Washington State Health Care Authority

Genomic microarray testing and whole exome sequencing

Clinical Expert

Amy Lawson Yuen, MD, PhD

Genomic Institute, MultiCare Health System
Tacoma, WA

[redacted]

AMY LAWSON YUEN, MD, PhD

PROFILE

10+ years in clinical genetics and pediatric care with experience in research and medical writing.

LICENSE AND CERTIFICATIONS

AMERICAN BOARD OF PEDIATRICS
Initial certification 2004, meeting requirements for Maintenance of Certification

AMERICAN BOARD OF MEDICAL GENETICS AND GENOMICS
Initial certification 2007, meeting requirements for Maintenance of Certification

WASHINGTON STATE MEDICAL LICENSE
2007 – current

EXPERIENCE

CLINICAL GENETICS - MULTICARE HEALTH SYSTEM/MARY BRIDGE CHILDREN'S HOSPITAL, TACOMA, WA
June 2013 – present
Clinical genetics.

PEDIATRICS AND CLINICAL - GENETICS WOODCREEK HEALTHCARE, PUYALLUP, WA
January 2008 – May 2013
Clinical genetics and pediatrics.

CLINICAL GENETICS/LOCUM TENENS - GROUP HEATH, SEATTLE, WA
July 2008 – August 2009
Locums clinical genetics.

SENIOR UPDATE EDITOR - GENEREVIEWS (WWW.GENETESTS.ORG), SEATTLE, WA
August 2007 – March 2008
Edited updates in GeneReviews articles.

VOLUNTEER POSITIONS

MULTICARE INTERNAL REVIEW BOARD (IRB), TACOMA, WA
September 2015 – Current
Scientific member of the MultiCare IRB.

MEDICAL ADVISOR, SYNDROMES WITHOUT A NAME (SWAN)
http://www.undiagnosed-usa.org
May 2013 – current
Provide clinical insight to the SWAN board as needed. Assisted with application for and establishment of PEER (Platform for Engaging Everyone Responsibly) registry supported by Genetic Alliance.

CLINICAL TRAINING

CLINICAL FELLOWSHIP
Genetics and Metabolism - Harvard Combined Program, Boston, MA
July 2004 - June 2007

RESIDENCY AND INTERNSHIP
Pediatrics - Massachusetts General Hospital, Boston, MA
July 2001 – June 2004

EDUCATION

MEDICAL AND GRADUATE EDUCATION
Medical College of Virginia Campus of Virginia Commonwealth University, Richmond, VA
August 1995 – May 2001
M.D. May 2001
Ph.D., Pharmacology and Toxicology, May 2001

UNDERGRADUATE EDUCATION
The Johns Hopkins University, Baltimore, MD
September 1991- May 1995
BA, Biophysics May 1995

AWARDS & GRANTS

2010, The European Journal of Human Genetics and Nature Publishing Group Prize to the three best cited papers published for every two

---

calendar year cycle for the publication “Familial deletion within NLGN4 associated with autism and Tourette syndrome.” Amy Lawson-Yuen, Juan-Sebastian Saldivar, Steve Sommer, and Jonathan Picker. Eur J Hum Genet. 2008 May;16(5):614-8.

2007, Harvard Medical School Genetics Training Program Award for Excellence in Clinical Genetics

2006, AAP Section on Genetics and Birth Defects Young Investigator Research Grant Award

1999, Lauren A. Woods Award for research excellence, in the Department of Pharmacology and Toxicology at Medical College of Virginia Campus of Virginia Commonwealth University

1998, Merit Travel Award, American Society of Hematology Meeting, Miami Florida

1995, Phi Beta Kappa Honor Society

1995, Golden Key Honor Society

1992, Howard Hughes Research Award for undergraduates

INVITED PRESENTATIONS

June 14, 2013, Tianjin International Symposium and Short Course on Hearing Loss, Tianjin, China, “Genetics and Clinical Genomics: Genetic Counseling”

February 3, 2009, Pediatric Grand Rounds, Mary Bridge Children’s Hospital, Tacoma, WA, “The Expanded Washington State Newborn Screen: An Overview for Primary Care Providers”

PUBLICATIONS

HUWE1 mutations cause dominant X-linked intellectual disability: a clinical and genetic study of 22 patients. Stéphanie Moortgat, Siren Berland, Ingvild Aukrust, Isabelle Maystadt, Laura Baker, Valerie Benoit, Nicola S. Cooper, François-Guillaume Debray, Laurence Faivre, Thatjana Gardeitchik, Bjørn I. Haukanes, Gunnar Houge, Emma Kivuva, Sarju Mehta, Marie-Cécile Nassogne, Nina Powell-Hamilton, Rolph Pfundt, Monica Rosello Piera, Trine Prescott, Pradeep Vaseduvan, Barbara van Loon, Christine Verellen-Dumoulin, Alain Verloes, Charlotte von der Lippe, Emma Wakeling, Andrew Wilkie, Louise Wilson, **Amy Yuen**, DDD study21,

Ruth. A Newbury-Ecob and Karen J. Low. European Journal of Human Genetics, in press.

DNM1 encephalopathy: a new disease of vesicle fission. Sarah von Spiczak, Katherine L Helbig, Deepali N Shinde, Robert Huether, Manuela Pendziwiat, Charles M Lourenco, Mark E Nunes, Dean P Sarco, Richard A Kaplan, Dennis J Dlugos, Heidi Kirsch, Anne Slavotinek, Maria R Cilio, Mackenzie C Cervenka, Julie S Cohen, Rebecca McClellan, Ali Fatemi, **Amy Yuen**, Yoshimi Sogawa, Rebecca Littlejohn, Scott D McLean, Laura Hernandez-Hernandez, Bridget Maher, Rikke S Møller, Elizabeth Palmer, John A Lawson, Colleen A Campbell, Charuta N Joshi, Diana L Kolbe, Georgie Hollingsworth, Bernd A Neubauer, Hiltrud Muhle, Ulrich Stephani, Ingrid E Scheffer, Sérgio D J Pena, Sanjay M Sisodiya, and Ingo Helbig. Neurology. 2017 Jul 25;89(4):385-394.

Recurrent duplications of 17q12 associated with variable phenotypes. Mitchell E, Douglas A, Kjaegaard S, Callewaert B, Vanlander A, Janssens S, **Yuen AL**, Skinner C, Failla P, Alberti A, Avola E, Fichera M, Kibaek M, Digilio MC, Hannibal MC, den Hollander NS, Bizzarri V, Renieri A, Mencarelli MA, Fitzgerald T, Piazzolla S, van Oudenhove E, Romano C, Schwartz C, Eichler EE, Slavotinek A, Escobar L, Rajan D, Crolla J, Carter N, Hodge JC, Mefford HC. Am J Med Genet A. 2015 Dec;167(12):3038-45.

Myhre syndrome with ataxia and cerebellar atrophy. Bachmann-Gagescu R, Hisama FM, **Yuen AL**. Clin Dysmorphol. 2011 Jul;20(3):156-9.

Betaine for Homocystinuria. **Amy Lawson-Yuen** and Harvey Levy, In: Small Molecule Therapy for Genetic Disease, edited by Jesse Thoene, Cambridge University Press, August 31, 2010, ISBN-13: 9780521517812.

Familial deletion within NLGN4 associated with autism and Tourette syndrome. **Amy Lawson-Yuen**, Juan-Sebastian Saldivar, Steve Sommer, and Jonathan Picker. Eur J Hum Genet. 2008 May;16(5):614-8.

Molecular studies of segmental aneusomy: FISHing for the atypical cry in del(5)(p15.3). J.C. Hodge, **A. Lawson-Yuen**, J.M., and A.H. Ligon. Cytogenet Genome Res. 2007; 119(1-2):15-20.

Ube3a mRNA and protein expression are not decreased in MeCP2R168X mutant mice. **Amy Lawson-Yuen**, Daniel Liu, Liqun Han, Zhichun I. Jiang, Guochuan E. Tsai, Alo C. Basu, Jonathan Picker, Jiamin Feng and Joseph T. Coyle. Brain Research. 2007 Nov 14;1180:1-6.

Atypical Cases of Angelman Syndrome. **Amy Lawson-Yuen**, Bai-Lin Wu, Va Lip, Trilochan Sahoo, and Virginia Kimonis. Am J Med Genet A. 2006 Nov 1;140(21):2361-4.

Patient with Novel Interstitial Deletion of Chromosome 3q13.1q13.3 and Agenesis of the Corpus Callosum. **Amy Lawson-Yuen**, Sue Ann Berend, Janet S Soul, and Mira Irons. Clin Dysmorphol. 2006 Oct;15(4):217-220.

The Use of Betaine in the Treatment of Elevated Homocysteine. **Amy Lawson-Yuen** and Harvey L. Levy. Mol Genet Metab. 2006 Jul;88(3):201-7.

Phosphatase inhibition promotes anti-apoptotic but not proliferative signaling pathways in EPO-dependent HCD57 cells. **Amy E. Lawson**, Haifeng Bao, Amittha Wickrema, Sarah M. Jacobs-Helber and Stephen T. Sawyer. Blood 2000 Sep 15;96(6):2084-92.

Protein Kinase B (c-Akt), Phosphatidylinositol 3-Kinase, and STAT5 Are Activated by Erythropoietin (EPO) in HCD57 Erythroid Cells. Haifeng Bao, Sarah M. Jacobs-Helber, **Amy E. Lawson**, Kalyani Penta, Amittha Wickrema, and Stephen T. Sawyer. Blood June 1999, Volume 93, Pages 3757-3773.

Human tryptase fibrinogenolysis is optimal at acidic pH and generates anticoagulant fragments in the presence of the anti-tryptase monoclonal antibody B12. Ren S, **Lawson AE**, Carr M, Baumgarten CM, and Schwartz LB. Journal of Immunology October 1997, Volume 159, Pages 3540-8.

Distinct signaling from stem cell factor and erythropoietin in HCD57 cells. Jacobs-Helber SM, Penta K, Sun Z, **Lawson A**, and Sawyer ST. Journal of Biological Chemistry March 1997, Volume 272, Pages 6850-3.

Agency medical director comments

Genomic microarray testing

Shana Johnson, MD
Clinical Quality - Care Transformation
Health Care Authority

January 19, 2018

Topic update

- Review of **whole exome sequencing** has been **removed** from this technology review.
- The scope of this evidence review was not adequate to address this technology.

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Genomic microarray

To review the safety, efficacy, and cost of chromosomal microarrays when used for the diagnosis and management of children with:

- Developmental delay and intellectual disability
- Autism spectrum disorder
- Congenital anomalies

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Reasons prompting microarray review

- Increasing utilization
- Increase in requests from tertiary care centers and community based practices (developmental pediatrics, general pediatrics, neurology)
- Increase in requests for children with mild to moderate delays (less then 2 standard deviations) and mild-moderate behavior challenges
- Request from medicaid medical directors

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The WA Medicaid program provides medical coverage to about 50% of the children in WA state

- 48,248 (FFS)
- 765,826 (MCO)
- 814,074 (Total children)

WA has approximately 1.6 million kids.
(2016 KC Data Center/ Annie E Casey Foundation)

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Health Technology Assessment

Utilization Analysis – Genomic MicroArray and Single Exome Sequencing

9/12/2017

	2013	2014	2015	2016	Overall
PEBB/UMP					
Unique Patients	1	1	6	17	25
Encounters	1	1	6	17	25
Average Encounters/Patient	1	1	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
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.*

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Approach to genetics policy

- How accurately and reliably the test measures the analyte of interest, such as gene or chromosomal variant
- Diagnostic accuracy; how accurately the test detects or predicts the clinical condition of interest
- When the test is used, does it improve clinical outcomes

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Clinical utility spectrum

- Change in treatment recommendations — hypothetical
- Change in treatment recommendations — actual

- Change in measures of decisional conflict
- Change in treatments rendered

- Change in surrogate clinical outcomes
- Change in critical patient important clinical outcomes

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Guidelines and payer policies

2011, National Institute for Health and Care Excellence (NICE)

- CMA testing should not be routinely done on all children with autism, but only in those with dysmorphic features or ID

2013, American College of Medical Genetics and Genomics (ACMG)

- CMA replace G-band karyotype for the clinical evaluation of ASDs

2014 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. CMA as a standard for diagnosis of patients with ASDs and MCAs.

2015 American Academy of Neurology (AAN)

- 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.

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State agency policy—Uniform Medical Plan

Chromosomal microarray may be considered medically necessary in children and adolescents (17 years or younger) when any of the following conditions are met:

- Apparent nonsyndromic cognitive developmental delay/ intellectual disability (DD/ID); or
- Autism spectrum disorder (ASD); or
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome. Congenital anomaly is defined as an anomaly that is present at birth.

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Aetna

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
- Targeted genetic testing, if or when indicated by clinical and family history, is negative
- Clinical presentation is not specific to a well-delineated genetic syndrome
- When the results of testing could impact the clinical management of the child

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Cigna

CMA medically necessary when phenotypic characteristics of a specific genetic disorder are absent for patients with ASD and nonsyndromic global DD/ID; MCAs are present and cannot be ascribed to a specific genetic syndrome.

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.

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Medicaid FFS

Chromosomal microarray may be considered medically necessary:

- Targeted genetic testing as indicated is negative
- Clinical presentation is not specific to a well-delineated genetic syndrome
- Multiple congenital anomalies are present
- DD/ID or ASD with mcas
- Results are expected to impact the clinical management

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Kaisier

CMA medically necessary for the evaluation of ID for individuals

- Significant dysmorphic features or congenital anomalies
- Results are expected to affect clinical management
- Genetic counseling by a health care professional with appropriate genetic training and experience has been conducted

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Microarray—etiologic diagnostic yield

- DD/ID and ASD without complex features are a clinical diagnosis
- Genetic tests are used to establish an etiologic diagnosis; whether a patient carries a specific genetic variant
- RTI review including studies from United States (US) 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
  - 5.4% (95% CI, 4.8% to 6.0%) of ASD

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- Health technology assessment (HTA) by Grant et al.
  - Diagnostic yield averaged 19% for global developmental delay or intellectual disability (ID)
  - 12% for ASD
- Frequency of disease-causing CNVs is highest (20-25%) in children with moderate to severe intellectual disability accompanied by malformations or dysmorphic features (Beaudet, AL. The utility of chromosomal microarray analysis in developmental and behavioral pediatrics. Child development. 2013 Jan-Feb;84(1):121-32.)
- Diagnostic yield among general population of adults and children: 0.7% (Estonia biobank had a pathogenic variant)

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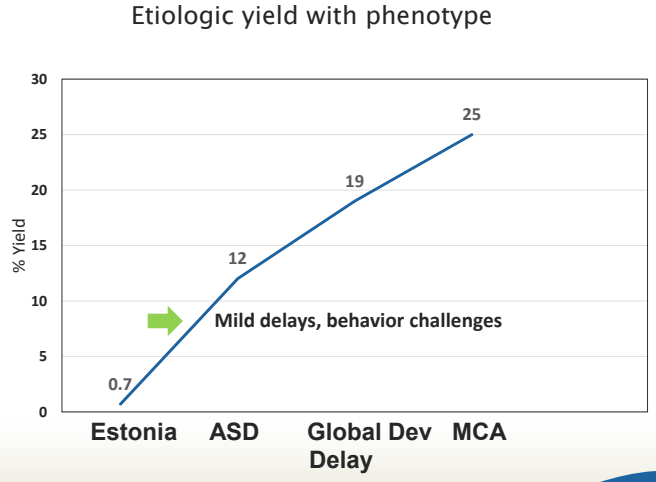
Microarray—etiologic diagnostic yield



Impact on clinical management

- From 27.1% to 93.8% of cases with a pathogenic variant had a change in management
- Cases with management changes represented 3.6% to 6.7% of all cases tested
  - Management changes = specialist referrals, diagnostic testing, change in medical surveillance or screening, surgical interventions or procedures, medications, lifestyle changes
- Clinical utility - recommended clinical action

DECISIONS
- Change in measures of decisional conflict
- Change in treatments rendered

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Table 2 Summary of recommendations made by health-care providers in response to abnormal CMA findings

Recommendation	Number of patients (%)[a] All indications for testing (n = 187)	Neurodevelopmental indications only (n = 38)[b]
Clinical action	**24 (12.8)**	**3 (7.9)**
Pharmacologic treatment	6 (3.2)	—
Angiotensin receptor blocker	1 (0.5)	—
Cysteamine	1 (0.5)	—
Growth hormone	3 (1.6)	—
Testosterone	1 (0.5)	—
Cancer-related screening or surveillance	11 (5.9)	3 (7.9)
APC deletion	3 (1.6)	1 (2.6)
VHL deletion	2 (1.1)	1 (2.6)
MLH1 deletion	1 (0.5)	1 (2.6)
NSD1 deletion	1 (0.5)	—
SMARCB1 deletion	1 (0.5)	—
CREBBP deletion	1 (0.5)	—
4q21 deletion	1 (0.5)	—
Mosaic monosomy 7	1 (0.5)	—
Cancer-related screening avoided	3 (1.6)	—
APC not deleted	2 (1.1)	—
VHL not deleted	1 (0.5)	—
Contraindication	4 (2.1)	—
Avoid excess calcium and vitamin D	3 (1.6)	—
Avoid live viral vaccines	1 (0.5)	—
Further clinical evaluation	**95 (50.8)**	**14 (36.8)**
Specialist referral	84 (44.9)	12 (31.6)
Cardiology	38 (20.3)	8 (21.1)
Audiology	36 (19.3)	1 (2.6)
Ophthalmology	33 (17.7)	2 (5.3)
Immunology	18 (9.6)	—
Neurology (includes brain MRI)	13 (7.0)	2 (5.3)
Endocrinology	11 (5.9)	1 (2.6)
Otolaryngology	9 (4.8)	—
Other[c]	15 (8.0)	1 (2.6)
Imaging[d]	38 (20.3)	6 (15.8)
Laboratory testing	29 (15.5)	2 (5.3)
Overall impact on clinical management	**102/187 (54.5)**	**16/38 (42.1)**

MRI, magnetic resonance imaging.

[a]Includes only those patients with abnormal chromosomal microarray (CMA) results and clinical follow-up available; percentages are not additive because some patients had multiple recommendations (see Table 3). [b]Includes only those patients with isolated neurodevelopmental indications, including developmental delay, learning disabilities, behavioral or psychiatric disorders, seizures, intellectual disability, and/or autism spectrum disorders. [c]Includes referrals for sleep study, orthopedics, nephrology, gastroenterology, pulmonology, hematology, and muscular dystrophy clinic. [d]Includes renal or abdominal ultrasound, X-ray, and skeletal survey.

Highly actionable findings all had MCAs per articles discussion section

Henderson LB, Applegate CD, Wohler E, et al. The impact of chromosomal microarray on clinical management: a retrospective analysis. Genet Med 2014 Sep;16(9):657-64.

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Clinical utility—strength of evidence

Table ES-9. 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

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Clinical utility of microarray testing in the absence of data on improved clinical outcomes:

- Value of etiologic diagnosis to the family
- Estimation of recurrence risk, reproductive counseling
- Value of early detection and early intervention

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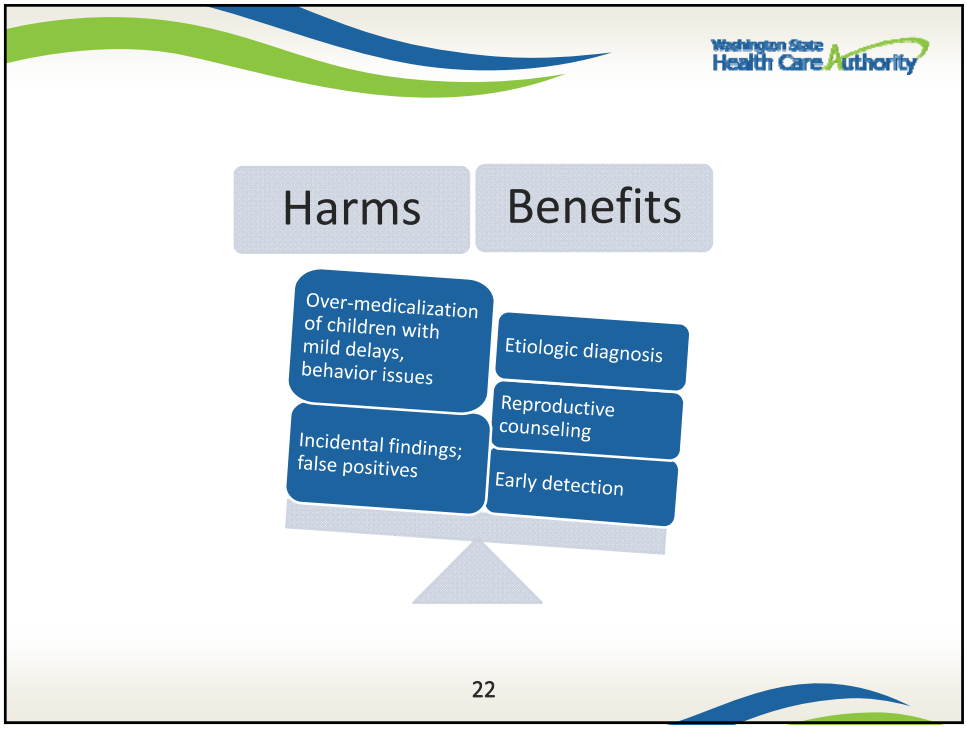

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Approach to genetics policy

Analytic Validity	Clinical Validity	Clinical Utility
• Supported	• Diagnostic yield supported	• Less supported SOE: Very Low • Actionable results seen more with congenital anomalies are present • Specialist referral more common with neurodevelopmental

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Agency recommendations

Cover with conditions

Genomic microarray for diagnosing genetic abnormalities in children with any one of the following:

- Multiple congenital anomalies
- Global developmental delay or intellectual disability
- Autism spectrum disorder

- Targeted genetic testing, as indicated, is negative
- Clinical presentation is not specific to a well-delineated genetic syndrome
- The results of testing could impact the clinical management

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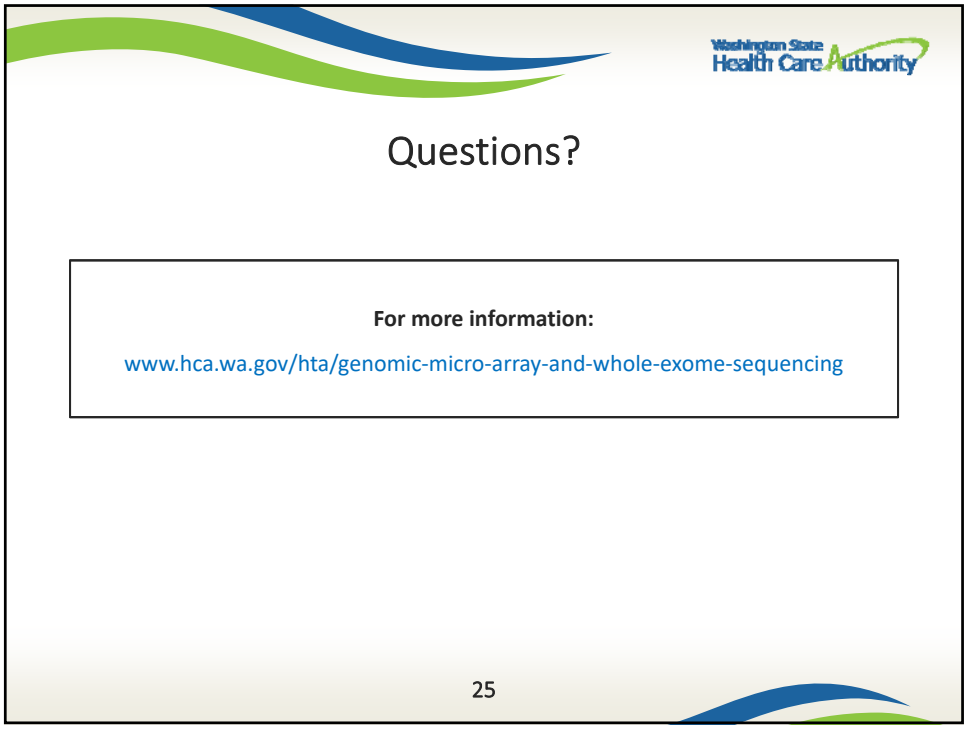
Washington State Health Care Authority
Questions?
For more information:
www.hca.wa.gov/hta/genomic-micro-array-and-whole-exome-sequencing
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Washington State Health Care Authority

Order of scheduled presentations

Genomic microarray testing and whole exome sequencing

	Name
1	
2	
3	
4	
5	
6	

No requests to provide public comment on this technology review were received.

Genomic microarray and whole exome sequencing

Health Technology Assessment for the State of Washington Health Care Authority

Nedra Whitehead, MS, PhD, CGC
RTI-UNC Evidence Based Practice Center

Abbreviations

- N, number
- CNV, copy number variants
- CMA, chromosomal (genomic) microarray
- WES, whole exome sequencing
- ID, intellectual disability
- DD, developmental disability
- MCA, multiple congenital anomalies

Background

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Contents

- Chromosomal abnormalities and their impact on health
- Chromosomal microarray and whole exome testing
- Test interpretation
- Regulation of the tests
- Scope of HTA

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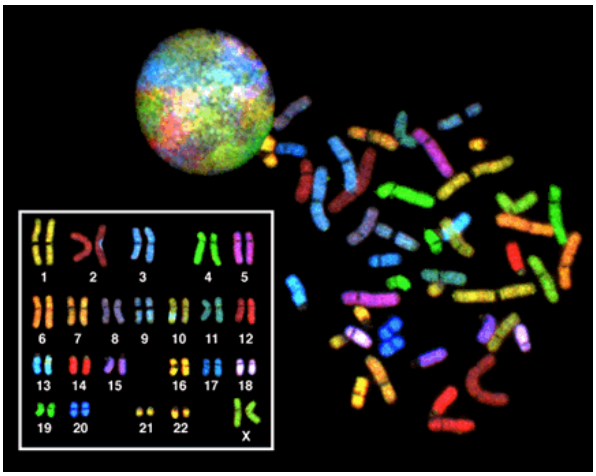
Chromosomes and chromosome abnormalities

- Chromosomes
  - Genetic structures of a cell and a person;
  - Humans normally have 23 pairs;
  - Each parent contributes half of each pair of chromosomes;
- Chromosome abnormalities
  - Occur during cell replication in production of egg or sperm;
  - Whole or parts of chromosomes are lost, gained or rearranged;
  - May be balanced (no gain or loss of DNA) or unbalanced.



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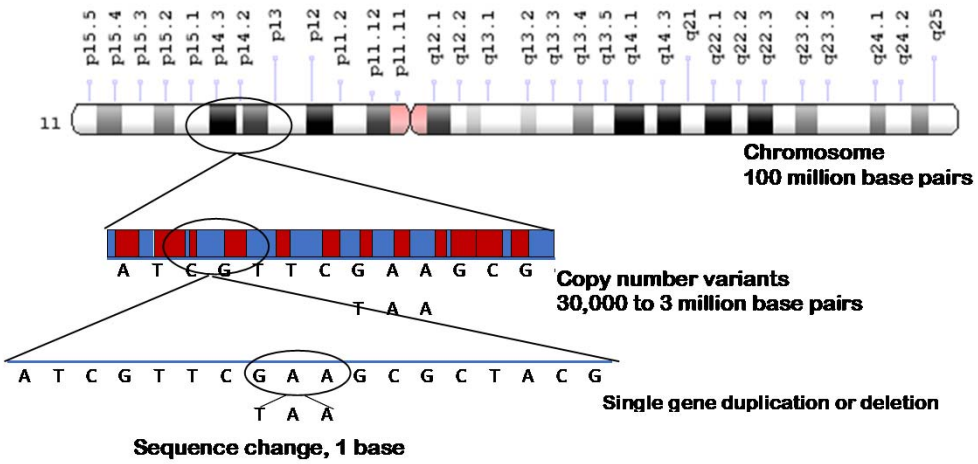
Genomic Variation from Chromosomes to Nucleotides



Clinical impact is not necessary correlated with size

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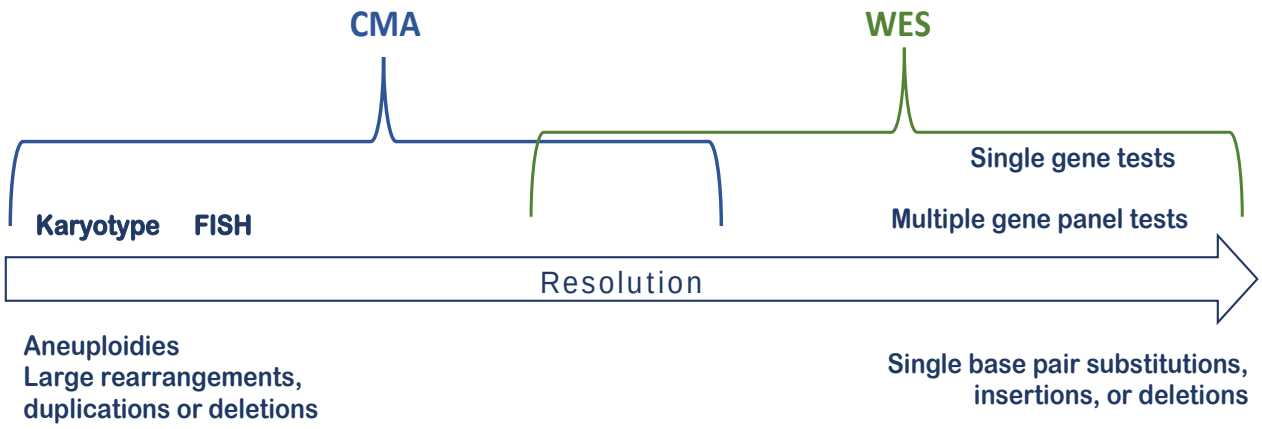
Graphics: Chromosome 11 schematic from National Institutes of Health.
Graphic based on https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/deciding-to-test

Chromosomal Microarray vs. Whole Exome Sequencing



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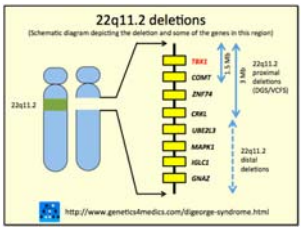
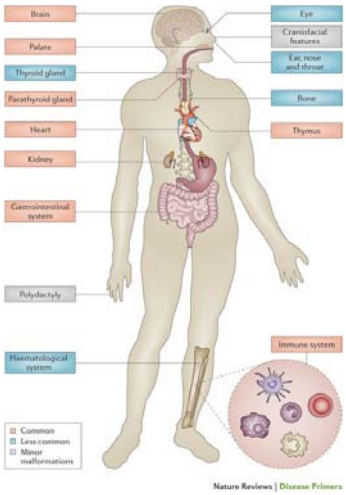
Burden of unbalanced chromosome abnormalities

- Prevalence
  - Any, 43.8/10,000 births of ≥ 20 weeks gestation
  - Rare, 7.4 /10,000 births
- Consequences
  - Size and location dependent
  - Fetal death, congenital defects, genetic disease, intellectual impairment





Organ and system involvement in 22q11.2 deletion syndrome.
Reproduced with permission from *22q11.2 deletion syndrome.* McDonald-McGinn et al. Nat Rev Dis Primers. ; 1: 15071. doi:10.1038/nrdp.2015.71.

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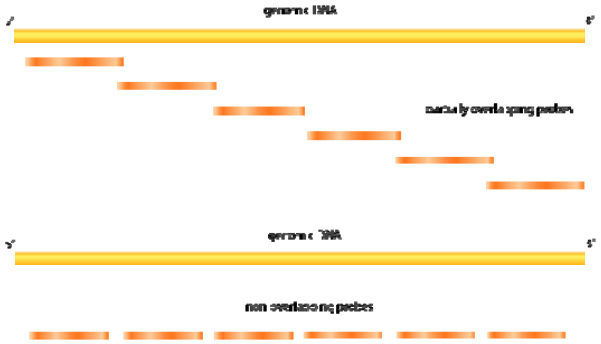
Chromosomal (genomic) microarray (CMA)

- Genome wide coverage
- Microarray
  - Immobilized probes to bind specimens with specific characteristics
  - Wash to remove unbound specimen
  - Detection system
- Probes detect
  - Genetic regions
  - Single nucleotide polymorphisms
  - Combination



By Danny556 (talk) - self-made, CC BY-SA 3.0, https://en.wikipedia.org/w/index.php?curid=16020178

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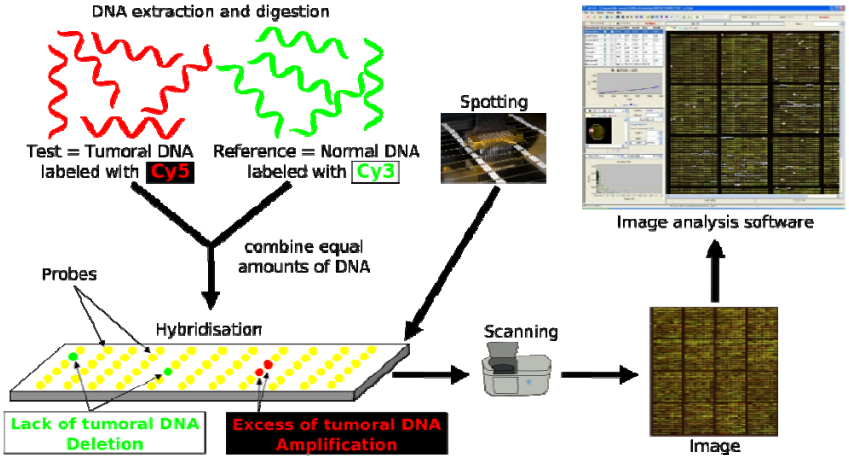
Array Procedure



Source: Emmanuel Barillot, Laurence Calzone, Philippe Hupé, Jean-Philippe Vert, Andrei Zinovyev, Computational Systems Biology of Cancer Chapman & Hall/CRC Mathematical & Computational Biology , 2012. Licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license

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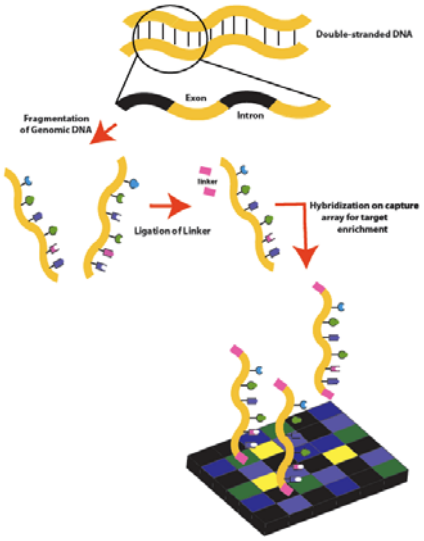
Whole exome sequencing

- Provides sequence of base pairs in protein coding regions (exons) across the genome
- Two step process
  - Exons identified and extracted
  - Exons sequenced



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Comparison of CMA and WES

- CMA
  - Duplications or deletions
    - Resolution: 30k to 60k bases
    - May detect changes in known regions < 1kb
    - Usually involve multiple genes
- WES
  - Duplications and deletions
    - Any size
    - In coding regions
  - Single base pair changes

- CMA or WES do not detect
  - Rearrangements that don't change overall DNA content
  - Small levels of mosaicism
  - Large inversions

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Test Interpretation

- Databases of known variants
  - Benign genetic variation
    - Database of Genetic Variation
  - Pathogenic genetic variation
    - ClinVar
    - Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER)

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Regulatory Status

- Laboratory developed tests
  - Not regulated by U.S. Food and Drug Administration (FDA)
  - Conducted within hospital or freestanding clinical laboratories meeting CLIA* standards for high complexity testing
- Kits sold for conducting CMA or WES testing require FDA approval
  - Affymetrix CytoScan® Dx assay (Affymetrix, Inc., Santa Clara, CA)
    - January 21, 2014
  - Agilent GenetiSure Dx Postnatal Assay (Agilent Technologies, Inc., Santa Clara, CA)
    - August 14, 2017
  - FDA-approved indications
    - Postnatal detection of duplications or deletions
    - Developmental delay, intellectual disability, congenital anomalies, or dysmorphic features

* Clinical Laboratory Improvement Amendments Program

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Policy Context for Washington

Topic selection

Area of concern	Level of concern
Safety	Medium
Efficacy	High
Cost	High

Considerations

- Practice guidelines recommend
  - chromosomal microarray as first-tier diagnostic test
    - development delay, intellectual disability, multiple congenital anomalies
    - Autism
- Increasing prevalence of autism

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Analytic Framework and Research Questions

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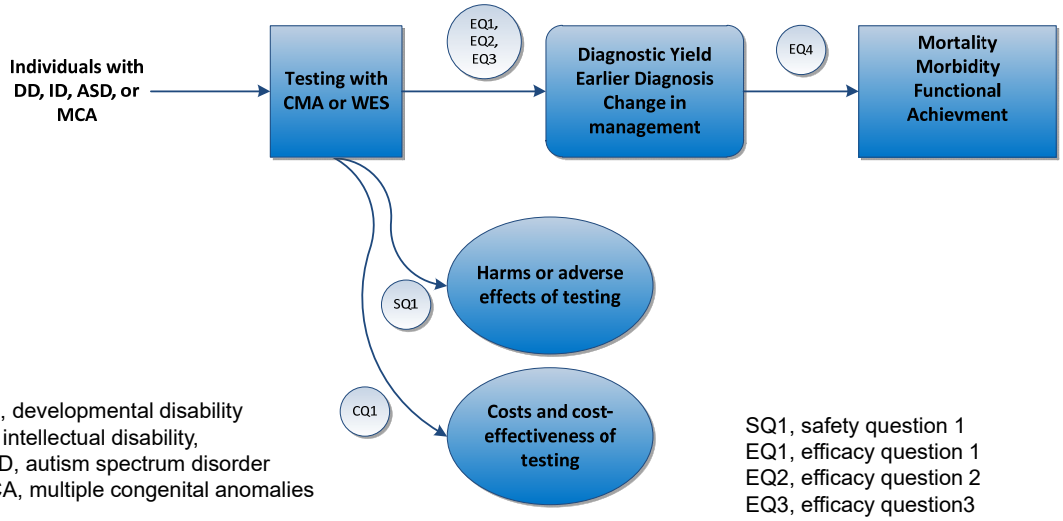
Analytic framework



DD, developmental disability
ID, intellectual disability,
ASD, autism spectrum disorder
MCA, multiple congenital anomalies

SQ1, safety question 1
EQ1, efficacy question 1
EQ2, efficacy question 2
EQ3, efficacy question3
CQ1, cost question 1

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Populations, Interventions, Comparators, Outcomes, Time Period, and Setting

Populations	Children with congenital defects, autism, intellectual disability or developmental disability without a clearly identifiable etiology.
Intervention	1. CMA testing with current platforms. 2. WES to identify chromosomal abnormalities
Comparator	EQ1, EQ2, SQ1: descriptive, may not have comparator groups. EQ3: Management before diagnosis or of undiagnosed children EQ4 and CQ1: No genetic diagnostic testing or genetic diagnostic testing did not include CMA or WES.
Safety Outcomes	SQ1. Harms 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, 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-US studies were excluded for EQ1 and EQ2.

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Exclusions

- Analytic validity of CMA or WES
  - Analytic validity assumed based on meeting CLIA standards.
- Use of CMA or WES in cancer management or prenatal testing.
- Use of WES to identify mutations within single genes.
- Harm, ethical considerations, or clinical utility of findings not related to conditions for which the tests were ordered.
- For EQ1 and EQ2 (diagnostic yield), we excluded
  - Studies conducted outside of the United States
  - Studies with CMA testing conducted prior to 2009 or that used obsolete testing platforms (e.g., bacterial artificial chromosomes)

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Methods

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Search and Selection

- Sources
  - MEDLINE® (via PubMed), clinicaltrials.gov, FDA device approval databases,
  - Websites of payers, professional societies, organizations that disseminate health technology assessments
- Search 1/1/2000–9/18/2017 in English
  - Excluded case reports, commentaries, or editorials
  - Blocks of terms: chromosomal abnormalities, chromosomal microarray or whole exome sequencing, children with intellectual disability, autism, or birth defects
- Review
  - Title and abstracts: single review. principal investigator reviewed abstracts excluded for testing platform and sample of other excluded abstracts
  - Full text review: a senior team member and the principal investigator screened each full-text article

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Abstraction and analysis

- Abstraction
  - Single abstraction into structured spreadsheet reviewed by principal investigator
- Risk of bias
  - Two independent assessments
  - QUADAS-2, ROBIS, or tailored questions from RTI question bank
- Qualitative synthesis for each research question
  - Adjusted all cost outcomes to 2010 US dollars
- Quantitative synthesis
  - 3 or more publications with similar approach and same outcome measure
  - OpenMetaAnalyst and method of Hedges and Olkin to estimate between-study variance.
- Graded strength of evidence using GRADE

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Results

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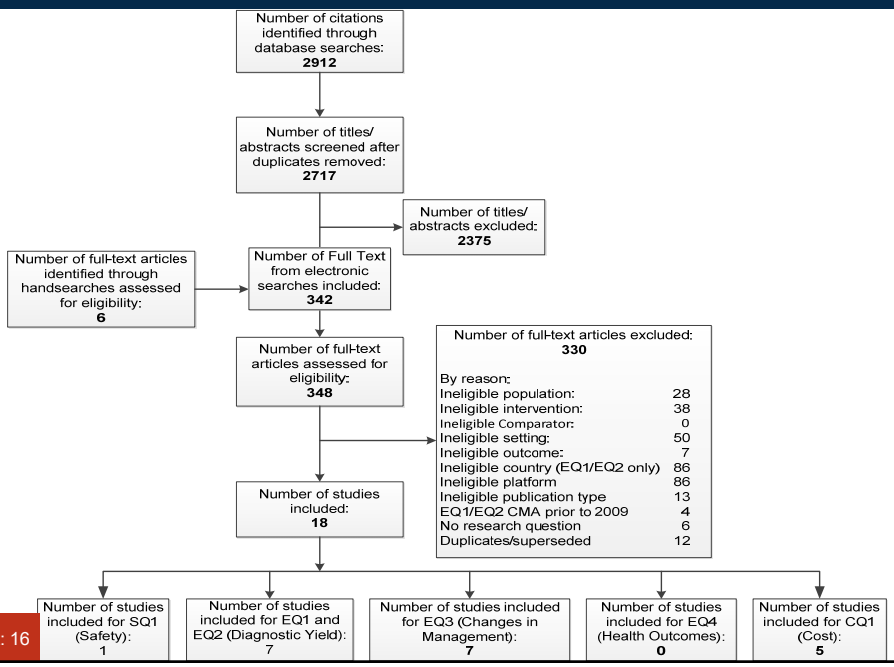
Search results



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Safety of CMA and WES

- Scope of review
  - Excluded non-US study reports on false negative or false positive
  - Incidental or secondary findings
- Included 1 study of discrimination resulting from test results

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What safety issues do CMA and WES pose?
Summary of Findings and Strength of Evidence

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

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

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Diagnostic Yield of CMA

- Diagnostic yield
  - The proportion of tested patient for whom CMA or WES reveals a pathogenic copy number variant that explains their clinical signs and symptoms (ie, phenotype).
  - Diagnostic yield of karyotype
    - ~ 3%
- Included studies
  - 4 consecutive series of patients or laboratory referrals
    - Indications varied and not well-defined
  - 1 study
    - Clinic recruited patients with specific clinical symptoms or diagnosis
  - 1 health technology assessment

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How often does CMA return an informative result?
Summary of Evidence

Author (Year)	Study Population; Sample Size; Test	Diagnostic Yield [Detection of A Pathogenic Variant] N (%)	Risk of Bias
Coulter (2011)	Patients of children's hospital; N =1,792, CMA	131 (7.3%)	Unclear
Henderson (2014)	Laboratory-based series of patients; N= 1,780; CMA	227 (12.7%)	Low
Ho (2016)	Laboratory-based series of patients with neurodevelopmental disorders; N=10,351; CMA	890 (8.6%)	Low
Roberts (2014)	Laboratory-based series of patients with mixed phenotypes of ID/MCA; N=215; CMA	32 (14.9%)	Low
Stobbe (2014)	Clinic-based study of adults with autism; N=25; CMA	2 (12.0%)	Low

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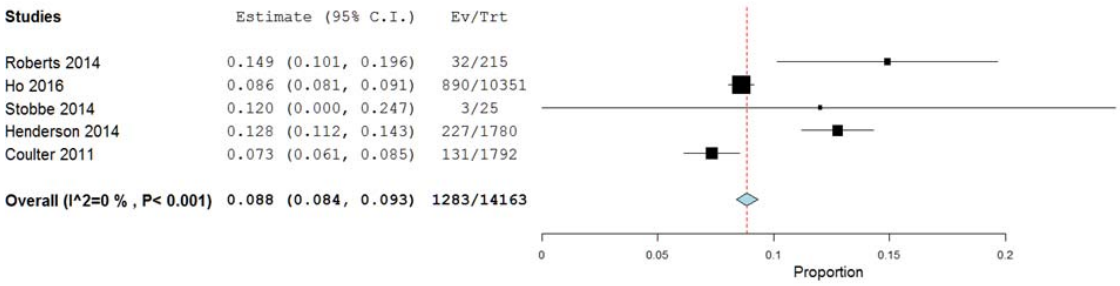
How often do CMA or WES return an informative result?
Summary of Evidence, cont.



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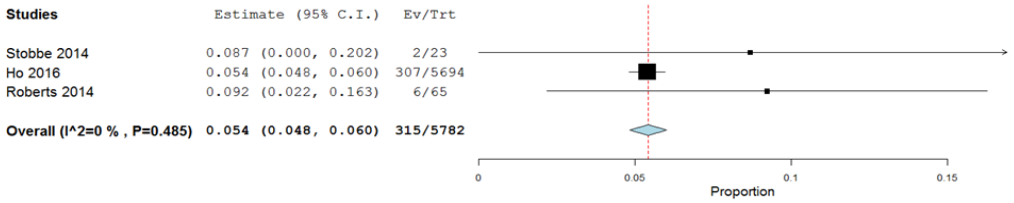
For what types of conditions is CMA most useful?
Summary of Evidence

- Few studies reported diagnostic yield by specific characteristics or diagnosis.
- Autism spectrum disorders: 3 studies
  - Pooled summary estimate: 5.4% (95% CI, 4.8% to 6.0%).



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How often does CMA return an informative result?
Summary of Evidence, cont.

- Grant et al. (2015)
  - Health technology assessment of chromosomal microarray
    - Global developmental delay
    - Intellectual disability
    - Autism spectrum disorders
    - US and non US studies published before June 24, 2015
  - Diagnostic yield
    - 55 studies, 21 from 2012 or later
    - 1% annual increase in diagnostic yield
    - Any indication, publication ≥ 2012: 19%
    - Autism spectrum disorders, publication ≥ 2012: 12.3% (4 studies)

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How often does CMA return an informative result?
Strength of Evidence

Outcome	No. of Studies, Subjects; Study Design	Risk of Bias	Inconsis-tency	Indirect-ness	Precision	Other consider-ations	Strength of Evidence Grade
Diagnostic yield of CMA Range: 7.3% to 14.9%	5; 14,163; Observational	Not serious	Not serious	Not serious	Not serious	Definition of outcome	Low
Grant et al: 19%*	21; 6,662 Observational						

*Published in 2012 or later

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Effect of CMA on Management

- Samples
  - Databases of cases (2 studies)
    - A priori identification of CNVs with management recommendations
  - Identification of management changes in response to CMA results (5 studies)
    - Patients with pathogenic or likely pathogenic variants
    - Physician survey or medical records abstraction
- Variant classification
  - Laboratory report
  - ACMG guidelines
  - Known microduplication or deletion syndromes, variant size, gene content
- Management changes
  - Specialist referrals
  - Diagnostic testing
  - Changes in medical surveillance or screening
  - Surgical or intervention procedures
  - Prescribed or contraindicated medications
  - Lifestyle changes
    - 2 studies

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Does the diagnosis of a chromosomal disorder change management?
Summary of Evidence

Author (Year)	Study Population; Sample Size	Outcome Definition	Result[1]	Risk of Bias
Coulter (2011)	Retrospective cohort Tested: 1,792, Pathogenic variant: 235 Eligible for follow-up study: 194	At least 1 management change due to pathogenic variant results	65 patients with management change (53.7% of follow-up study; 3.6% of all tested)	Cannot determine
Ellison (2012)	Retrospective cohort Total tested: 46,298 Clinically actionable CNV: 1,996 Patients whose physicians were surveyed: 122 Responses received: 81	Clinically actionable CNV At least one guideline-recommended management change	1,996 cases with clinically actionable CNV (4.3%) 74 patients whose physicians reported at least 1 clinical action (93.8%)	High
Hayeems (2015)	Retrospective cohort of children followed at tertiary pediatric hospital; N=752	Mean number of recommendations due to pathogenic CNV	Mean 2.35 recommendations per patient	Low
Henderson (2014)	Retrospective cohort Tested: N=1,780 Pathogenic CNV: 227 Follow-up available: 187	At least one management change due to pathogenic CNV	102 cases with management change (54.5% of follow-up study; 5.7% of total tested)	Low

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Does the diagnosis of a chromosomal disorder change management?
Summary of Evidence

Author (Year)	Study Population; Sample Size	Outcome Definition	Result[1]	Risk of Bias
Riggs (2014)	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
Saam (2008)	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)	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 recommended change in management (75.7%)	Low

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Does the diagnosis of a chromosomal disorder change management?
Strength of Evidence

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	Serious	Serious	Serious	None	Very low

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Do children tested with CMA have better health outcomes?

- We found no evidence on this question.

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What is the cost and cost-effectiveness of CMA?

- We found no studies that reported cost-effectiveness.
- We identified 5 non-US studies that reported cost per additional diagnosis for CMA as a first-line test in patients with ID, DD or both relative to diagnosis without CMA testing.
- Cost per additional diagnosis represents the incremental cost of testing per incremental change in diagnostic yield

$$\frac{\text{Cost}_{\text{with CMA}} - \text{Cost}_{\text{without CMA}}}{\text{\# of diagnosed}_{\text{with CMA}} - \text{\# diagnosed}_{\text{without CMA}}}$$

  - A negative number represents cost savings per additional diagnosis with CMA
  - A positive number represents additional costs per additional diagnosis with CMA

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What is the cost and cost-effectiveness of CMA?
Summary of evidence

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

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*All costs presented by study authors converted and presented here in 2010 US$.

What is the cost and cost-effectiveness of CMA?
Strength of evidence

Outcome	No. Studies; Subjects; Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Strength of Evidence Grade
Cost per additional diagnosis range $-88,919 to $12,296	5; 1,750 Observational and decision analyses	Not serious	Serious	Serious	Very serious	None	Very low

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Discussion

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Summary of evidence

- Strength of evidence for all questions was very low or low
- Safety concerns
  - Evidence of discrimination but evidence insufficient to determine frequency
- Diagnostic yield
  - US, 2009 or later:
    - Any indication: 8.8% (95% CI, 8.4% to 9.3%), ASD: 5.4% (95% CI, 4.8% to 6.0%)
  - Grant et al., 2012 or later and including non-US studies
    - Global developmental delay or intellectual disability: 19%; ASD: 12%
- Impact on management
  - Changes due to CMA results
    - 27% to 94% of patients with a pathogenic variant, 3.6% to 6.7% of all patients tested
- Costs
  - Cost per additional diagnosis in 2010 US dollars varied widely.

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Limitations of the Evidence Base

- For all research questions
  - Studies of chromosomal abnormalities almost all used CMA
  - Sparse methodological details
  - Conflicts of interest – several studies stated goal of obtaining coverage for testing
- Evidence on diagnostic yield
  - Cases differed in diagnosis and prior diagnostic testing.
  - Arrays, software, and access to family history or parent samples varied across studies.
- Evidence on safety, impact on management, and cost
  - Limited in size, risk of bias, and applicability
  - Differences in variants among studies of management impact likely contributed to the large heterogeneity in estimated impact.
  - No cost studies conducted in the US or with a societal perspective.
  - Extreme clinical and methodological heterogeneity among cost studies.
  - Cost studies may no longer be applicable due to changing diagnostic processes and assay costs.

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Limitations of HTA

- Search limitations
  - Only studies published in English
  - Two US-based databases
  - Offset by extensive hand searches of bibliographies
- Citation review
  - Single reviewer to screen titles and abstracts
  - Offset by excellent concordance with test set; PI review of sample of abstracts
- Inclusions
  - Only US studies published in 2009 or greater for diagnostic yield
  - Did not systematically assess analytic validity or reproducibility
  - Did not conduct in-depth analysis of cases, breakpoints, or other information on variants.

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Practice guidelines endorsing chromosomal microarray

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

- Endorse as first-tier test
  - Children with development delay, intellectual disability, multiple congenital anomalies;
    - Dysmorphic features
    - Symptoms not consistent with single gene disorder

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Payer coverage

- Centers for Medicare and Medicaid Services have no national coverage determination for CMA;
- Private payers
  - Generally covered as first-line diagnostic test for developmental delay, intellectual disability, or autism spectrum disorders when:
    - Relevant biochemical or metabolic disease have been ruled out;
    - Clinical presentation not specific to a well-delineated genetic syndrome
    - Results could impact clinical management
  - Some variations in criteria for coverage among payers

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Conclusions

- Chromosomal microarray identifies a pathogenic or likely pathogenic variant
  - In nearly 9% of all children referred for testing
  - In 5% of those referred because of autism spectrum disorders
  - Findings are based on a low strength of evidence
- Chromosomal microarray results prompt management changes
  - In management of over 50% of children with a pathogenic variant
  - Finding is based on very low strength of evidence.
- Cost per additional diagnosis varies
- Limited evidence on safety
- No evidence regarding impact on health outcomes

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More Information

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Additional Details

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Payer coverage for CMA and WES testing

Payer	CMA Testing	WES Testing
Aetna[17]	Covered for specific indications	Not covered
Blue Cross (Premera)[18]	Covered for specific indications	Covered for specific indications
Regence Blue Shield Regence[19,20]	Covered for specific indications	Not covered
Cigna[21,22]	Covered for specific indications	Covered for specific indications
Humana[23]	Covered for specific indications	Not covered
Kaiser Permanente[24]	Covered for specific indications	Not covered
Medicare Fee for Service	None	None
Medicaid[15,25,26]	Not all states have policies; those that do typically cover for specific indications	Unknown
UnitedHealthcare[27]	Covered for specific indications	Covered for specific indications

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Data abstraction and quality assessment

- Abstraction
  - Single abstraction into structured abstraction form
  - Principal investigator reviewed abstractions for accuracy and consistency.
- Risk of bias assessment
  - Two independent risk of bias assessments
  - Disagreements reconciled by discussion, consultation with principal investigator as needed
  - Risk of bias assessment instruments
    - QUADAS-2 instrument for diagnostics test studies
    - RTI item bank questions for observational studies for selection bias, confounding, and measurement bias
    - ROBIS instrument for systematic reviews

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Data sources and search

- MEDLINE® (via PubMed)
- A clinical trials registry (clinicaltrials.gov)
- FDA device approval databases (https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/default.htm#databases)
- Websites of payers, professional societies, organizations that conduct and disseminate health technology assessments

Websites searched

- US 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)
- US Agency for Healthcare Research and Quality
- American Academy of Pediatrics
- American Academy of Neurology
- American College of Medical Genetics and Genomics

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How often does WES return an informative result? Summary and Strength of Evidence

Summary of Evidence

Author (Year)	Study Population; Sample Size; Test	Diagnostic Yield [Detection of A Pathogenic Variant] N (%)	Risk of Bias
Bowling (2017)	Clinic-based family recruitment of children with mild to severe ID, age ≥ 2; N=632; WES	100 (27.1%)	Low

Strength of Evidence

Outcome	No. of Studies, Subjects; Study Design	Risk of Bias	Inconsis-tency	Indirect-ness	Precision	Other consider-ations	Strength of Evidence Grade
Diagnostic yield of WES 27%	1; 632; Observational		NA, single study	Not serious	Serious	None	Very low

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Contextual information – Analytic validity and diagnostic yield

- Diagnostic yield among general population of adults and children
  - 0.7% of samples in Estonia biobank had a DECIPHER-listed pathogenic variant
    - 70% of individuals with a variant reported clinical features consistent with their genetic variant.
- False negatives
  - CMA did not detect 0.24% of all cases with a variant identified by either karyotype or FISH.
    - 6 of 43 cases of mosaicism
    - 29 of 30 balanced rearrangements
  - Moderate resolution oligo-array versus 4 high resolution SNP arrays
    - Oligo array identified only 3 of 6 pathogenic abnormalities detected by SNP arrays.
- False positives
  - Moderate resolution oligo-array versus 4 high resolution SNP arrays
    - Falsely identified variants ranged from 0% to 5.8% of all identified variants
    - Resulted from false calls by software or failure to identify variant in parent.

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Contextual information – Implications and Impact

- Incidental findings from WES
  - 2.0% of parents had an ACMG-identified clinically actionable variant
  - 4.6% were carriers of an autosomal recessive disorder
    - 1 couple were carriers for the same disorder, giving them a 25% chance of having a child with the disorder
- Impact on management and outcomes
  - CMA results increased access to services, such as public health insurance

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Research questions

SQ1	What, if any, safety issues do CMA and WES pose beyond those associated with phlebotomy?
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, intellectual disability or developmental disability tested with CMA or WES have better health outcomes?
CQ1	What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with CMA or WES?

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Grading the Strength of the Evidence

- GRADE
  - Domains
    - risk of bias, inconsistency, imprecision, indirectness, and other considerations, such as reporting bias.
  - Strength of evidence
    - Very low, low, moderate, or high
      - Observational evidence starts at low.
- Downgrading
  - Serious
    - Risk of Bias
    - Inconsistency
    - Indirectness
    - Imprecision
  - Likely publication bias
- Upgrading
  - Large sample size
  - Dose-response gradient
  - Effect not explained by plausible confounding

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Ongoing and future research

- Randomized clinical trials or well-designed observational studies
  - Comparative strategies for chromosomal microarray or whole exome sequencing as part of diagnostic evaluation
    - Whole exome sequencing versus single gene sequencing or mutation panels.
- Systematic review of chromosomal microarray versus karyotype as first-tier test for prenatal diagnosis

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Washington State Health Care Authority

Final key questions and background

Genomic micro-array and whole exome sequencing

Policy context

This health technology assessment (HTA) will review the efficacy, cost, and potential harms in the use of genomic microarrays (GAs) or whole exome sequencing (WES) to identify chromosomal abnormalities, including aneuploidies, rearrangements, and copy number variants for the diagnosis and management of children with autism, intellectual disability, birth defects, or undiagnosed genetic disease. When present at conception or acquired during prenatal development, chromosomal abnormalities can cause genetic diseases, congenital structural defects, or developmental disabilities.[1, 2] GAs or WES can identify smaller rearrangements and copy number variants than karyotype or fluorescent in-situ hybridization (FISH) analysis.[3]

Background

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 or gain of genetic material, or unbalanced.

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.[4] Chromosomal abnormalities occur in 43.8 per 10,000 births that survive to 20 weeks gestation or later.[5] 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.[5] Small pathological duplications or deletions occur in 1 of 270 pregnancies.[6] Studies examining the prevalence of chromosomal abnormalities have focused on the prenatal period,[5] the prevalence at birth,[7] or the prevalence among individuals with specific structural defects[8] or developmental disabilities.[9]

The number of living children or adults with a chromosomal abnormality is unknown. Although the life expectancy for individuals with a chromosomal abnormality may be significantly shortened by birth defects and other conditions, the life span of affected individuals has increased in recent years

Proposed scope

Population: Children and fetuses diagnosed with or suspected of having congenital defects, autism, intellectual disability or developmental disability.

For question 1 only: Populations not at increased risk of chromosomal rearrangements, including unselected prenatal or newborn populations.

Interventions: Genomic micro-array testing and whole exome sequencing.

Comparators:

Questions 1 – 2: are descriptive.

Question 3: Management before and after diagnosis; management of similarly affected undiagnosed children.

Question 4: No genetic diagnostic testing OR genetic diagnostic testing did not include GA or WES.

Outcomes:

1. Earlier diagnosis
2. Mortality during infancy or childhood
3. Development of co-morbidities
4. Functional achievement
5. Medical or educational interventions

Time period: 2000 to 1017

Settings: Clinical genetic laboratories, medical genetic clinics, general and specialty pediatric clinics

Key questions

1. What, if any, safety issues do GA and WES pose beyond those associated with phlebotomy?
2. How often do GA or WES return an informative result?
3. For what types of conditions are GA or WES most useful?
4. Does the diagnosis of a chromosomal disorder change the child's management?
5. Do children with congenital defects, autism, intellectual disability or developmental disability tested with GA or WES have better health outcomes?
6. What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with GA or WES?

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HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: .http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: .http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
    - Refer to evidence identification document and discussion.
    - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
    - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
    - What are the known conditions/criteria and evidence state
    - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion Document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety Outcomes	Importance of Outcome	Safety Evidence / Confidence in Evidence
Adverse events		
Harms associated with testing		

Efficacy – Effectiveness Outcomes	Importance of Outcome	Efficacy / Effectiveness Evidence
Diagnostic yield		
Earlier diagnosis potential		
Change in management (medical or educational)		

Cost Outcomes	Importance of Outcome	Cost Evidence
Costs of testing		
Cost effectiveness		

Special Population / Considerations Outcomes	Importance of Outcome	Special Populations/ Considerations Evidence
Mortality		
Morbidity		
Functional achievement		

For Safety: Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Efficacy/Effectiveness: Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Cost Outcomes/Cost-Effectiveness: Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered _____ Covered Unconditionally _____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.

Medicare and Coverage Guidelines

[From page 9 of the Final Evidence Report]

The Centers for Medicare and Medicaid Services (CMS) has no national coverage determination for the use of CMA or WES.

Guidelines

[From page 7/8 of Final Evidence Report – **Bold added**]

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]