studies evaluated the use of CMA as a first-line test for diagnostic evaluation, in comparison to karyotype as a first-line test in three studies,[64-66] and in comparison to metabolic, genetic, imaging, or tissue biopsy testing in two studies.[62,63] All studies reported cost-related outcomes from a payer perspective, and studies were highly varied as to what type of costs were included, and the currency year for which outcomes were reported. Because of this heterogeneity, we did not quantitatively synthesize findings. The authors conducted these studies from 2005 to 2009. Three studies used a retrospective cohort design with sample sizes ranging from 46 to 1,590,[62-64] while two studies used decision analysis with a hypothetical cohort of participants.[65,66] Three studies were conducted in the United Kingdom[62,64,66] and two were conducted in Canada.[63,65] We rated all included studies for the cost outcomes as having a low risk of bias.

Findings

Costs per array varied across studies and by testing platforms; these costs ranged from $271 to $1,575 (in 2010 U.S. dollars). These costs reflect the cost per array, which was only one of several costs used to estimate overall costs of CMA testing compared to no CMA testing. The wide variation in costs per array can largely be attributed to the use of different testing platforms, in different years and the use of commercial laboratories (higher cost per array) compared with hospital-based laboratories (lower cost per array).

The cost per patient and cost per diagnosis estimated with CMA testing compared to no CMA testing is summarized in ***Table 14*** and is organized by phenotypes evaluated. We converted and reported all outcomes in 2010 U.S. dollars for comparison across studies. ***Appendix C, Table C-5B,*** provides this same data in the currency and year reported by study authors. Studies reported cost per patient tested, cost per diagnosis rendered, and cost per additional diagnosis rendered,

Table 14. Summary of Findings of Studies Evaluating Cost Outcomes of Chromosomal Microarray Testing, Outcomes Reported in 2010 U.S. Dollars

Phenotype	No. of Studies (No. of Participants)	Cost Per Patient or Diagnosis (95% CI)			Difference in Cost (95% CI)	Cost per additional diagnosis
		Outcome	CMA Testing	No CMA Testing		
Intellectual Disability	2 (NA[a])	Cost per diagnosis[65]	$2,919[b] (2,671 to $3,188)	$2,707 (2,448 to 2,990)	$213 (168 to 256)	$2,592 ($1,586 to $5,188)
		Cost per diagnosis[66]	$6,269[c] (NR)	Range $4,280 to $9,966[d]	Range -$3,697 to $1,988[d]	Range[e] -$370 to $199
Developmental Delay	1 (114)[63]	Cost per patient	NR	NR	-$101 (98% CI, -$186 to -$16)[f] $402 (98% CI, $227 to $577)[g]	NA
		Cost per diagnosis	NR	NR	NR	$1,317 (NR)[f]; $12,296 (NR)[g]
Intellectual disability or developmental delay or both	2(1,636)	Cost per patient	$2,536 (NR)[62] $415 (range $271 to $1,792)[64]	$3,223 (NR)[62] $759 (range $556 to $2,029)[64]	-$687 (NR, p=0.34)[62] -$344 (95% CI, -$366 to -$322)[64]	NA
		Cost per diagnosis	Range $4,381 to $7,757[62] $3,625 (NR)[64]	NR[62] $6,866 (NR)[64]	NR[62] $-3,241 (95% CI NR)[64]	$4,381 (NR)[62] $-88,819 (NR)[64]

Abbreviations: CMA=chromosomal microarray; CI=confidence interval; NA=not applicable; NR=not reported.

[a] Both studies were conducted using decision analyses using hypothetical cohorts; thus, the sample size is not applicable

[b] Assumes that CMA testing increases diagnostic yield from 19.2% to 27.5%

[c] Assumes that CMA testing increases diagnostic yield from 8% to 18%, cost per diagnosis is 2440 with a 15% absolute increase in diagnostic yield.

[d] Depending on which kinds of follow-up testing after karyotype used.

[e] Calculated based on data provided in the study.

[f] When using local hospital laboratory for testing.

[g] When using commercial laboratory for testing

which is the outcome that measures the incremental cost of first line CMA testing versus testing without CMA per the additional diagnoses rendered by CMA testing compared to testing without CMA. A negative value for this outcome suggests that first-line CMA testing compared to no CMA testing provides additional diagnoses at a cost savings. A positive value for this outcome suggests that testing does not save money, but could be cost-effective depending on the amount a decisionmaker is willing to pay for a higher diagnostic yield.

Cost Per Additional Diagnosis: Intellectual Disability. Regier et al. and Wordsworth et al. studied children with ID using decision analyses conducted with hypothetical cohorts.[65,66] The cost per diagnosis was higher in both arms of one study[66] compared with the other study.[65] However, the study with lower costs per diagnosis estimated a higher cost *per additional* diagnosis ($2,592 [95% CI $1,586 to $5,188]) compared with the other study (range estimated to be between $-370 to $199 *per additional* diagnosis). These studies did not use similar cost inputs and assumed different diagnostic yield estimates, both of which explain the variation in estimates.

Cost Per Additional Diagnosis: DD. Trakadis et al., studied cost outcomes among children with DD.[63] In this retrospective cohort of 114 children, eight additional diagnoses were made as a result of CMA testing compared with no CMA testing. This study estimated that the difference in cost per patient tested (CMA tested versus not CMA tested) was -$101 (98% CI, -$186 to -$16) when array testing was performed by a local hospital laboratory and $402 (98% CI, $227 to $577) when testing was performed by a commercial laboratory. This translated to a cost *per additional* diagnosis of $1,317 (local hospital laboratory) to $12,296 (commercial laboratory).

Cost Per Additional Diagnosis: Mixed Populations. Finally, Newman et al. and Sagoo et al. studied cost outcomes among children with ID, DD, or both. Although the costs per patient tested were much higher in both arms in one study[62] compared with the other study,[64] the difference in cost per patient (CMA tested versus not tested) between studies was similar (-$687 and -$344, respectively). Newman et al. reported a cost *per additional* diagnosis of $4,381 while Sagoo et al. reported a cost *per additional* diagnosis of $-88,819. The difference in findings between these two studies can largely be explained by a large difference in cost per diagnosis favoring CMA testing in the Sagoo et al. study since the absolute increase in diagnostic yield in Sagoo et al. was minimal (11.05% in non-CMA tested arm, 11.44% in CMA tested arm).

Summary and Strength of Evidence: Cost and Cost Effectiveness

The cost *per additional* diagnosis across this body of evidence ranged from $-88,819 to $12,296 (in 2010 U.S. dollars). ***Table 15*** summarizes the strength for evidence about the cost-effectiveness of diagnostic evaluations that use first-line CMA testing compared with those that do not use first-line CMA testing. Although this body of evidence did not have any serious concerns for risk of bias, we identified serious concerns related to inconsistency and imprecision. Further, we rated the indirectness the outcome reported (costs per additional diagnosis) as having very serious concerns given that this measure is a surrogate outcome and not a direct reflection of patient health outcomes. Because of these concerns, we graded the certainty of this estimate as very low.

Table 15. Strength of Evidence for Findings Related to the Cost-Effectiveness of Chromosomal Microarray Testing Compared to No Testing (CQ1)

Outcome	Number of Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirect-ness	Imprecision	Other Consider-ations	Strength of Evidence Grade
Cost per additional diagnosis range $-88,919 to $12,296	5; 1,750[a] Observational and decision analyses	Not serious	Serious[b]	Serious[c]	Very serious[d]	None	Very low

[a] Total sample size from three retrospective cohort studies; two additional studies generated outcomes based on decision analyses among hypothetical cohorts.

[b] Clinical and methodological heterogeneity likely explains most of inconsistency in results, though it is unclear to what extent these factors can explain the degree of inconsistency noted.

[c] Cost per additional diagnosis is a surrogate outcome; this outcome presumes that additional diagnoses would leave to changes in management that ultimately would lead to improved health outcomes.

[d] Few studies provided confidence intervals around estimates; optimal information size criteria likely not met by any included studies.

Discussion

Summary of the Evidence

The strength of the evidence for all included research questions was very low (safety, impact on clinical management, and costs) or low (diagnostic yield). We identified no eligible studies addressing the impact of chromosomal microarray (CMA) or whole exome sequencing (WES) testing on patient health outcomes. Key findings include:

- Safety: The only safety concern that we identified based on one included study is discrimination because of the test results. The body of evidence was not sufficient to determine the frequency with which these issues may arise in CMA testing compared to other types of genetic tests. We graded the strength of the evidence related to safety as very low. We identified no studies that reported safety outcomes related to WES testing.
- Diagnostic yield: In studies that conducted testing in the U.S. in 2009 or later, CMA testing identified pathogenic or likely pathogenic variants in 8.8% (95% CI, 8.4% to 9.3%) of children tested for any reason, and 5.4% (95% CI, 4.8% to 6.0%) of children referred for an autism spectrum disorder (ASD). A previous health technology assessment (HTA) by Grant et al. that included U.S. and international studies found that among studies published in 2012 or later, the diagnostic yield averaged 19% for global developmental disability (GDD) with or without intellectual disability (ID) and 12% for ASD.[40] This HTA also reported that diagnostic yield increased 1% per year on average between 2004 and 2015. We graded the strength of the evidence for diagnostic yield of CMA testing as low. One primary research study of WES reported a diagnostic yield of

27% (95% CI, NR) and we graded the strength of evidence on diagnostic yield of WES testing as very low.

- Impact on clinical management: CMA results prompted changes in clinical management in 27% to 94% of patients with a pathogenic variant, which was 3.6% to 6.7% of all patients tested. Considering only studies that measured management changes by medical record review, CMA results changed clinical management in 54% to 76% of patients. We graded the strength of this evidence as very low. We identified no studies reported on change in management related to WES testing.

- Costs: The cost per additional diagnosis across this body of evidence ranged from $-88,819 to $12,296 (in 2010 U.S. dollars). No studies reported on cost-effectiveness (i.e., cost per quality-adjusted or disability-adjusted life year). We graded the strength of evidence on costs as very low.

Additional Context for Interpreting Findings

Our review revealed some aspects of CMA and WES testing that, though outside the scope of our systematic review, may add to the interpretation of our results.

Diagnostic Yield of CMA in General Population

CMA testing among biobank samples drawn from the general population of Estonia and tied to a database with phenotype information found 56 (0.7%) of 7,877 enrollees had a DECIPHER-listed pathogenic variant.[67] The study did not include a clinical evaluation, but 70% of the 56 individuals with a pathogenic variant reported clinical features consistent with their genetic findings.

Analytic Validity of Commercial CMA Kits

Compared to sequencing, the Affymetrix® CytoScan® Dx Assay identified 98.8% (95% CI: 93.5%, 99.8%) of duplications and 97.3% (92.3%, 99.1%) of deletions with a size of 1000 base pairs or more. The false positive rate, compared to sequencing, was 1.2% (0.2%, 6.5%) for duplications and 2.7% (0.9%, 7.7%) for deletions of 1000 base pairs or larger. The Agilent GenetiSure Dx Postnatal Assay identified 81.0% (74.3%, 86.2%) of duplications and 88.2% (84.6%, 91.0%) of deletions that were 1,000 to 10,000 base pairs. The false positive rate for 1,000 to 10,000 base pair duplications was 19.0% (13.8%, 25.7%) and 11.8% (9.0%, 15.4%) for deletions of this size. For copy number variants (CNVs) of 10,000 base pairs or larger, the kit identified 97.6% (94.0%, 99.1%) of duplications and 96.9% (93.4%, 98.6%) of deletions, with false positive rates of 2.4% (0.9%, 6.0%) and 3.1% (1.4%, 6.6%), respectively.

False Negatives

As reported by D'Amours et al.,[81] some array software may return false positive results by incorrectly calling a CNV that does not exist, or falsely identifying an inherited variant as de novo. None of the studies included in this review reported the number of false negative results, which is the failure to identify a chromosomal abnormality identified by karyotype or fluorescent in situ hybridization (FISH). Bi et al.[16] reported that CMA failed to detect an abnormality in 0.24% of all cases tests by CMA and karyotype. CMA missed 6 of 43 cases of mosaicism and 29 of 30 balanced rearrangements; thus, testing with CMA may not identify low-level mosaicism or most balanced translocations.

False positives

D'Amours et al.[81] compared CMA results for 21 children with DD or ID across four high-resolution SNP arrays and the moderate-resolution oligo-array in use for clinical diagnosis at the time of the study. All four SNP arrays identified pathogenic abnormalities in six (28.6%) patients; the oligo-array only identified three (14.3%) of the six abnormalities. Three of the four SNP platforms identified a total of 17 false CNVs. The false positive rate among these arrays ranged from 0% to 5.8%. The false positives resulted from false calls by the platform software or incorrect assignment as de novo because the software did not detect the parental CNV. The authors concluded that high-resolution SNP arrays increase diagnostic yield, but that different platforms vary significantly regarding false positive CNV identification and breakpoint accuracy.

Incidental Findings

Ethical issues concerning secondary findings from genetic sequencing have been widely discussed, resulting in American College of Medical Genetics (ACMG) guidelines on reporting clinically actionable findings.[23,87] Bowling et al.[56] found 55 (9%) pathogenic or likely pathogenic genetic variants unrelated to DD or ID among 605 tested parents of affected children. Nine variants (1.5%) were related to a disorder that the parent self-reported, 12 (2.0%) were one of 56 genes ACMG identified as having potentially clinically actionable variants, and 28 parents were carriers for an autosomal recessive disorder. One couple both carried an allele for the same autosomal recessive disorder, giving them a 25% risk of having a child with the disorder.

Impact on Management and Outcomes

Although we did not identify any eligible studies that evaluated the impact of CMA and WES testing on health outcomes, Saam et al. reported that CMA testing increased access to services, such as public health insurance, among children with a pathogenic variant.[60] Children referred for CMA testing have complex medical and developmental conditions. As reported in our results section, Hayeems et al.[58] found 80% of children with a reportable variant and 62% of children with a benign variant received medical recommendations after their CMA testing. Improved access to insurance or to early invention services may improve long-term health or social outcomes for children with DD, ID, or ASD.[88-90]

Limitations of the Evidence Base

The body of evidence on safety, impact on management changes, and cost was limited in size, risk of bias, and applicability, limiting our ability to draw strong conclusions for these research questions. Further, almost all studies we included focused on CMA. Clinical use of WES is still new, and the body of evidence regarding its impact is limited.

Most of the studies reporting on diagnostic yield included some cases for indications other than our population of interest. In addition, prior diagnostic testing received by the cases varied. Diagnostic yield may differ among more homogenous case series. This factors may explain some of the difference between our summary estimate of 9% and the median diagnostic yield of 19% among studies published since 2012 that was observed by Grant et al.[40] Differences in methods of calling pathogenic variants or access to family history or parent samples may contribute to the differences in diagnostic yield.

Studies evaluating the impact of testing on management were small, so each included only a small portion of known microduplication or microdeletion syndromes. The clinical features of these syndromes and the appropriate management actions vary accordingly, and are likely an explanation for the large heterogeneity of estimates on impact on management we observed across studies. Further, the estimated proportion of cases whose management is impacted by their CMA results may not apply across the population of children for whom CMA is ordered because most included studies were limited to patients followed by a single institution. The two studies that included a broader population of patients measured outcomes by physician survey or interview, which could be subject to recall bias, reporting bias, and response bias.

The body of evidence related to cost and cost-effectiveness is limited by the lack of studies conducted in the United States and the absence of a societal perspective in any of the analyses. Given large differences in the access to health care and its financing between the U.S. and non-U.S. countries, it is not clear whether the findings observed in the studies we identified apply to U.S. settings. Further, this body of evidence is limited by extreme clinical and methodological heterogeneity, which most likely explains the inconsistency in costs per additional diagnosis that we observed. Because CMA and WES tests have rapidly evolved over the past decade, the genetic assay costs used in the included studies may no longer be accurate. Further, the precise role of these tests in the overall sequence and approach to diagnostic evaluation in children with DD, ID, and ASD has also evolved: the cost of the diagnostic journey with or without CMA testing reflected in the included studies may no longer be relevant to current clinical practice.

Across the body of evidence for all research questions, study design, study population, and outcome measurement details were often sparse, resulting in our inability to assess the risk of bias for some studies. One aspect of evaluating the risk of bias not addressed in existing instruments we used are the financial or intellectual conflicts of interest of the study authors. Authors of several included studies stated that a goal of the research was to provide evidence of clinical utility to get CMA covered by payors, potentially providing a strong incentive for analytic decisions that would increase the estimate of diagnostic yield or impact on management.

Limitations of this HTA

We did not include studies published in languages other than English and only searched two U.S.-based electronic databases. These were pragmatic decisions but may have resulted in missing relevant studies; however, we conducted extensive hand searches of the reference lists of included studies and believe the possibility of missing a study that would have altered the findings to be low. For pragmatic reasons, we used a single reviewer to screen most titles/abstracts, which may have led to studies inappropriately excluded. However, we had an excellent concordance initial set of 20 independently dual-reviewed set of titles/abstracts; the principal investigator checked all studies excluded for ineligible intervention and randomly checked a subset of other excluded studies to minimize this possibility. WES studies may have been more likely to be missed or inappropriately excluded because the distinction between test validation and clinical studies was unclear, and because we did not identify any systematic reviews or HTAs of this test.

For the research question related to diagnostic yield (EQ1), we restricted eligibility to U.S. studies that conducted CMA testing in 2009 or later that used current testing platforms to reduce heterogeneity and provide results more applicable to what is in current clinical use. We did not

assess analytic validity or reproducibility and did not conduct an in-depth analysis or synthesis of the cases, breakpoints, or other information related to CNV findings that were presented by study authors.

In addition, our review was limited to the use of WES to detect chromosomal abnormalities. Although WES can detect chromosomal abnormalities, it is primarily used to detect pathogenic mutations or small insertions or deletions within single genes after chromosomal abnormalities have been ruled out by CMA.

Ongoing Research and Future Research Needs

We found no registered studies of research on this topic in clinical trials.gov registry. We identify the following future research needs:

- We need randomized clinical trials or well-designed observational studies to evaluate comparative strategies for using CMA or WES as part of the diagnostic evaluation of children with DD, ID, ASD, or MCA. Clinical genetic testing will likely continue to incorporate WES and whole genome sequencing as replacements for single gene sequencing and mutation panels.
- Karyotype is still the first-line test for the prenatal diagnosis of chromosomal abnormalities, but CMA is increasingly being emphasized as the first-tier test for prenatal diagnosis. In our search for this HTA, we identified many studies focused on the use in prenatal testing, and a systematic review focused on prenatal use of would synthesize the efficacy, safety, and costs when these tests are used in the prenatal context.

Conclusion

Chromosomal microarray identifies a pathogenic or likely pathogenic variant in nearly 9% of all children referred for testing and in 5% of those referred because of autism spectrum disorders; these findings are based on a low strength of evidence. The results of chromosomal microarray tests generate changes in management in over half of children who are identified as having a pathogenic or likely pathogenic variant; this finding is based on very low strength of evidence. The evidence is very limited with respect to the safety of testing and we identified no evidence related to the impact of testing on health outcomes or cost-effectiveness. The cost per additional diagnosis for chromosomal microarray testing as a first-line diagnostic test varies.

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Appendix A. Search Strategy

PubMed searched from 1/1/200-9/18/2017

Condition being Diagnosed (#1)

#1 "Chromosome Aberrations"[Mesh] OR "Chromosome Disorders"[Mesh] OR "Translocation, Genetic"[Mesh] OR "Chromosome Deletion"[Mesh] OR "DNA Copy Number Variations"[Mesh] OR "Gene Dosage"[Mesh] OR "Genomic Structural Variation"[Mesh] OR (("Allelic Imbalance"[Mesh] OR "Genomic Instability"[Mesh] OR "Chromosomes"[Mesh] OR "Aneuploidy"[Majr]) AND ("copy number"[Title/Abstract] OR "CNV"[Title/Abstract] OR "structural"[Title/Abstract] OR "rearrangement"[Title/Abstract] OR "translocation"[Title/Abstract] OR "imbalance"[Title/Abstract] OR "imbalances"[Title/Abstract] OR "inversion"[Title/Abstract] OR "deletion"[Title/Abstract] OR "duplication"[Title/Abstract])) OR "copy number variants"[Title/Abstract] OR "copy number changes"[Title/Abstract] OR "copy number variation"[Title/Abstract] OR "CNV"[Title/Abstract] OR "CNVs"[Title/Abstract] OR "chromosomal rearrangements"[Title/Abstract] OR "translocation"[Title/Abstract] OR "translocations"[Title/Abstract] OR "causal abnormality"[Title/Abstract] Filters: Publication date from 2000/01/01; English

Yield: 174,578

Laboratory Testing Methods (Genetic Microarray or Whole Exome Sequencing) (#2)

#2 "Microarray Analysis"[Mesh] OR "Comparative Genomic Hybridization"[Mesh] OR "Oligonucleotide Array Sequence Analysis"[Mesh] OR (("In Situ Hybridization"[Mesh] OR "Karyotyping"[Mesh] OR "Cytogenetics"[Mesh]) AND ("array"[Title/Abstract] OR "microarray"[Title/Abstract] OR "CGH"[Title/Abstract] OR "array-CGH"[Title/Abstract] OR "comparative genomic hybridization"[Title/Abstract] OR "fluorescent in situ hybridization"[Title/Abstract])) OR (("Genetic Testing"[Mesh] OR "Molecular Sequence Data"[Mesh] OR "Sequence Analysis"[Mesh] OR "Sequence Analysis, DNA"[Mesh]) AND ("exome"[Title/Abstract] OR "next generation sequencing"[Title/Abstract])) OR "array-CGH"[Title/Abstract] OR "CGH"[Title/Abstract] OR "comparative genomic hybridization"[Title/Abstract] OR "array-based comparative genomic hybridization"[Title/Abstract] OR "genome-wide array"[Title/Abstract] OR "exome"[Title/Abstract] OR "congenital anomaly registers"[Title/Abstract] OR "high resolution testing"[Title/Abstract] Filters: Publication date from 2000/01/01; English

Yield: 131,811

Clinical Population (Children with Intellectual Disability, Autism, or Birth Defects) OR Non-Clinical Population (#3)

#3 "Autistic Disorder"[Mesh] OR "Asperger Syndrome"[Mesh] OR "Intellectual Disability"[Mesh] OR "Abnormalities, Multiple"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Developmental Disabilities"[Mesh] OR "Learning Disorders"[Mesh] OR "ASD"[Title/Abstract] OR "autism"[Title/Abstract] OR "mental retardation"[Title/Abstract] OR "mentally retarded"[Title/Abstract] OR "birth defects"[Title/Abstract] OR "mental deficiency"[Title/Abstract] OR chromosome abnormalit*[Title/Abstract] OR "phenotypically abnormal"[Title/Abstract] OR genetic disease*[Title/Abstract] OR "Down syndrome"[Title/Abstract] OR (("Genetics, Population"[Mesh] OR "Prenatal Diagnosis"[Mesh] OR "Genome, Human"[Mesh] OR "Phenotype"[Mesh] OR "Pregnancy"[Mesh] OR "Genetic Variation"[Mesh]) AND ("not at increased risk"[Title/Abstract] OR "phenotypically normal"[Title/Abstract] OR "normal phenotype"[Title/Abstract] OR (("population"[Title/Abstract] OR "populations"[Title/Abstract] OR "individuals"[Title/Abstract]) AND

("general"[Title/Abstract] OR "unselected"[Title/Abstract] OR "normal"[Title/Abstract] OR "disease-free"[Title/Abstract]))) Filters: Publication date from 2000/01/01; English

Yield: 311,528

Combining #1, #2, #3

#4 (#1 AND #2 AND #3) Filters: Publication date from 2000/01/01; English 4318
#5 #4 NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type]) Filters: Publication date from 2000/01/01; English

Total Yield: 2,264

ClinicalTrials.Gov Search from inception to 10/11/2017

Terms: Microarray, limit Child

Total Yield: 101

Terms: Whole Exome, limit Child

Total Yield: 4

Other Data

The following websites were searched using the terms genetic or chromosomal microarray, whole exome, WES, and CMA to identify information relevant to this health technology assessment.

U.S. Food and Drug Administration

Centers for Medicare and Medicaid Services

Aetna

UnitedHealth

Humana

BlueCross BlueShield (Premera and Regence)

Kaiser Permanente

National Institute for Health and Care Excellence (UK)

U.S. Agency for Healthcare Research and Quality

American Academy of Pediatrics

American Academy of Neurology

American College of Medical Genetics and Genomics

Appendix B. Additional Methods

The following exchanges rates were used to convert foreign costs reported to U.S. dollars:

	U.S. $	British Pound	Canadian $
Year 2005	1	0.605	-
Year 2006	1	0.534	-
Year 2007	1	-	1.069
Year 2010	1	-	1.047
Year 2013	1	0.66	-

Source: U.S. Department of Treasury. Treasury Reporting Rates of Exchange. Historical Rates for June 30, 2005; June 30, 2006; June 30, 2007; June 30, 2010; and June 30, 2013. Available at: https://www.fiscal.treasury.gov/fsreports/rpt/treasRptRateExch/historicalRates.htm Accessed October 19, 2017.

The following chain-weighted, average year consumer price indices were used to adjust all reported costs to 2010 dollars.

Year	Annual Average CPI
2005	113.7
2006	117.0
2007	119.957
2010	125.615
2013	133.592

Source: U.S. Department of Labor, Bureau of Labor Statistics. CPI Databases. All Urban Consumers (Chained CPI). Average Annual Indices. Available at: https://www.bls.gov/cpi/data.htm . Accessed October 19, 2017.

Appendix C. Evidence Tables

Table C-1. Characteristics of Included Studies

Author (Year) Key Questions	Population, Age Group Other Clinical Characteristics Setting Time Period of Study Time Period of Testing	Study Design Sample Selection Inclusion / Exclusion Criteria Sample Size	Genetic Test Type Platform Resolution Specimen Type	Variant Classification: Benign; Pathologic; Unknown Significance
Bowling (2017)[56] SQ1, EQ1, EQ2	Intellectual Disabilities, Children North Alabama Children's Specialists, Huntsville, AL, USA NR NR	Cross-sectional Clinic-based, family recruitment INC: Clinical relationship with co-investigator, mild to severe ID, ≥ 2 years old, weight ≥ 19.8 lbs EXC: Abnormal CMA 371	WGS/WES SNP Probe spacing: 5 kb Blood	Benign: Allele frequency higher than observed frequency of disease Pathogenic: Loss-of-function where known disease mechanism; Missense mutation known or computationally predicted to mechanism of disease; de novo and predicted to be damaging or LOF in dominant disease gene; Recessive or compound heterozygous in gene with known recessive genetic disease, at frequencies low enough to plausible for disease, predicted to be damaging VUS: Variant is de novo and computationally predicted to be damaging; is very rare, predicted to be damaging, and exist in compound heterozygous or recessive states; impacts a gene with a specific, plausible biological connection to disease; impacts a gene predicted to be intolerant of variation; conflicting evidence.
Coulter (2011)[51] EQ3	Mixed, Mixed Children's hospital USA 7/1/2009 - 7/1/2010 2009-2010	Retrospective cohort No sampling. 2 missing, no clear reason for exclusion. INC: CMA result of pathogenic or possible pathogenic CNV during study period; EXC: Down Sx known or suspected (8); VUS with missing parental studies (31/104); Total tested: 1792 Total with pathogenic or VUS: 235	Microarray NR NR - testing done prior to study NR	Benign: Previously reported in unaffected individuals Pathologic: Known microduplication or deletion sx; deletion of genes known to cause disease when haploinsufficient; large duplications or deletions Possible pathogenetic: CNV that overlap known sx, contain genes suspected of causing disease, possible unmasking of autosomal recessive

Author (Year) Key Questions	Population, Age Group Other Clinical Characteristics Setting Time Period of Study Time Period of Testing	Study Design Sample Selection Inclusion / Exclusion Criteria Sample Size	Genetic Test Type Platform Resolution Specimen Type	Variant Classification: Benign; Pathologic; Unknown Significance
		Total in analysis: 194, 121 pathogenic CNV and 73 with VUS		VUS: CNV not in literature or available databases and does not include genes known to be related to disease.
Ellison (2012)[57] EQ3	Mixed, Mixed Genetics laboratory. USA 4/29/2004-10/21/2011 2004-2011	Retrospective case series, in silico review Physician survey for case follow-up Cases with likely impact: all eligible. Physician survey cases - Disorders with obvious and straightforward clinical actions Total CMA tested: 46298 Physician survey: 122 patients, response for 81, 46 responding clinicians	Microarray Other Changed over study period from BAC to oliognucleotides Blood	Benign: NA Pathologic: Associated with 1) established microdeletion or duplication syndrome with features that require specific follow-up, 2) increased cancer susceptibility, 3) phenotypes with obvious medical follow-up caused by CNV in dosage sensitive genes VUS: NR
Hamilton (2015)[50] SQ1	Mixed, Children Glasgow, UK 8/1/2012-7/31/2013 2012-2013	Cross-sectional Clinic-based Case report 6	Microarray NR NR NR	NR NR NR NR
Hayeems (2015)[58] EQ3	Mixed, Children Clinical genetics laboratory. Canada 2009-2011	Retrospective cohort All cases with variants and sample of benign cases. INC: Clinical follow-up at Tertiary Hospital Performing the study. EXC: Child died before results received 752	Microarray Agilent 75 kb Blood	All: Based on laboratory report. If not specified in report, assigned based on ACMG guidelines and verified by expert review.
Henderson (2014)[52] EQ3, EQ1	Mixed, Children Genetics laboratory. USA 2009-2012 Minimum follow-up period: 13 months 2009-2012	Retrospective, pre-post All eligible Benign/VUS variant, No follow-up available CMA tested, 1780 Pathogenic variant, 227 Clinical follow-up available, 187	Microarray Other Illumina Omni1. NR Blood	Benign: Does not involve disease genes, reported in healthy populations, seen in > 1% of parents Pathologic: Known syndromes, encompassed or interrupted disease associated gene, included numerous genes and not found in healthy individuals. > 10 Mb region of homozygosity VUS: Did not fulfill definitions of pathologic, > 200 kb deletion or > 500 kp

Author (Year) Key Questions	Population, Age Group Other Clinical Characteristics Setting Time Period of Study Time Period of Testing	Study Design Sample Selection Inclusion / Exclusion Criteria Sample Size	Genetic Test Type Platform Resolution Specimen Type	Variant Classification: Benign; Pathologic; Unknown Significance
				duplication, rarely reported in healthy individuals
Ho (2016)[53] EQ1, EQ2	Mixed, Mixed Clinical testing laboratory, USA 7/2012-9/2016 4.2 Years	Cross-sectional Clinic-based Consecutive series of patients with neurodevelopmental disorders 10,351	Microarray Affymetrix Ultra-high resolution Affymetrix CytoscanHD® platform plus 88,435 custom probes yeilding 2.8 million probes Other	Benign: In databases of benign variants (DGV) Pathologic: CNVs of <1% population frequency and at least two independent reports that haploinsufficiency or triplosensitivity of the region or gene(s) is causative of clinical features VUS: Preliminary evidence for a causative role or areas of absence of heterozygosity (AOH) that may increase risk of autosomal recessive or imprinting conditions. NR
Newman (2007)[62] Cost	Mixed, Children Regional genetics clinical service. United Kingdom NR 2005	Cohort (retrospective) Clinic-based INC: phenotype with undiagnosed ID/DD with or without dysmorphic features with normal karyotype EXC: None noted 46	Microarray Bacterial artificial chromosomes (BAC) 1-Mb Blood	NR NR NR NR
Regier (2010)[65] Cost	Intellectual Disabilities, Children NA Canada 2007 NA	Decision Analysis NA NA NA	Microarray NA NA NA	NA NA NA NA
Riggs (2014)[59] EQ3	Mixed, Mixed In silico. USA In ISCA database March 2012 NA	Cross-sectional, survey NSGC or ACMG membership INC: Pathogenic, clinically actionable phenotypes EXC: Phenotypes with no appropriate clinical action Evidence in database: 4125 CNVs, 28,526 cases	Microarray NR NR-Test results retrieved from database NR	On ISCA array (384 genes), Well-described sx (GeneReviews, DECIPHER, ISCA) (153 genes, 235 phenotypes), diagnosable by CMA (186)

Author (Year) Key Questions	Population, Age Group Other Clinical Characteristics Setting Time Period of Study Time Period of Testing	Study Design Sample Selection Inclusion / Exclusion Criteria Sample Size	Genetic Test Type Platform Resolution Specimen Type	Variant Classification: Benign; Pathologic; Unknown Significance
Roberts (2014)[54] EQ1, EQ2	Mixed, Mixed Clinical genetics clinic, USA 2009-2012 2009-2012	Cross-sectional Clinic-based EXC: Patients with recognized syndrome or single gene disorders 215	Microarray Oligionuecleotide 105K array, 21 kb. 180K array, 16 kb. Blood	Benign: NR Pathologic: Previously reported as associated with ASD or learning disability. Evaluated with UCSC Genome Browser, DGV, OMIN, DECIPHER, CombiTrak (internal database), dbVar VUS: NR
Saam (2008)[60] EQ3	DD, Children Clinical genetics laboratory. USA 1/1/02005-3/8/2007 2005-2007	Retrospective INC: Clinically abnormal patients with normal karyotype EXC: Patients too young to determine if DD or ID Patients with abnormality: 87: Physicians contacted: 22 (70 patients) Physician respondents: 14 (48 patients)	Microarray Bacterial artificial chromosomes (BAC) 1 Mb Blood	Benign: Identified as normal in DGV or U of Utah database Pathologic: Believed or suspected to be of clinical significance based on laboratory report. VUS: NR
Sagoo (2015)[64] Cost	ID/DD, Mixed Clinical genetics service; United Kingdom 2006-2013 2006-2009	Cohort (retrospective) and Decision Analysis Clinic-based INC: Undiagnosed ID plus one of the following: family history of learning disability, overgrowth or growth failure, behavioral problems, clinical or radiologic dysmporphism or anomalies. EXC: Already had a known diagnosis 1590	Microarray BAC Agilent 1 Mb 44k Blood	Benign: In DGV as present in normal individuals in as least 3 studies Pathogenic: Known syndrome, deleted genes relative to phenotype VUS: NR
Stobbe (2014)[55] EQ1, EQ2	Autism, Adults Autism Genetics Clinic, USA 7/1/09-4/30/12 2009-2012	Retrospective cohort Clinic-based EXC: Patient tested with fragile X. 36 aCGH: 25	Microarray Oligionuecleotide 135k nucleotide probes (NimbleGen CGX-3 v1.0;	Likely Benign: No genes in the interval, reported in databases of variants in general population but not common.

Author (Year) Key Questions	Population, Age Group Other Clinical Characteristics Setting Time Period of Study Time Period of Testing	Study Design Sample Selection Inclusion / Exclusion Criteria Sample Size	Genetic Test Type Platform Resolution Specimen Type	Variant Classification: Benign; Pathologic; Unknown Significance
			Roche NimbleGen, Madison, WI) Blood	Likely pathogenic: Prior case report with well-defined breakpoints & phenotype, or gene in CNV compelling & specific for the phenotype. VUS: Genes in CNV, but dose sensitivity unknown, or multiple contradictory publications or databases (DGV, db VAR, ISCA, DECIPHER, OMIN, UCSC Genome Bioinformatics, European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations, and literature search.
Tao (2014)[61] **EQ3**	Mixed, Children Genetics laboratory. Hong Kong 1/2011-5/2013 2011-2013	Retrospective, pre-post Clinic-based EXC: Clinically recognized syndrome, patients who had prenatal CMA testing or parents who chose not to receive the test results 327	Microarray Oligo-SNP (Nimblegen CGX-135K) Probe spacing: 140 kb Blood	Classification by ACMG practice guidelines. Used Signature Genomics database, Tsan Yuk Hospital internal database, DGV, ISCA, DECIPHER, OMIN.
Trakadis (2011)[63] **Cost**	DD, Children Academic pediatric neurology practice; Canada 2006-2009 2006-2009	Cohort (retrospective) Clinic-based INC: Final diagnosis of DD, age < 6.5 years, had complete history and physical exam, and laboratory testing	Microarray Bacterial artificial chromosomes (BAC) and oligonucleotides (for N=6 subjects)	NR NR NR NR

Author (Year) Key Questions	Population, Age Group Other Clinical Characteristics Setting Time Period of Study Time Period of Testing	Study Design Sample Selection Inclusion / Exclusion Criteria Sample Size	Genetic Test Type Platform Resolution Specimen Type	Variant Classification: Benign; Pathologic; Unknown Significance
		completed as part of diagnostic assessment EXC: Patients referred for assessment but for whom all testing/evaluation was not completed. 114	NR for BAC, 105K for oligonucleotide Blood	
Wordsworth (2011)[66] Cost	ID, Children Clinical genetics laboratories; United Kingdom 2005 2006	Decision Analysis NA NA NA	Microarray Agilent 44K NA	NA NA NA NA

ACMG=American College of Medical Genetics, CNV=copy number variant, CGX= DD=developmental delay, DECIPHER=DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources, DGV=Database of Genomic Variants, EXC= Excluded, ID=intellectual disabilities, GCAD=Genoglyphix Chromosome Aberration Database, INC= Included, ISCA=International Standards for Cytogenomic Arrays, NA=not applicable, NR=not reported, NSGC=National Society of Genetic Counselors, OMIN=Online Mendelian Inheritance in Man, SNP=single nucleotide polymorphism, Sx=syndrome, VUS=variant of unknown significance, UCSC=University of California at Santa Cruz, WES=whole exome sequencing, WGS=whole genome sequencing.

Table C-2. Individual Study Findings Related to Safety of Chromosomal Microarray or Whole Exome Sequencing Testing (SQ1)

Author (Year)	Subgroup	CMA/WES Tested Safety Issue Total Experienced issue N (%) Characteristics of affected
Hamilton (2015)[50]		Withdrawn adoption application due to chromosomal abnormality: 1 Total cohort: 6 (16.7%)

CMA=chromosomal microarray, CNV=copy number variant, SNP=single nucleotide polymorphism, SQ=safety question, WES=whole exome sequencing

Table C-3. Individual Study Findings Related to Safety of Chromosomal Microarray or Whole Exome Sequencing Testing (EQ1)

Author (Year)	Analytic Method	Subgroup	Sample Size	Diagnostic Result N (%)
Bowling (2017)[56]	Descriptive: Count, percents	ID/DD, Probands	371	Pathogenic: 100 (27%) Benign: NR VUS: 42 (11.3%)
Bowling (2017)[56]	Descriptive: Count, percents	Probands, CNV only	371	Pathogenic: 42 (11.3%) Benign: NR VUS: NR
Bowling (2017)[56]	Descriptive: Count, percents	Families with no affected relatives	93	Pathogenic: 35 (37.6%) Benign: NR VUS: NR
Bowling (2017)[56]	Descriptive: Count, percents	No affected 1st degree relatives ≥1 2nd/3rd degree affected	85	Pathogenic: 22 (26.0%) Benign: NR VUS: NR
Bowling (2017)[56]	Descriptive: Count, percents	≥ 1 affected first degree relative)	123	Pathogenic: 24 (20%) Benign: NR VUS: NR
Coulter (2011)[51]	Descriptive: Count, percents	All	1792	Pathogenic: 131 (7.3%) VUS: 104 (5.8%)H
Henderson (2014)[52]	Counts, percentages	All	1780	Pathogenic: 227 (12.7%) Benign: 1313 (73.8%) VUS: 240 (13.5%)
Ho (2016)[53]	Descriptive: Count, percents	All	10351	Pathogenic: 890 (8.6%) Benign: NR VUS: 2008 (19.4%)
Ho (2016)[53]	Descriptive: Count, percents	Non-ASD	4657	Pathogenic: 583 (12.5%) Benign: 3140 (67.4%) VUS: 934 (20.1%)
Ho (2016)[53]	Descriptive: Count, percents	Any ASD	5694	Pathogenic: 307 (5.4%) Benign: 4306 (75.6%) VUS: 1081 (19%)

Author (Year)	Analytic Method	Subgroup	Sample Size	Diagnostic Result N (%)
Ho (2016)[53]	Descriptive: Count, percents	ASD+other indication	2844	Pathogenic: 184 (6.5%) Benign: 2108 (74.1) VUS: 552 (19.4%)
Ho (2016)[53]	Descriptive: Count, percents	ASD only	2850	Pathogenic: 125 (4.4%) Benign: 2195 (77%) VUS: 529 (18.5%)
Roberts (2014)[54]	Descriptive (# of CNVs): Count, percents	All	215	Pathogenic: 32 (14.9%) Benign: 170 (79%) VUS: 17 (8%)
Roberts (2014)[54]	Descriptive (# of CNVs): Count, percents	ASD	65	Pathogenic: 6 (9.2%) Benign: 52 (80%) VUS: 8 (64%)
Roberts (2014)[54]	Descriptive (# of CNVs): Count, percents	ID/DD	150	Pathogenic: 26 (17.3%) Benign: 118 (79%) VUS: 9 (26%)
Stobbe (2014)[55]	Count, percent, two-tailed P value, Fisher's exact test	All	25	Pathogenic: 3 (12%) Benign: NR VUS: NR
Stobbe (2014)[55]	Count, percent, two-tailed P value, Fisher's exact test	Confirmed ASD	23	Pathogenic: 2 (8.7%) Benign: NR VUS: 9 (39%)

ASD=autism spectrum disorders; CNV=copy number variant, DD=developmental delay, ID=intellectual disabilities, NR=Not reported, VUS=Variant of unknown significance.

Table C-4. Individual Study Findings Related to Changes in Management Resulting from Testing with Chromosomal Microarray or Whole Exome Sequencing Testing (EQ3)

Author (Year) Key Questions	Analytic Method Method of Adjustment Stratification / Regression Variables	Management Changes	GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Not GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Effect of GA/WES Unadjusted: RR (95% CI), p-value Adjusted: RR (95% CI), p-value
Coulter (2011)[51]	Descriptive	INC: Recommendations made because of CMA results: specialist referral, imaging study, diagnostic test, medication prescription. EXC: standard CMA follow-up	Pathologic CNV: Total: 121 Any recommendation: 65 (54%) Referral: 67 (60%) Diagnostic testing (imaging and laboratory): 45 (37%) Stop diagnostic odyssey/avoid other diagnostic testing: 110 (90%) Possible pathogenic variant: Total: 73 Any recommendation: 25 (34%) Referral: 11 (29%) Diagnostic testing: 27 (38%) Stop diagnostic odyssey/avoid other diagnostic testing: 61 (84%)	NA	NA
Ellison (2012)[57]	Descriptive	Actionable disorders diagnosed by CMA: Microdeletion or microduplication syndromes with organ or endocrine abnormalities that require specific follow-up; Conditions associated with increased cancer susceptibility; Duplications or deletions of dosage sensitive genes that result in genetic disease requiring follow-up.	Total cases tested by CMA: 46298 Any actionable disorder: 1996 (4.3%) Syndromes that require clinical action: 1733 (3.7%) Increased cancer screening: 189 (0.4%) Genetic disease management due to deletion of dosage sensitive genes: 74 (0.16%) Physician-reported actions Total cases: 81 At least 1 appropriate action taken: 76 (94%)	NA	NA
Hayeems (2015)[58]	Descriptive	Chart review showed any of the following prompted by CMA results: 1) recurrent surveillance, 2) specialist referral 3) imaging	Definitely pathologic: 114 Mean recommendations per patient: All recommendation: 2.35 Specialist referrals: 1.20	NA	NA

Author (Year) Key Questions	Analytic Method Method of Adjustment Stratification / Regression Variables	Management Changes	GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Not GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Effect of GA/WES Unadjusted: RR (95% CI), p-value Adjusted: RR (95% CI), p-value
		tests 4) laboratory tests 5) surveillance protocols 6) family member investigations.	Medical imaging: 0.05 Laboratory tests: 0.15 Surveillance/screening: 0.46 Definitely or likely pathologic: 186 Mean recommendations per patient: All recommendation: 2.25 Specialist referrals: 1.02 Medical imaging: 0.52 Laboratory tests: 0.17 Surveillance/screening:0.39		
Hayeems (2015)[58]	Comparative. Binominal log-link regression with single variable. Pathogenic versus benign		Any recommendation after CMA: Children with reportable variants: 79.6%	Any recommendation after CMA: Children with benign variants: 62.4%	1.36 (1.21, 1.53)
Henderson (2014)[52]	Descriptive	Impact on management any of the following actions in clinical notes that reference or deemed to be a direct consequence of the CMA results: Direct clinical action (pharmacologic treatment or contraindications, cancer-related screening, avoidance of cancer screening), specialist referrals, diagnostic (imaging or laboratory) tests.	Total, any indication: 187 Any impact on clinical management: 102 (54.5%) Any direct clinical action: 24 (12.8%) Specialist referral: 84 (44.9%) Imaging: 38 (20.3%) Laboratory test: 29 (15.5%) Pharmacologic treatment: 6 (3.2%) Cancer screening recommended: 11 (5.9%) Cancer screening avoided: 3 (1.6%) Contraindication: 3 (1.6%) Total, neurodevelopmental indication: 38 Any impact on clinical management: 16 (42.1%) Any direct clinical action: 3: (7.9%) Specialist referral: 12 (31.6%) Imaging: 6 (15.8%) Laboratory test: 2 (5.3%) Pharmacologic treatment: 0	NA	NA

Author (Year) Key Questions	Analytic Method Method of Adjustment Stratification / Regression Variables	Management Changes	GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Not GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Effect of GA/WES Unadjusted: RR (95% CI), p-value Adjusted: RR (95% CI), p-value
			Cancer screening recommended: 3 (7.9%) Cancer screening avoided: 0 Contraindication: 0		
Riggs (2014)[59]	Descriptive	INC: Clinically actionable phenotype if at least one of following recommended in guidelines (Level 1) or literature (Level 2): specialist referral, diagnostic testing (includes imaging), surgical/interventional procedures, medication or lifestyle changes.	Pathogenic and likely pathogenic CNVs: Total: 4125 Any Level 1 or 2 recommendation: 1908 (46%) All cases in ISCA: Total: 28526 Any Level 1 or 2 recommendation: NR (7.0%)	NA	NA
Saam (2008)[60]	Descriptive	Physician-reported recommendations made because of clinically significant CMA results. INC: Specialist referral, recommendation for medical screening, stop previously recommended screening, family testing, improved access to services.	Total: 48 Any change in management: 34 (70.8%) At least one recommendation: 13 (27%) Referral: 7 (14.6%) Medical screening: 8 (16.7%) Stop medical screening: 1 (2.1%) Stop diagnostic odyssey, avoid additional testing: 20 (41.7%) Improved access to services: 12 (25.0%) Counseling on recurrence risk: 17 (35.4%) All patients for whom CMA ordered: 490 Any recommendation: 34 (6.9%)	NA	NA
Tao (2014)[61]	Descriptive	Management change: Any of the following when prompted by CMA results: 1) recurrent surveillance, 2) specialist referral 3) diagnostic intervention, 4) medical surgical procedure, 5) pharmacologic, 6) lifestyle and other recommendations	Total with pathogenic variant: 37 At least 1 clinical action: 28 (75.7%) Surveillance/screening): 19 (51.4%) Specialist referral: 24 (64.9%) Diagnostic tests: 25 (67.6%) Medical/surgical procedure: 7 (18.9%) Pharmacologic treatment: 15 (40.5%) Lifestyle: 12 (32.4%)	NA	NA

Author (Year) Key Questions	Analytic Method Method of Adjustment Stratification / Regression Variables	Management Changes	GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Not GA/WES Tested Treatment Type Total Received Treatment: N (%, SD) Other	Effect of GA/WES Unadjusted: RR (95% CI), p-value Adjusted: RR (95% CI), p-value
		Level 1 evidence: professional association guidelines, Level 2 peer-reviewed literature: Level 3: peer-review literature/clinical judgement, Level 4: Managed symptomatically	Level 1 evidence: 9 (24.3%) Level 2 evidence: 10 (27.0%) Level 3 evidence: 8 (21.6%) Level 4 evidence: 1 (2.7%) Total with VUS: 40 At least 1 clinical action: 1 (2.5%)		

CMA=chromosomal microarray; CNV=copy number variant, EXC=excluded, INC=included, ISCA=International Standards for Cytogenomic Arrays, SD=standard deviation, VUS=variant of unknown significance.

Table C-5A. Individual Study Findings Related to Costs and Cost-effectiveness of Testing with Chromosomal Microarray or Whole Exome Sequencing Testing (CQ1)

Author (Year) Key Questions	Analytic Method Currency, Year	CMA/WES Tested No. Participants Cost per Patient Cost per Diagnosis Services Included	Not CMA/WES Tested No. Participants Cost per Patient Cost per Diagnosis Services Included	Difference in Cost Difference (SD or CI), p-value
Newman (2007)[62]	2-tailed student's t-test British Pounds (£), 2005	Participants: 36 Cost per patient: £1389 Cost per diagnosis: £2399-£4248 Services included: Varied by patient but includes CMA plus a variety of metabolic tests (e.g., amino acids, thyroid, mucopolysaccharide, and others), fragile X testing, FISH-specific probes, subtelomeric probes, MRI, skeletal surveys, EEG, cranial computerized tomogram, 15q methylation, homocysteine, specific syndromic testing (e.g., UBE3A (Angelman's syndrome, and others), myotonic dystrophy, chromosome breakage studies.	Participants: 10 Cost per patient: £1765 Cost per diagnosis: NR Services included: Varied by patient but includes a variety of metabolic tests (e.g., amino acids, thyroid, mucopolysaccharide, and others), fragile X testing, FISH-specific probes, subtelomeric probes, MRI, skeletal surveys, EEG, cranial computerized tomogram, 15q methylation, homocysteine, specific syndromic testing (e.g., UBE3A (Angelman's syndrome, and others), myotonic dystrophy, chromosome breakage studies.	Cost per patient: £376 (NR), 0.34 Cost per diagnosis: NR
Trakadis (2011)[63]	2-tailed student's t-test Canadian Dollars ($), 2010	Participants: 33 Cost per patient: NR Cost per diagnosis: NR	Participants: 81 Cost per patient: NR Cost per diagnosis: NR	Additional cost per patient: $421 (98% CI, $238 to $604) if using a private, commercial laboratory to

Author (Year) Key Questions	Analytic Method Currency, Year	CMA/WES Tested No. Participants Cost per Patient Cost per Diagnosis Services Included	Not CMA/WES Tested No. Participants Cost per Patient Cost per Diagnosis Services Included	Difference in Cost Difference (SD or CI), p-value
		Services included: Varied by patient but includes aCGH, metabolic tests, methylation studies, skin and muscle biopsies, molecular genotyping/sequencing for specific syndromes, CT, MRI, bone age, EEG, EMG.	Services included: Varied by patient but includes metabolic tests, methylation studies, skin and muscle biopsies, molecular genotyping/sequencing for specific syndromes, CT, MRI, bone age, EEG, EMG.	$106 (98% CI, $-17 to -$195) if using local hospital laboratory, NR Cost per additional diagnosis: $12874(NR) if using private, commercial laboratory to $1379 (NR) if using local hospital laboratory, NR
Sagoo (2015)[64]	NR British Pounds (£), 2013	Participants: 848 Cost per patient: £291.05 (range £190-£1258) Cost per diagnosis: £2544.42 Services included: aCGH as first line test, plus any other testing or consultation conducted to establish a diagnosis.	Participants: 742 Cost per patient: £532.61 (range £390-£1424) Cost per diagnosis: £4819.44 Services included: Karyotype as first line test, with aCGH as second-line test if no variation detected, plus any other testing or consultation conducted to establish a diagnosis.	Cost per patient: £-241.56 (95% CI, £-256.93 to £ -226.19), p< 0.001 Cost per diagnosis: £-2275.02 (95% CI NR), NR Cost per additional diagnosis: £-62,342.94 (NR), NR
Regier (2010)[65]	Decision analysis, Canadian dollars ($), 2007	Participants: NA (model) Cost per patient: NR Cost per diagnosis: $2980 (95% CI, $2727 to $3254) Services included: aCGH as first line test, followed by targeted FISH and/or karyotyping (unless trisomy suspected in which case karyotyping was first and aCGH only used if karyotype did not establish a diagnosis).	Participants: NA (model) Cost per patient: NR Cost per diagnosis: $2763 (95% CI, $2499 to $3052) Cost per diagnosis: NR Services included: Karyotype as first line test, with targeted FISH or subtelomeric FISH.	Cost per diagnosis: $217 (95% CI, $172 to $261) Cost per additional diagnosis: $2646 (95% CI, $1619 to $5296), NR
Wordsworth (2011)[66]	Decision analysis, British pounds (£), 2006	Participants: NA (model) Cost per patient: Varies by results of testing and need for follow-up testing. Cost per diagnosis: £3118 Services included: aCGH as first-line test, with FISH tests for imbalances of unknown clinical relevance, and parental FISH or MLPA testing to identify de novo variants.	Participants: NA (model) Cost per patient: Varies by results of testing and need for follow-up testing. Cost per diagnosis: £4957 with follow-up multi-telomere FISH for normal karyotype or £2129 with follow-up multi-telomere MLPA for normal karyotype	Cost per diagnosis: -£1839(NR) if multi-telomere FISH used for follow-up after normal karyotype or £989 (NR) if multi-telomere MLPA used for follow-up after normal karyotype), NR Cost per additional diagnosis:

Author (Year) Key Questions	Analytic Method Currency, Year	CMA/WES Tested No. Participants Cost per Patient Cost per Diagnosis Services Included	Not CMA/WES Tested No. Participants Cost per Patient Cost per Diagnosis Services Included	Difference in Cost Difference (SD or CI), p-value
		Assumes diagnostic yield of 18%. Does not include any other testing to establish a diagnosis, though authors claim no further testing for genomic imbalances required in those without diagnosis.	Services included: Karyotype as first line test, with karyotype of parents if results are of unknown clinical relevance. If karyotype normal, additional FISH or multi-telomere FISH or MLPA. Assumes diagnostic yield of 8%. Does not include follow-up testing in patients with normal karyotype and normal FISH/MLPA that would likely need additional testing to rule out genetic imbalances as diagnostic etiology.	-£183.90 to £98.80 depending on which follow-up testing used, NR

aCGH= array comparative genomic hybridization, CMA=chromosomal microarray, CT=computerized tomography, EEG=electroencephalogram, EMG=electromyography, FISH=Fluorescent in situ hybridization, MLPA=Multiplex ligation-dependent probe amplification, MRI=magnetic resonance imaging, NR=not reported, WES=whole exome sequencing.

Table C-5B. Summary of findings from five studies evaluating cost or cost-effectiveness of genetic microarray testing, data provided in currency units and years reported by studies

Phenotype	No. of Studies (No. of Participants)	Cost Per Patient or Diagnosis (95% CI)			Difference in Cost (95% CI)	Incremental Cost-Effectiveness
		Outcome (currency, year)	GA Testing	No CMA Testing		
Intellectual Disability	2 (NA[a])	Cost per diagnosis (CD, 2007)[65]	2980[b] (2727 to 3254)	2763 (2499 to 3052)	217 (172 to 261)	Cost per additional diagnosis: 2646 (1619 to 5296)
		Cost per diagnosis[b] (GBP, 2006)[66]	3118[c] (NR)	Range 2129 to 4957[d]	Range -1839 to 989[d]	Range of cost per additional diagnosis[e]: -183.90 to 98.90
Developmental Delay	1 (114)[63]	Cost per patient (CD, 2010)	NR	NR	-106 (98% CI -195 to -17)[f] 421 (98% CI, 238 to 604)[g]	NA
		Cost per diagnosis (CD, 2010)	NR	NR	NR	Cost per additional diagnosis: 1379 (NR)[f] 12874 (NR)[g]
Intellectual disability or developmental delay or both	2(1636)	Cost per patient (GBP, 2005[62], 2013[64])	1389 (NR)[62] 291.05 (Range 190 to 1258)[64]	1765 (NR)[62] 532.61 (Range 390 to 1424)[64]	-376 (NR, p=0.34)[62] -241.56 (95% CI, -256.93 to -226.19)[64]	Cost per additional diagnosi:[62] 2399
		Cost per diagnosis (GBP, 2005)	Range 2399 to 4248 (NR)[62] 2544.42 (NR)[64]	NR[62] 4819.44 (NR) [64]	NR[62] -2275.02 (95% CI NR) [64]	Additional cost per diagnosis for various levels of diagnostic yield:[62] 5% 8244 10% 3678 13.8% 2399 20% 1394 51.3% 0 Cost per additional diagnosis:[64] -62342.94

Abbreviations: CD= Canadian Dollars; CI=confidence interval; GBP=British Pound; NA= not applicable; NR=not reported

[a] Both studies were conducted using decision analyses using hypothetical cohorts.

[b] Assumes that CMA testing increases diagnostic yield from 19.2% to 27.5%

[c] Assumes that CMA testing increases diagnostic yield from 8% to 18%, cost per diagnosis is 2440 with a 15% absolute increase in diagnostic yield.

[d] Depending on which kinds of follow-up testing after karyotype used.

[e] Calculated based on data provided in the study.

[f] When using local hospital lab for testing.

[g] When using commercial lab for testing.

Appendix D. Excluded Studies

List of Exclusion Codes

X1: Ineligible publication type

X2: Ineligible population

X3: Ineligible or no intervention

X4: Ineligible comparator

X5: Ineligible or no outcome

X6: EQ1 Study Published before 2010

X7: No Key Question

X8: Old Platform

X9: Ineligible setting

X10: EQ1 Ineligible country

X11: Duplicates/superseded by more recent publications

Abdelmoity AT, LePichon JB, Nyp SS, et al. 15q11.2 proximal imbalances associated with a diverse array of neuropsychiatric disorders and mild dysmorphic features. J Dev Behav Pediatr. 2012 Sep;33(7):570-6. doi: 10.1097/DBP.0b013e31826052ae. PMID: 22922608. Exclusion Code: X9.

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Al-Mamari W, Al-Saegh A, Al-Kindy A, et al. Diagnostic Yield of Chromosomal Microarray Analysis in a Cohort of Patients with Autism Spectrum Disorders from a Highly Consanguineous Population. J Autism Dev Disord. 2015 Aug;45(8):2323-8. doi: 10.1007/s10803-015-2394-9. PMID: 25703031. Exclusion Code: X10.

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Appendix E. Individual Study Risk of Bias Assessments

Table E-1A. Risk of Bias Assessment: Sample Selection and Description of Test

Author (Year)	Overall Risk of Bias Rating	Was a consecutive or random sample of patients enrolled?	Were inclusion/ exclusion criteria appropriate?	Comments on Sample Selection	What is the level of detail the authors used to describe the test?	Comments on Test Description
Bowling (2017)[56]	Low	Cannot determine	Yes	None	High, clear, all details provided	None
Coulter (2011)[51]	Cannot determine	Yes	Yes	None	Medium, somewhat clear, most details provided	Resolution not reported
Ellison (2012)[57]	High	Yes	No	Sample includes all patients tested with CMA and does not include/exclude patients based on phenotype. Thus, the sample tested cannot be characterized based on phenotype.	High, clear, all details provided	None
Hamilton (2015)[50]	High	No	No	High potential for selection bias given the manner in which sample recruited.	Low, unclear, many details missing	None
Hayeems (2015)[58]	Low	Yes	Cannot determine	Unclear whether the exclusion of children not followed by the same tertiary pediatric hospital where genetic labs is located would result in selection bias, as presumably 'sicker' kids are followed at the tertiary center versus kids followed in the community.	High, clear, all details provided	None
Henderson (2014)[52]	Low	Yes	Yes	None	High, clear, all details provided	Only missing genome build
Ho (2016)[53]	Low	Cannot determine	Yes	None	High, clear, most details provided.	Uses same platform as BioMed Research Intl [91] paper excluded because of overlapping study population.
Newman (2007)[62]	Low	Yes	Yes	None	Medium, somewhat clear, most details provided	Article references a separate article for details.
Regier (2010)[65]	Low	NA	Yes	Decision analysis using a hypothetical cohort	Low, unclear, many details missing	None

Author (Year)	Overall Risk of Bias Rating	Was a consecutive or random sample of patients enrolled?	Were inclusion/ exclusion criteria appropriate?	Comments on Sample Selection	What is the level of detail the authors used to describe the test?	Comments on Test Description
Riggs (2014)[59]	High	NA	Yes	No patients. Used CMA diagnosable phenotypes and cases in a database.	NA. No actual testing.	Include only well described symptoms in study
Roberts (2014)[54]	Low	Yes	Yes	None	Medium, somewhat clear, most details provided	None
Saam (2008)[60]	Cannot determine	Yes	Yes	Consecutive sample for EQ1 and EQ2, non-consecutive sample for EQ 3 as study only included patients with positive CMA results.	Medium, somewhat clear, most details provided	None
Sagoo (2015)[64]	Low	Yes	Yes	None	Low, unclear, many details missing	None
Stobbe (2014)[55]	Low	Yes	Yes	None	Medium, somewhat clear, most details provided	Missing resolution
Tao (2014)[61]	Low	Yes	Yes	None	High, clear, all details provided	None
Trakadis (2011)[63]	Low	Yes	Yes	None	Medium, somewhat clear, most details provided	None
Wordsworth (2011)[66]	Low	NA	Yes	Decision analysis using a hypothetical cohort	Low, unclear, many details missing	None

CMA=chromosomal microarray, EQ=efficacy question.

Table E-1B. Risk of Bias Assessment: Variant Classification (continued) Author (Year)	7. Are the variant classification methods valid?	Comments on Variant Classification	8. Is the selection of the comparison group appropriate after considering feasibility and ethical considerations?	9. Does the analysis control for baseline differences between groups?	10. Are the measures and statistical methods used to assess outcomes appropriate?	11. Are the results believable taking study limitations into consideration?	Comments on Selection, Confounding, Measurement, or Analyses
Riggs (2014)[59]	Yes	Likely conservative	NA-single arm(before/after)	NA-single arm(before/after)	Yes	Yes	Cases with well-described symptoms may be less likely to be entered in database once they are well described. May underestimate the proportion with clinical impact.
Roberts (2014)[54]	Yes	None	NA	NA	NA	NA	NA
Saam (2008)[60]	Cannot determine	Defined as alterations believed or suspected to be of clinical significance, but no additional details are provided.	NA-single arm(before/after)	NA-single arm(before/after)	Partially	Yes	Measurement of changes in management based on physician survey/recall.
Sagoo (2015)[64]	Cannot determine	None	Yes	No	Yes	Yes	None
Stobbe (2014)[55]	Yes	ACMG guidelines	NA	NA	NA	NA	NA
Tao (2014)[61]	Yes	ACMG guidelines	NA-single arm(before/after)	NA-single arm(before/after)	Yes	Yes	None
Trakadis (2011)[63]	No	None	NA-single arm(before/after)	NA-single arm(before/after)	Yes	Yes	None
Wordsworth (2011)[66]	Yes	None	NA	NA	NA	NA	NA

NA=not applicable.

Table E-2. Risk of Bias Assessment Items Specific to Cost Studies

Author (Year)	12. Was the perspective (societal vs. payer) stated?	13. Does the analysis clearly identify the costs used and how they were valued?	14. Were all relevant costs included for the perspective used?	15. Was the analysis appropriate (i.e., appropriate discount rate, sensitivity analyses conducted)?
Newman (2007)[62]	Yes	Yes	Yes	Yes
Regier (2010)[65]	Yes	Yes	Partially	Yes
Sagoo (2015)[64]	Yes	Yes	Yes	Yes
Trakadis (2011)[63]	Yes	Yes	Yes	Yes
Wordsworth (2011)[66]	Yes	Yes	Yes	Yes

Table E-3A. Risk of Bias Assessment for Included Systematic Review: Study Eligibility Criteria

Author (Year)	1.1 Pre-defined objectives and eligibility criteria?	1.2 Criteria appropriate for the review question?	1.3 Eligibility criteria unambiguous?	1.4. All restrictions in criteria based on study characteristics appropriate?	1.5 Restrictions based on sources of information appropriate?	Concerns regarding study eligibility criteria.	Comments
Grant (2015)[40]	Yes	Yes	Yes	Yes	Yes	Low	None

Table E-3B. Risk of Bias Assessment for Included Systematic Review: Identification and Selection of Studies

Author (Year)	2.1 Appropriate range of databases/ electronic sources used?	2.2 Were methods in addition to database searching used to identify relevant reports?	2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	2.4 Were restrictions based on date, publication format, or language appropriate?	2.5 Were efforts made to minimize error in selection of studies?	Concerns regarding methods used to select studies.	Comments
Grant (2015)[40]	Yes	No	Probably yes	Yes	Yes	Low	None

Table E-3C. Risk of Bias Assessment for Included Systematic Review: Data Collection and Study Appraisal

Author (Year)	3.1 Were efforts made to minimize errors in data collection?	3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret results?	3.3 Were all relevant study results collected for use in the synthesis?	3.4 Was risk of bias formally assessed using appropriate criteria?	3.5 Were efforts made to minimize error in risk of bias assessment?	Concerns regarding methods used to select studies.	Comments
Grant (2015)[40]	No information	Yes	Yes	No	No information	Unclear	No information provided about attempts to assess individual study risk of bias.

Table E-3D. Risk of Bias Assessment for Included Systematic Review: Synthesis and Findings

Author (Year)	4.1 Did the synthesis include all studies that it should?	4.2 Were all pre-defined analyses reported or departures explained?	4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs, and outcomes across included studies?	4.4 Was between study variation minimal or addressed in the synthesis?	4.5 Were the findings robust?	4.6 Were biases in primary studies minimal or addressed in the synthesis?	Concerns Regarding Methods Used to Select Studies	Comments
Grant (2015)[40]	Yes	Yes	Yes	Yes	No information	No information	Low	Given topic, sensitivity analyses probably not needed

Table E-3E. Risk of Bias Assessment for Included Systematic Review: Overall Risk of Bias Assessment

Author (Year)	Concerns Regarding Study Eligibility Criteria	Concerns Regarding Methods Used to Identify or Select Studies	Concerns Regarding Methods Used to Collect Data and Appraise Risk of Bias	Concerns Regarding the Synthesis of Findings	Did Interpretation of Findings Address all of Concerns Identified in Domains 1-4?	Was the Relevance of Identified Studies to the Review's Research Question Appropriately Considered?	Did the Reviewers Avoid Emphasizing Results on the Basis of Their Statistical Significance?	Overall Risk of Bias in the Review
Grant (2015)[40]	Low	Low	Unclear	Low	Yes	Yes	Yes	Unclear