Washington State Health Care Authority

Whole exome sequencing (WES)

Clinical Expert

Amy Lawson Yuen, MD, PhD

Director Mary Bridge Genetics, Tacoma, WA

Clinical Genetics, Multicare Health System/ Mary Bridge Children's Hospital

NPI Number: 1164412813

AMY LAWSON YUEN, MD, PhD

PROFILE

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

LICENSE AND CERTIFICATIONS

AMERICAN BOARD OF PEDIATRICS
Initial certification 2004, meeting requirements for MOC

AMERICAN BOARD OF MEDICAL GENETICS AND GENOMICS
Initial certification 2007, meeting requirements for MOC

WASHINGTON STATE MEDICAL LICENSE
2007 – current

EXPERIENCE

DIRECTOR MARY BRIDGE GENETICS
July 2018 – present

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 HEALTH, SEATTLE, WA
July 2008 – August 2009
Clinical genetics.

SENIOR UPDATE EDITOR - GENEREVIEWS, SEATTLE, WA
August 2007 – March 2008

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.

SERVICE COMMITTEES

INVITED CLINIAL EXPERT for the Health Technology Clinical Committee of the Health Technology Authority of Washington State for the discussion of Genomic microarray and whole exome sequencing.
January 19, 2018
https://www.hca.wa.gov/about-hca/health-technology-assessment/genomic-micro-array-and-whole-exome-sequencing

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 per 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 and Golden Key Honor Society

1992, Howard Hughes Research Award for undergraduates

PUBLICATIONS

Homozygous 15q13.3 Microdeletion in a Child with Hypotonia and Impaired Vision: A New Report and Review of the Literature. Julie Simon, Katie Stoll, Roger Fick, Jared Mott, **Amy Lawson Yuen**. *Submitted,* Clinical Case Reports.

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. Eur J Hum Genet. 2018 Jan;26(1):64-74.

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.

Applicant Name Amy Yuen MD PhD

Address 315 Martin Luther King Jr. Way
PO Box 5299, Mail stop 315-P4 GENE
Tacoma, WA 98415

1. Business Activities

(a) If you or a member of your household was ***an officer or director of a business*** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business Name & Address	Business Type
Not applicable		

(b) If you or a member of your household ***did business under an assumed business name*** during the immediately preceding calendar year or the current year to date, provide the following information:

Business Name	Business Address	Business Type
Not applicable		

2. Honorarium

If you ***received an honorarium of more than $100*** during the immediately preceding calendar year and the current year to date, list all such honoraria:

Received From	Organization Address	Service Performed
Not applicable		

3. Sources of Income

(a) Identify ***income source(s) that contributed 10% or more of the combined total gross household income*** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source Name & Address	Received By	Source Type
MultiCare Health System	myself	Salary
Enterprise Strategy Group	spouse - Edwin Yuen	Salary
Amazon	spouse - Edwin Yuen	Salary

(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☐ Yes ☑ No

If "yes", describe:

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

☐ Yes ☑ No

If "yes", describe:

4. Business Shared With a Lobbyist

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

Lobbyist Name	Business Name	Type Business Shared
Not applicable		

Provide the information requested in items 5, 6, and 7 below only if:
(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.
(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than $1,000

List each source (***not amounts***) of income over $1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

Income Source	Address	Description of Income Source
Not applicable		

6. Business Investments of More Than $1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

Business Name	Business Address	Description of Business
Microsoft	Redmond, WA	stocks

7. Service Fee of More Than $1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of Service
Not applicable	

* *

I certify that I have read and understand this Conflict of Interest Form and the information I have provided is true and correct as of this date.

Print Name Amy Yuen MD PhD

Check One: ☐ Committee Member ☐ Subgroup Member ☑ Contractor (clinical expert)

[redacted]

7/5/2019
Date

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Agency medical director comments

WHOLE EXOME SEQUENCING

Charissa Fotinos, MD, MSc
Deputy Chief Medical Officer
Washington State Health Care Authority

November 22, 2019

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Whole Exome Sequencing

June 2017	"Genomic Micro-array and Whole Exome Sequencing" topic proposed by the HCA Director
September 2017	WES affirmed as out-of-scope. Evidence-based topic continues as "Micro-array"
June 2019	WES selected as stand-alone topic for HTCC review

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Agency Medical Director Concerns

Whole Exome Sequencing

SAFETY =	High
EFFICACY =	Medium
COST =	Medium

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Clinical Uses for WES

- Establishing a clinical diagnosis in a greater proportion of patients
- Explaining phenotypic abnormality of unknown etiology
- Enabling more appropriate and tailored patient management and timely initiation of treatment
- Enabling patients to benefit from existing and emerging treatment trials
- Allowing accurate genetic counselling of family members
- Enabling carrier testing of at risk relatives
- Offering the option of accurate prenatal or pre-implantation diagnosis
- Enabling predictive testing for late onset disorders

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Measuring the Benefits of WES

Phases	Individual health domain	Family health domain	Health system domain
Return of results	• Individual understanding • Perception of disease risk • Psychological adjustments • Behavioural changes	• Collection of family health history • Family communication • Family understanding	• Accessibility of results and interpretation • Clinician understanding • Genetic counselling capacity
Application to clinical practice	• Application to risk prediction • Additional screening for genomic diagnosis • Receipt of individualised intervention	• Cascade testing of at-risk family • Screening for genomic diagnoses • Receipt of individualised intervention	• Clinician response to clinical decision support
Longitudinal follow-up	• Diagnosis of individual genomic syndromes • Drug response (pharmacogenomics) • Mortality, morbidity, and quality of life	• Diagnosis of familial genomic syndromes • Reproductive decision making	• Health-care utilisation • Cost-effectiveness

Figure: Potential outcomes measured within individuals, families, and health systems

Petersen, J.F. et. al. Building evidence and measuring clinical outcomes for genomic medicine. Lancet 2019; 394: 604-10.

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Key Question 1

Effectiveness - Clinical Utility

In what proportion of patients does testing with WES result in:

- A clinically actionable finding (treated, prevented, or mitigated)?
- An actual change to the patient's medical management medication or therapies, follow-up testing, medical monitoring or genetic counseling?

What is the effect of testing pathways that include WES on:

- Medical management?
- Genetic risk counseling?
- Compared to testing pathways that do not include WES?

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Key Question 2

Effectiveness - Health Outcomes

What are the health outcomes, including mortality:

- Among patients who have WES testing?
- Of patients who receive testing pathways that include WES compared to alternative testing pathways with or without WES?

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Key Question 3

Safety and Harms

How many patients receive erroneous results after WES testing:

- Either false positive or false negative results?
- What harms are caused by these test results
- How many patients experience these harms?

What harms are caused by:

- Uncertain WES results?
- Lack of diagnosis after WES testing?

How many patients receive reports on ACMG-defined medically actionable variants after WES testing?

- What harms do they experience, and how many patients experience these harms?

How frequently do WES results cause harm to family relationships?

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Key Question 4

Cost

What is the cost of Whole Exome Sequencing?

- Cost per diagnosis of pathways that include WES testing?
- Cost per additional diagnosis comparing a pathway with WES to an alternative pathway with or without WES?
- What is the cost-effectiveness of testing with WES?

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Procedure Codes

Whole Exome Sequencing

CPT	Who/What Tested?	Procedure Code Description
81415	Individual	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Individual's Parents and Siblings	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417	Individual's Existing Test	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)

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2015 – 2018

Utilization: Whole Exome Sequencing

CPT 81415, 81416, 81417

PEBB incurred less than the minimum allowable utilization required for public reporting, therefore the claims are excluded from reporting LNI incurred no claims.

Year	Unique Patients	WES	Total Paid
2015	21	23	$72,191
2016	41	75	$46,510
2017	58	108	$78,995
2018	91	184	$163,346

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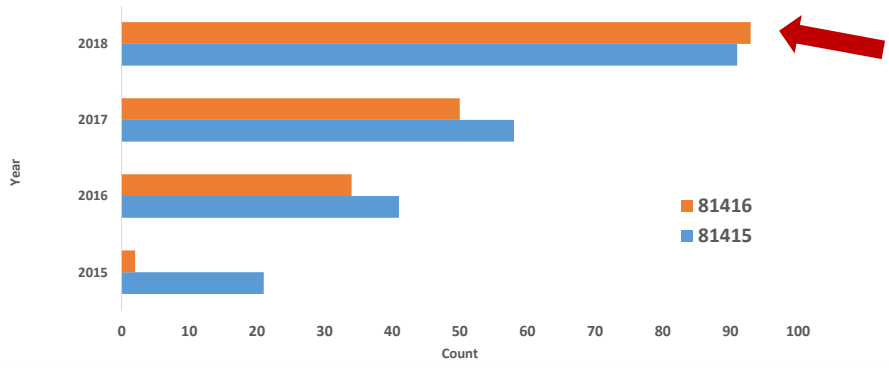
2015 - 2018

Medicaid FFS and MCO
Utilization: Whole Exome Sequencing

CPT 81415 (N=210) & 81416 (N=179)



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2015 - 2018

Medicaid FFS and MCO
Primary Diagnoses Representing Fifty Percent of Patients with a CPT 81415 Whole Exome Sequencing
N = 105

Unspecified Lack of Expected Normal Physiological Development in Child	Other Symptoms & Signs involved: Musculoskeletal	Sensorineural Hearing Loss, Bilateral
Multiple Congenital Malformations	Macrocephaly	Short Stature Child
Other Disorders of Psychological Development	Epilepsy UNS Not Intractable w/o Status Epilepticus	Other Hypertrophic Cardiomyopathy
Autistic Disorder	Microcephaly	Unspecified Convulsions
Encounter for Nonprocreative Genetic Counseling	Other Specified Counseling	Supraventricular Tachycardia
Delayed Milestone in Childhood	Encounter for Procreative Genetic Counseling	Hypopituitarism

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Medicaid
Physician Related Services Fee Schedule
Prior Auth Required

Fee Schedule Effective July 1, 2019

Code	Max Allowable NFS	Max Allowable FS
81415	$4,502.76	$4,502.76
81416	$11,304.00	$11,304.00
81417	$301.44	$301.44

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WES
Current State Agency Policy

Agency	Status	Most Recent Update
PEBB/UMP	Investigational	7.1.2019
Medicaid	Covered w/Prior Auth	7.1.2019
Labor and Industries	Not Cover	7.1.2019

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Benefit Coverage - Other Payers

Regence: Whole exome sequencing and whole genome sequencing is considered investigational for all indications, including but not limited to, diagnosis in patients with suspected genetic disorders, preimplantation or prenatal (fetal) testing, and general screening. 7.1.2019

Aetna: Considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorder in children ≤ 21 years of age when *all* of their criteria are met. 5.16.2019

Cigna: Considered medically necessary when disease specific criteria* are met and when a recommendation for testing is confirmed by ONE of their named specialists. 11.15.2018

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Benefit Coverage - Other Payers

CMS:

Patient has:

- either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and,
- either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and,
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

The diagnostic laboratory test using NGS must have:

- Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
- an FDA-approved or -cleared indication for use in that patient's cancer; and,
- results provided to the treating physician for management of the patient using a report template to specify treatment options. 4/8/2019

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Evidence Summary

Whole Exome Sequencing - WES

Key Questions	Certainty of evidence
Clinical utility	Very low
Health outcomes	Unable to determine
Safety	Low
Cost effectiveness	Very low

Using only the evidence:

Recommendation - Not Cover

however……

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Given the state of the evidence: What else should be a consideration?

- There are currently an array of costly diagnostic tests and strategies used to identify presumed genetic conditions often with low diagnostic yield.

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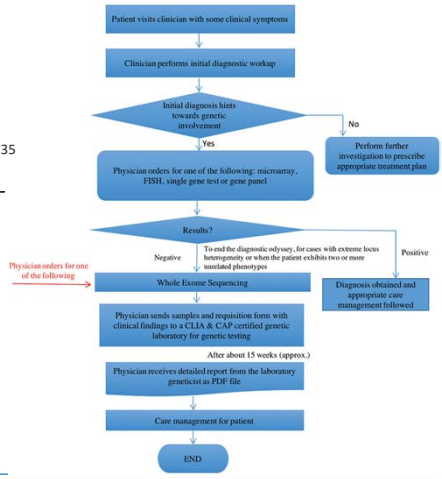
We Already Pay for Genetic Tests

FISH $159
Single gene $37-$735
Panels $3k-$15K
CMA $1092
~ $5000

WES **$4503**



Journal of the American Medical Informatics Association, Volume 24, Issue 6, November 2017, Pages 1184–1191, https://doi.org/10.1093/jamia/ocx048

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Given the state of the evidence: What else should be a consideration?

- There are currently an array of diagnostic tests and strategies used to identify presumed genetic conditions often with low diagnostic yield
- The field is complex and the interpretation of findings is nuanced

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What to order?

	Example
Single gene	
Minimal locus heterogeneity (only one or a small number of genes is known to cause the condition)	*CFTR* for cystic fibrosis
Distinctive clinical findings that clearly indicate a specific gene	*PAH* for phenylketonuria
Gene panel	
Locus heterogeneity (multiple genes are known to cause the same condition or similar conditions)	Muscular dystrophy panel
Disorders with overlapping phenotypes	Cardiomyopathy panel
Disorders that share one manifestation but can have very different presentations	Epilepsy panel
Disorders associated with genes from a common pathway or structure	RASopathy panel
Exome	
Extreme heterogeneity and de novo mutations common	Autism, intellectual disability
Two or more unrelated phenotypes in one patient	Oculocutaneous albinism and neutropenia
No distinctive phenotypic features present	Kabuki syndrome
Phenotype indistinct and underlying cause is not clear	Congenital diarrhoea, Zellweger syndrome
Genome*	
Non-coding variation is suspected as a cause	Hypertrophic cardiomyopathy[9]
Structural variation is suspected as a cause	DiGeorge syndrome[79]
Exome sequencing has already been performed and was non-diagnostic	Undiagnosed Diseases Network[38]
Rapid generation of sequencing data needed for patients who are critically ill	Neonates in intensive care[5]

*Indications for exome also apply to genome, with the addition of those listed below.

Table 1: **Indications for single gene, gene panel, exome, and genome sequencing[39]**

Manolio, T.A. et.al. Opportunities, resources and techniques for implementing genomics In clinical care. Lancet 2019; 394-511-20.

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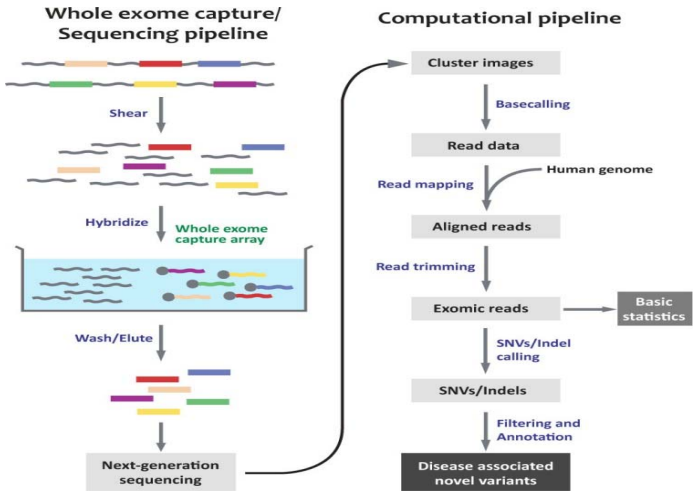

Goh, Gerald & Choi, Murim. (2012). Application of Whole Exome Sequencing to Identify Disease-Causing Variants in Inherited Human Diseases. Genomics & informatics. 10. 214-9. 10.5808/GI.2012.10.4.214.

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Grading Variants

Richards et al. Page 29

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder *BA1/BS1* OR observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Genet Med. 2015 May ; 17(5): 405–424. doi:10.1038/gim.2015.30.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4544753/pdf/nihms697486.pdf

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Given the state of the evidence: What else should be a consideration?

- There are currently an array of diagnostic tests and strategies used to identify presumed genetic conditions often with low diagnostic yield
- The field is complex and the interpretation of findings is nuanced
- As more people are tested, knowledge of different variants and their significance across different populations will expand
- The identification of American College of Medical Genetics actionable secondary findings may lead to improved outcomes

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Clinical uses for WES for persons covered by Medicaid

- Establishing a clinical diagnosis in a greater proportion of patients
- Explaining phenotypic abnormality of unknown etiology
- Enabling more appropriate and tailored patient management and timely initiation of treatment
- Enabling patients to benefit from existing and emerging treatment trials
- Offering the option of accurate prenatal or pre-implantation diagnosis
- Enabling predictive testing for late onset disorders
- Allowing accurate genetic counselling of family members
- Enabling carrier testing of at risk relatives

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WES Summary

- **Cover with conditions:**

  WES is covered when:
  - Multiple congenital abnormalities affecting unrelated organ systems are present
    - **AND**
  - Single gene tests or gene panels have not or are not expected to yield a diagnosis based on clinical presentation
    - **AND**
  - The constellation of clinical findings can be found in more than one genetically associated condition
    - **AND**
  - The test is recommended by or as a result of a documented consultation with a medical geneticist or a board certified genetic counselor
    - **AND**

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WES Summary

- Genetic counselling is provided before the test is performed and after the findings are known
  - **AND**
- No other causative circumstances (e.g. environmental exposures, injury, infection) can explain the symptoms
  - **AND**
- One or more of the following are expected to occur once a diagnosis is reached
  - Medication or other treatments are initiated or discontinued as appropriate
  - Contraindicated care is discontinued
  - Palliative care is initiated
  - Care is withdrawn
- **OR**

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Agency Medical Director Recommendations

Whole Exome Sequencing

Covered when at least two of the following are present:

- Either autism, global developmental delay, intellectual disability, complex behavioral disorders or severe neuropsychiatric symptoms
- An abnormality affecting at least one other organ system and not described in the previous bullet
- Family history strongly suggestive of a genetic etiology
- Period of unexplained developmental regression (unrelated to autism or epilepsy)
- Biochemical findings suggesting an inborn error of metabolism

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Agency Medical Director Recommendations

Whole Exome Sequencing

Not covered for:

- Autism or developmental delay or intellectual disability or complex behavioral disorders or severe neuropsychiatric symptoms alone or in combination
- Asymptomatic 1st degree relatives of the person receiving results unless an ACMG medically actionable secondary finding was identified as a secondary finding in the person initially tested
- Reducing diagnostic uncertainty
- Carrier testing for 'at risk' relatives
- Prenatal or pre-implantation testing
- Future pregnancy counseling for a parent or a sibling of a child that has been identified as having a genetic condition unless the condition is heritable and the birth parent is covered by an HCA plan

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Questions?

More Information:

https://www.hca.wa.gov/about-hca/health-technology-assessment/whole-exome-sequencing

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Washington State Health Care Authority

Order of scheduled presentations:

Whole exome sequencing

	Name
1	Sarah Clowes Candadai, MS, LCGC Seattle Children's Hospital, Department of Laboratories
2	Jessie Conta Seattle Children's Hospital, Department of Laboratories

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources: I am an employee of Seattle Children's Department of Laboratories. We do not perform exome testing at our lab.

If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may ***attach additional sheets*** *explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 10/30/2019 Sarah Clowes Candadai

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: sarah.clowescandadai@seattlechildrens.org

Phone Number: 206-818-6992

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		✓
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	✓	

If yes to #7, provide name and funding Sources: I am an employee of Seattle Children's, within the Dept of Laboratories + Director of Genetic Counseling Services for PLUGS, a non-profit laboratory stewardship collaboration run out of the Dept of Labs. Part of PLUGS mission is insurance alignment + partnering with payers on policies for medically appropriate tests.

If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may ***attach additional sheets*** *explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 10/30/19 Jessie Conta

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: jessie.conta@seattlechildrens.org

Phone Number: 206-802-8791

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RTI-University of North Carolina Evidence-based Practice Center

Whole Exome Sequencing

Health Technology Assessment
State of Washington Health Care Authority

Contributors:
Nedra Whitehead, MS, PhD, *Lead Investigator*
Leila Kahwati, MD, MPH; *Co-Investigator*
Amy Moore, PhD, *Co-Investigator*
Sara Kennedy, MPH; *Project Coordinator and Research Analyst*
Christine Hill, MPA; *Research Analyst*
Rachel Weber, PhD; *Scientific Reviewer*
Christiane Voisin, *MSLS, Health Sciences Librarian*

Presented by:
Nedra Whitehead, MS, PhD
November 22, 2019
nwhitehead@rti.org

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Overview of Presentation

- Background
- Methods
- Results
  - Contextual questions on diagnostic yield
  - Primary research synthesis
- Discussion

2

Definitions

Variant classification: The classification of a DNA change as disease-causing (pathogenic) or normal variation (benign) using a variety of information.

Variants of unknown significance: Variants which cannot be classified as pathogenic or benign due to lack of information.

Causal: Determination that a DNA variant is the cause of the patient's symptoms.

Clinical validity of sequencing: The accuracy of the classification of a variant as pathogenic or benign and causal or not causal.

Secondary finding: Identification of a DNA variant that causes a disease different from the one for which the patient sought testing

3

Background

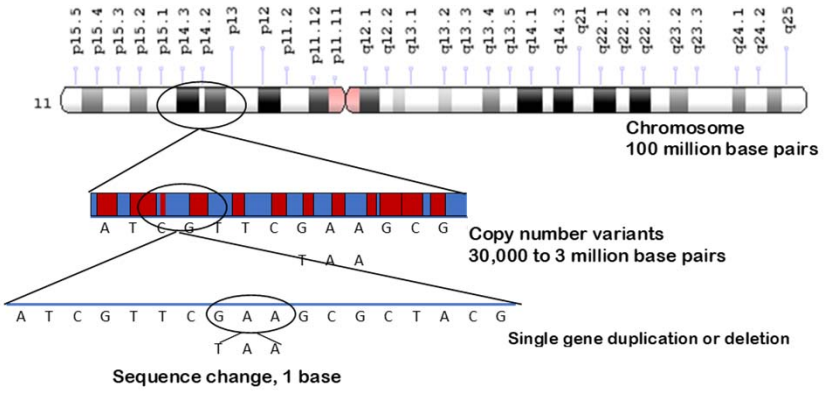
4

Context for Review

- Review of chromosomal microarray for diagnosis of chromosomal abnormalities in children presented at the January 2018 HTCC Meeting
- Original scope included whole exome sequencing (WES)
  - Primary purpose of WES is identification of small changes in a single gene when you do not know which gene is likely to be mutated
  - Limited analysis of WES for identification of chromosomal abnormalities
    - Severely restricted the evidence on WES and underestimated the efficacy of WES
    - Body of evidence inadequate for policy determination

5 Pages in Report: 2-3

Genomic Variation from Chromosomes to Nucleotides

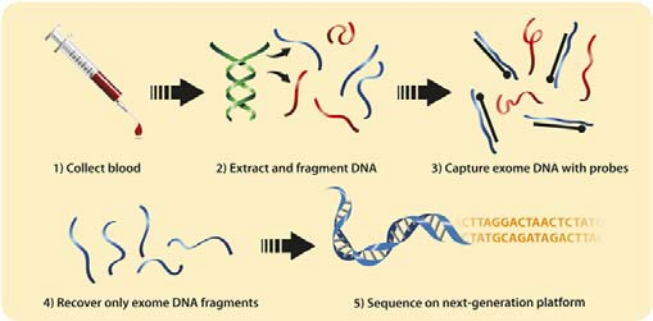


Clinical impact is not necessarily correlated with size

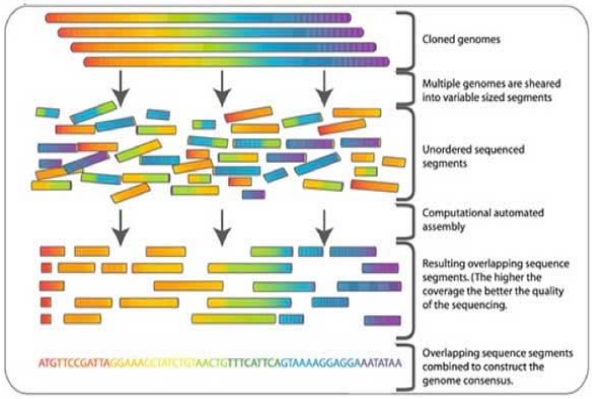
Graphics: Chromosome 11 schematic from National Institutes of Health.
Graphic based on https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/deciding-to-test

6 Pages in Report: 3-4

What is Whole Exome Sequencing?



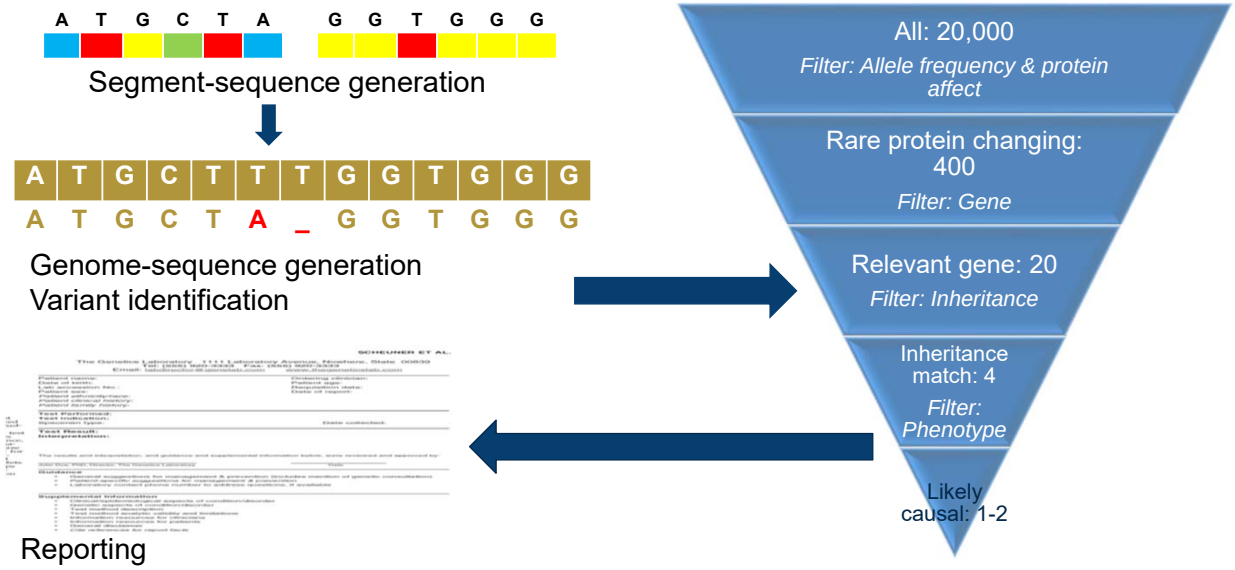
Source: EpilepsyU website



Source: Commins, J., Toft, C., Fares, M. A. CC BY-SA 2.5, via Wikimedia Commons. Whole genome shotgun sequencing.

7 Pages in Report: 3-4

Bioinformatics



8 Page in Report: 4

Source: Scheuner MT et al. A report template for molecular genetic tests designed to improve communication between the clinician and laboratory. Genet Test Mol Biomarkers. 2012 Jul;16(7):761-9.

How is WES Used?

- Disease burden
  - > 6,000 known human genetic disorders
  - Collectively affect 1 in 17 individuals
  - Inpatient charges for US pediatric patients $14-57 billion
- Tests for a wide range of genetic diseases
- Commonly used when a patient
  - Is suspected of having a genetic disorder that not clinically recognizable;
  - Has a phenotype consistent with multiple genetic disorders;
  - Has a phenotype that may be blended from two or more genetic disorders;
- May identify genetic disorders other than those that cause the patient's phenotype (i.e., secondary findings)

9 Page in Report: 4

Examples of WES for Diagnosis

Example 1. Siblings

- Symptoms: Hypotonia, oculogyric crises, developmental delay
- Onset: Age 2 months
- No relevant family history

- Differential diagnosis
  - L-amino acid decarboxylase deficiency, other neurotransmitter deficiency
    - Genetic testing, management and treatment options differ

Example 2. 29-year old woman with endometrial cancer

- Family history includes multiple cases of different cancers in young adults

- Differential diagnosis
  - Lynch syndrome, Li-Fraumeni syndrome, other inherited cancer syndromes
    - Genetic testing, high risk cancers, management and treatment options differ

10 Pages in Report: 4-5

Regulatory Status

- FDA
  - Does not regulate WES as a diagnostic test
  - Approves sequencing platforms if marketed for clinical testing
    - Demonstration of analytic validity is sufficient for approval
  - Does not regulate laboratory developed tests
- Laboratories conducting clinical WES
  - Accredited by the CMS under Clinical and Laboratory Improvement Act (CLIA) to conduct high complexity testing
  - Are usually at large, tertiary medical centers or commercial genetic laboratories

11 Page in Report: 5

Policy Context for Washington

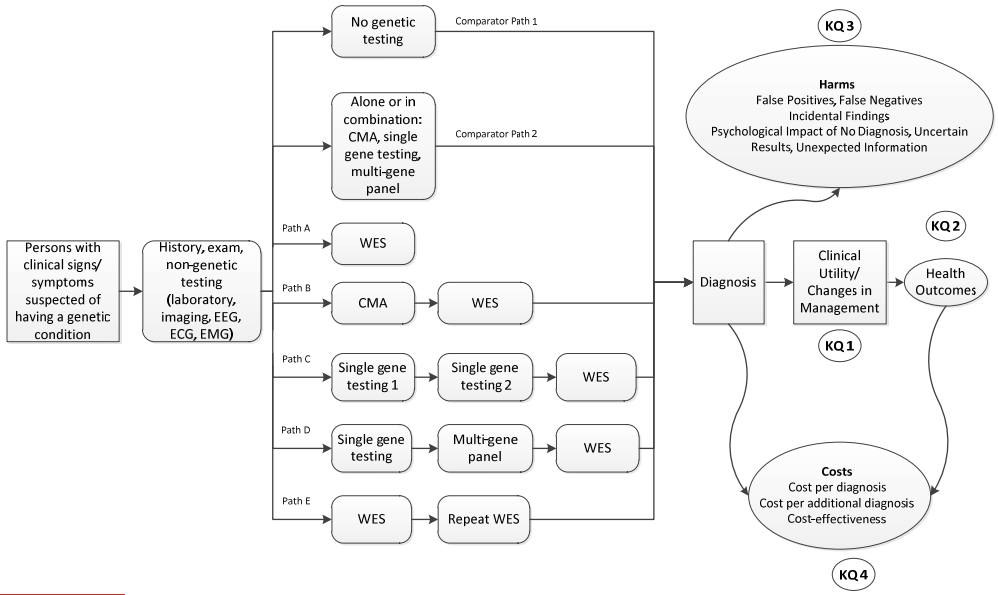
- This topic was selected for review by the state because of:
  - High concerns for safety
  - Medium concerns for efficacy
  - Medium concerns for cost

12 Page in Report: 5

Methods

13

Analytic Framework



14 Page in Report: 7, Figure 2

Abbreviations: CMA = chromosomal microarray; ECG = electrocardiography; EMB – electromyography; KQ = key question, WES = whole exome sequencing

Study Selection for Primary Research Synthesis

Population	• Children or adults with suspected genetic disease
Intervention	• WES used for clinical diagnosis alone or with other diagnostic investigations.
Comparator	• Standard clinical diagnostic investigation (i.e., usual care) • Testing pathways that use chromosomal microarray analysis (CMA), single gene testing, or multigene panels. • WES used in different places within the testing pathway • Did not require studies to have a comparator testing strategy
Outcomes	• Clinical utility (results change clinical management or genetic counseling) • Health outcomes (mortality, length of survival, morbidity, cognitive ability, functional outcomes) • Harms (misdiagnosis, proportion with ACMG-defined medically actionable variants, psychosocial harms, and employment or insurance discrimination), and • Cost outcomes (cost of WES test, cost per patient of strategy with WES, cost per diagnosis, cost, cost per additional diagnosis [compared to other strategies], cost effectiveness)

15 Pages in Report: 8-9

Study Selection for Primary Research Synthesis (con't)

Settings	• Inpatient or outpatient clinical settings from countries with a development rating designated as *very high* on the United Nations Human Development Index
Study Design	• Single-arm or controlled clinical trials or observational cohort studies with more than 10 participants, case control studies, case series (between 5 to 10 participants), cost-benefit analyses, cost-utility analyses, cost-effectiveness analyses, modeling studies, and qualitative research studies (for safety and harms outcomes only).
Other	• English-language, published in 2010 or later (WES was not used clinically before this time)

16 Pages in Report: 9-10

Challenge: Evaluating Risk of Bias (ROB)

- Existing ROB instruments are not designed for single arm observational studies, which comprise the bulk of the evidence base for this topic
  - Most ROB instruments are designed for comparative studies
  - ROB instruments for costs studies are designed for cost-effectiveness analyses
- Existing risk of bias instruments for diagnostic tests are not designed for genetic studies
  - Absence of gold standard
  - Evolving databases of genetic information to call variants
- Developed ROB instrument to evaluate major ROB domains of selection, performance, and measurement for efficacy and safety outcomes; Quality of Health Economic Studies Instrument for cost outcomes

17 Page in Report: 12

Risk of Bias Assessment

- Two team members independently assessed the risk of bias for all included studies
- Each study assessed as having one of the following risks:
  - High risk of bias
  - Some concerns for bias
  - Low risk of bias

18 Page in Report: 12

Abbreviation: RCT = randomized controlled trial

Quality of the Evidence – GRADE approach

- **Domains considered:**
  - Risk of bias
  - Consistency
  - Directness
  - Precision
  - Publication bias
- **Quality of evidence**
  - ⊕○○○ VERY LOW
  - ⊕⊕○○ LOW
  - ⊕⊕⊕○ MODERATE
  - ⊕⊕⊕⊕ HIGH

- Bodies of RCT evidence start at ***HIGH***
- Observational studies start at ***LOW*** because of limitations with this study design
- Quality level may be downgraded based on domain assessments:
  - No concerns
  - Serious concerns (↓ one level)
  - Very serious concerns (↓ two levels)
- Observational evidence may be upgraded based on:
  - Large effect (↑ one level)
  - Dose response (↑ one level)
  - Plausible confounding and bias accounted for (↑ one level)

19 Pages in Report: 12-13

Challenge: Applying GRADE/Strength of Evidence Methods

- GRADE was developed to evaluate RCTs of therapeutic interventions
- Genetics testing does not fit well into this framework
  - WES evidence base is largely single-arm, observational studies
    - By GRADE design, outcomes cannot be graded higher than a LOW strength of evidence
    - Many will be further downgraded for study limitations, landing at a VERY LOW strength of evidence
- Ideal RCTs of clinical WES may be impractical because WES is often part of a highly individualized diagnostic odyssey.

20 Pages in Report: 12-13

Results

21

Search Results

- Titles/abstracts screened: **5,567**
- Full text articles screened: **431**
- Included studies: **57 studies (60 articles)**

EQ: 30 studies
1 CCS
26 UCS
1 CS
1 QS

SQ: 26 studies
1 MS
5 QS
20 UCS

CQ: 17 studies
1 MS
2 CCS
13 UCS
1 Other

- Contextual Question

103 studies
4 SR
1 CCS, 98 UCS

22 Pages in Report: 13-14

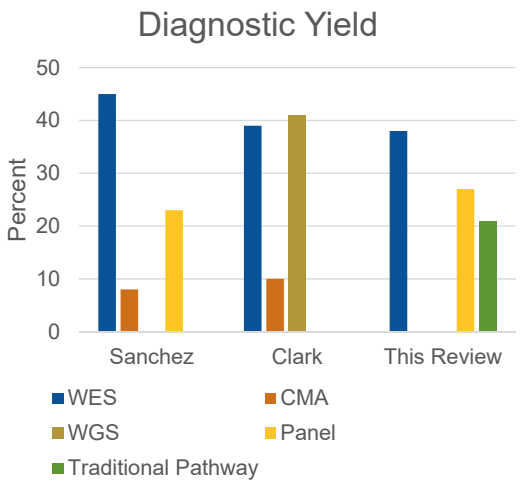
Abbreviations: CCS = controlled cohort study; CQ = cost question; CS = case series, EQ = efficacy question; MS = modeling study, QS= qualitative study, RCT = randomized controlled trial; SQ = safety question, SR= systematic review, UCS = uncontrolled cohort study

Contextual Question
Diagnostic Yield

23

Diagnostic Yield of WES

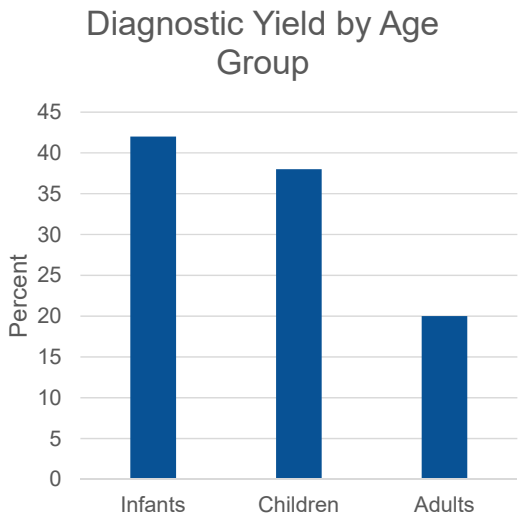
Author (Year) Number of Studies; Total Patients	Included Age Group and Phenotype
Schwarze (2018) WES: 27; NR WGS: 3; NR	• Any age group or phenotype
Sanchez (2019) Any genetic test: 20, NR WES: 6; 1,193	• Any age group • Phenotype of epilepsy
Clark (2018) WES: 26; 9,014	• Children • Any phenotype
Alam (2019) WES: 11, NR	• Children • Any phenotype
This review WES: 99; 22,460	• Any age group or phenotype



24 Page in Report: 15

Abbreviations: CMA = chromosomal microarray, NR = Not reported, WES = whole exome sequencing, WGS = Whole genome sequencing

Patient Characteristics That Affect Diagnostic Yield



Phenotype	Diagnostic Yield (%)
Epilepsy	40
Intellectual or Developmental Disability	29
Neurologic Disorders	33
Neurodevelopmental Disorders	28
Limb-girdle Muscular Dystrophy	48
Peripheral Neuropathy	32
Undiagnosed After Standard Workup	31

25 Page in Report: 16

Effect of Reanalysis on Diagnostic Yield

- Previously undiagnosed patients' diagnosis: 17% (8 studies)
- Previous diagnosis retracted: 12% of patients with developmental disabilities (1 study)
  - 7% using current interpretation guidelines
- WES Reanalysis vs. WGS: 6% (7 of 112) of patients diagnosed by WGS were not diagnosed by WES reanalysis (1 study)

26 Page in Report: 16

Analytic Validity

- Genotype discordance between multiple runs (1 study)
  - All single nucleotide variants: 0.2% to 0.5%
  - Rare variants: 4% to 6%
- Discordance between WES and Sanger sequencing (gold standard): 3% (1 study)

27 Page in Report: 17

Effectiveness Questions

1. Clinical Utility
2. Health Outcomes

28

Clinical Utility - Summary of the Studies

Study Design	Years Published	Years of Testing	Countries	Industry Funding	Risk of Bias
All, 30 CCS, 1 UCS, 26 CS, 1 QS, 1 Other, 1	2014-2019	2011-2018	U.S., 16 Australia, 6 Canada, 2 Germany, 2 Other, 4	None, 12 Some, 7 All, 3 Unclear, 8	Low, 0 Some, 15 High, 14 QS–NA, 1

29 Pages in Report: 17-18

Abbreviations: CCS = controlled cohort study; CS = case series, QS = Qualitative Study, NA = Not applicable, UCS = uncontrolled cohort study

Clinical Utility - Summary of the Population

Study Size	Gender	Age	Ethnicity	Phenotype	Family Testing
6 – 278	32 – 68% female	Median: 26 days to 66 years Age group, studies: Infants, 3 Children, 13 Adults, 1 Any, 12	55% to 98% European	Diverse, 18 Epilepsy, 5 Other, 7	None, 10 Parents, 10 Other, 6 NR, 4

30 Page in Report: Table C-1

Abbreviations: NR = Not reported

Clinical Utility of WES Testing

No. of Studies: 1 CCS, 26 UCS, 1 CS, 1 QS, 1 Other
⊕◯◯◯ VERY LOW

Phenotype, No. of Studies	Key Findings
Diverse, 18	• Any change in clinical management: 12% - 100% • Change in medication: 5% - 25% • Counseling and genetic testing for family members: 4% - 97%
Epilepsy, 5	• Any change in clinical management: 0% - 31% • Change in medication: 0% - 20%
Other, 7	• All reported some change • Data too heterogenous for synthesis

31 Page in Report: 17

Abbreviations: CCS = controlled cohort study; CS = case series, No. = number, QS = Qualitative Study, UCS = uncontrolled cohort study

Health Outcomes- Summary of the Studies

Study Design	Years Published	Years of Testing	Countries	Industry Funding	Risk of Bias
All, 7 1 CCS 5 UCS 1 CS	2014-2019	2011-2017	US, 3 Australia, 2 Other, 2	None, 3 Some, 2 Unclear, 2	Low, 0 Some, 2 High, 5

32 Page in Report: 30

Abbreviations: CCS = controlled cohort study; CS = case series, UCS = uncontrolled cohort study

Health Outcomes - Summary of the Population

Study Size	Gender	Age	Ethnicity	Phenotype	Family Testing
6 - 278	40% to 52% female	Median: 26 days to 32.5 years Age group: Infants, 2 Children, 3 Any, 2	NR	Diverse, 3 Epilepsy, 3 Other, 1	None, 2 Parents, 3 NR, 2

33 Pages in Report: 30

Abbreviations: NR = Not reported

Health Outcomes from WES Testing

No. of Studies: 1 CCS, 5 UCS, 1 CS
○○○○ UNABLE TO ASSESS

Phenotype, No. of Studies	Key Findings
Mortality, 4	• Range, 17% to 57% • Studies conducted among infants in NICUs or hospitalized children with acute illness
Improved seizure control or behavior management, 2	• 0% to 3% of study participants

34 Page in Report: 30

Abbreviations: CCS = controlled cohort study; CS = case series, No. = number. UCS = uncontrolled cohort study

Safety Outcomes

1. Misdiagnosis
2. Secondary findings (ACMG medically actionable variants)
3. Psychosocial harms

35

Misdiagnosis- Summary of the Studies

Study Design	Years Published	Years Conducted	Countries	Industry Funding	Risk of Bias
UCS, 1	2017	2011-2015	Netherlands	No	Some

36 Page in Report: 36

Abbreviations: UCS = uncontrolled cohort study

Misdiagnosis - Summary of the Population

Study Size	Gender	Age	Ethnicity	Phenotype	Family Testing
150	47% female	Children	NR	Neurological	None

37 Page in Report: 36

Abbreviations: NR = Not reported

Safety Outcomes from WES Testing

Misdiagnosis

No. of Studies: 1 UCS ○○○○ UNABLE TO ASSESS	• 2% percent of patients diagnosed with standard testing were not diagnosed by WES. • Undiagnosed patients had genetic variants not diagnosed well by WES at time of study

38 Pages in Report: 35-36

Abbreviations: No. = Number, UCS = uncontrolled cohort study

Secondary Findings- Summary of the Studies

Study Design	Years Published	Years Conducted	Countries	Industry Funding	Risk of Bias
All, 22 UCS, 19 MS, 1 QS, 2	2014-2019	1998-2017	US, 15 Australia, 2 Other, 5	None, 14 Some, 1 All, 3 Unclear, 4	Low, 11 Some, 7 High, 2 QS–NA, 2

Abbreviations: CCS = controlled cohort study; CS = case series, QS = Qualitative Study, NA = Not applicable, UCS = uncontrolled cohort study

39 Pages in Report: 36-37

Secondary Findings - Summary of the Population

Study Size	Gender	Age	Ethnicity	Phenotype	Family Testing
6 – 2,382	16% - 84% female	Infants, 1 Children, 6 Adults, 3 Any, 9	65% - 100% Caucasian	Diverse, 15 Single, 7	None, 6 Parents, 7 Other, 6 NR, 3

40 Page in Report: Table C-1

Abbreviations: NR = Not reported

Secondary Findings from WES Testing

No. of Studies:19 UCS, 1 MS, 2 QS ⊕⊕◯◯ LOW	• 4% of patients had an ACMG-medically actionable variant among 13 studies with data suitable for pooling • 90% of patients chose to receive secondary findings

41 Page in Report: 35

Abbreviations: No. = Number, MS = modeling study, QS = qualitative study, UCS = uncontrolled cohort study

Psychosocial Harms - Summary of the Studies

Study Design	Years Published	Years Conducted	Countries	Industry Funding	Risk of Bias
All, 8 UCS, 3 QS, 5	2014-2019	2016 - 2016	US, 8	None, 5 Some, 0 All, 1 NR, 2	Low, 2 Some, 0 High, 1 QS, Not assessed

Abbreviations: NR = Not reported, QS= qualitative study, UCS = uncontrolled cohort study

42 Pages in Report: 39-40

Psychosocial Harms - Summary of the Population

Study Size	Gender	Age	Ethnicity	Phenotype	Family Testing
10 - 2,000	44% to 84% female	Adults, 4 Mixed, 2 NR, 2	47% to 100% Caucasian	Diverse, 8	None, 2 Parents, 1 NR, 5

Abbreviations: NR = Not reported

43 Page in Report: Table C-1

Psychosocial Harms from WES Testing

No. of Studies: 3 UCS, 5 QS ○○○○ UNABLE TO ASSESS	• Most patients or parents of patients did not experience psychosocial harms from receiving negative or uncertain WES results.

44 Page in Report: 35

Abbreviations: No. = Number, QS = qualitative study, UCS = uncontrolled cohort study

Cost Question

45

Cost - Summary of the Studies

Study Design	Years Published	Years Conducted	Countries	Industry Funding	Risk of Bias
All, 17 CCS, 2 MS, 1 UCS, 13 Other, 1	2014-2018	1998-2017	Australia, 8 Netherlands, 3 Canada, 2 US, 2 Other, 2	None, 5 Some, 8 Unclear, 4	Low, 0 Some, 11 High, 6

Abbreviations: CCS = controlled cohort study; MS = modeling study, UCS = uncontrolled cohort study

46 Page in Report: 42

Cost - Summary of the Population

Study Size	Gender	Age	Ethnicity	Phenotype	Family Testing
14 - 370	34% - 59% female	Children, 11 Any, 3 NR, 3	NR	Diverse, 10 Single, 7	None, 8 Parents, 9

Abbreviations: NR = Not reported

47 Page in Report: Table C-1

Costs of WES Testing

No. of Studies: 2 CCS, 1 MS, 13 UCS, 1 Other ⊕◯◯◯ VERY LOW	• US$ 1,000 to US $15,000 • Trio WES costs more than singleton • Additional cost per diagnosis of WES compared to standard testing: <$0 to $8,559 • Pathways with earlier WES testing were more likely to be cost savings than pathways that used WES later in the testing pathway or as a last resort strategy.

48 Pages in Report: 41-42

Abbreviations: No. = Number, CCS = controlled cohort study, MS = modeling study, QS = qualitative study, UCS = uncontrolled cohort study, WES = whole exome sequencing

Guidelines, Assessments, and Policies

49

Clinical Practice Guideline Synthesis

- Clinical practice guidelines: 0*
- Professional society recommendations for WES

Indications	Contraindications
Phenotype or family history indicate genetic etiology (ACMG)	Phenotype indicates specific genetic disorder for which single gene testing available (ACMG)
Defined disorder that is highly genetically heterogenous, disorder (ACMG)	Lack of diagnostic evaluation by professionals experienced evaluation of genetic disease
Undiagnosed after specific genetic testing (ACMG, AAN)	Lack of appropriate pre-test genetic counseling (AAN)
Nonspecific or clinically heterogenous phenotype (AAN)	Lack of clinical expertise to interpret findings or render care based on results (AAN)
Undiagnosed after complete evaluation (AAN)	

50 Page in Report: 60

*Publicly available
Abbreviations: AAN, American Academy of Neurology ACMG = American College of Medical Genetics and Genomics

Health Technology Assessments

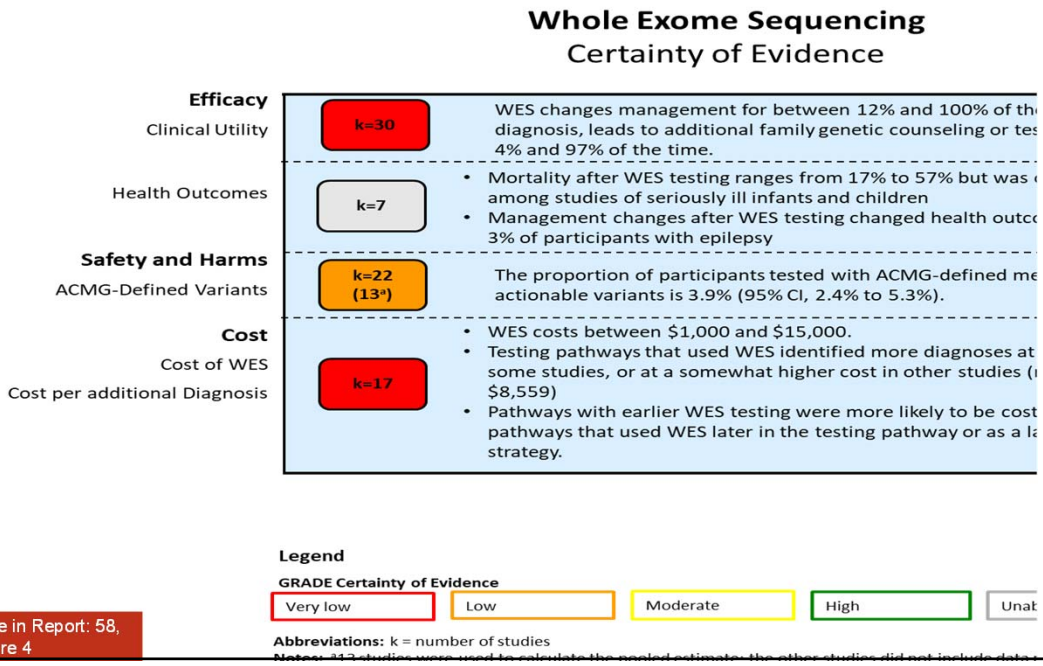
- Health technology assessments: 4
  - Not published in English: 2
  - Assessments from Blue Cross and Hayes, Inc require subscriptions

51 Page in Report: 60

Discussion

52

Evidence Map – Whole Exome Sequencing



53 Page in Report: 58, Figure 4

Limitations of the Evidence Base

- No randomized trials comparing WES to non-WES testing pathways
- Few prospective studies of clinical utility or health outcomes
- Very few studies report standardized protocols for outcome data collection
  - Medical records data without described protocols for abstraction
- Few studies included a comparison group, only allowing for estimates of the frequency of outcomes within a single group

54 Page in Report: 59

Payer Coverage (through September 9, 2019)

- CMS: No national coverage determination
- Five commercial payers cover whole exome sequencing when beneficiaries meet specific clinical criteria

Payor	Coverage status
Medicare	—
Medicaid	—
Aetna	✓
Cigna	✓
Humana	X
Kaiser	✓
Premera	✓
Regence	X
TRICARE	—
UnitedHealthcare	✓

Notes: ✓ = Covered; X = Not covered, — = No policy identified

55 Pages in Report: 61-67, Table 17

Ongoing Studies

Sponsor	Description	Number of Participants	Estimated Completion Date
University of North Carolina at Chapel Hill	RCT, children and adults with diverse phenotypes Randomized to 1 of 4 study arms 1) pre-visit preparation with usual care and exome sequencing 2) pre-visit preparation with usual care 3) no pre-visit prep with exome sequencing 4) pre-visit prep with usual care	1,700	5/2021

- 14 single arm observational studies

Source: ClinicalTrials.gov

56 Pages in Report: 68-70

Limitations of this Health Technology Assessment

- Scope
  - English-language articles only
  - Key questions focused on clinical utility outcomes, health outcomes, safety outcomes and cost outcomes
  - Studies of diagnostic yield assessed as a contextual question, so did not undergo risk of bias or GRADE assessment
- Process
  - Search limited to 3 databases
    - Hand search of bibliographies

57 Page in Report: 68

Abbreviations: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation

Conclusion

Conclusion	Certainty
WES increases diagnostic yield over standard diagnostic testing	Not Assessed
WES changes clinical management for some patients	⊕○○○ Very Low
About 4% of patients tested with WES will have an ACMG medically actionable variant	⊕⊕○○ Moderate
WES may be cost effective in terms of diagnosis	⊕○○○ Very Low

Legend

GRADE Quality of Evidence

Very low | Low | Moderate | High

k = number of studies
N = total number of participants
RCT = randomized controlled trial
CCS = controlled cohort study
Note: placement of shape along the X-axis does not indicate magnitude of effect

58 Page in Report: 70

Back Up Slides

59

Abbreviations

- CNV, copy number variants
- CMA, chromosomal microarray
- N, number
- WES, whole exome sequencing
- WGS, whole genome sequencing

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Definitions

Genome: The entire DNA sequence of an organism

Exome: The parts of the genome that code for a protein

Whole genome sequencing: Determining the base pair sequence of an entire genome

Whole exome sequencing: Determining the base pair sequence of an entire exome

Next generation (Nextgen) sequencing: A method of sequencing that involves cutting many copies of the same DNA or RNA into random, short sequences, sequencing the small segments, and using bioinformatics to order the small segments.

Sequencing accuracy: Accuracy of measured DNA changes. Includes laboratory and bioinformatic analysis of sequencing (analytic validity).

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Contextual Questions

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

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

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Key Question 1: Effectiveness (Clinical Utility)

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

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

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

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Key Question 2: Effectiveness (Health Outcomes)

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

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

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Key Question 3: Safety and Harms

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

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

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

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

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Key Question 4: Cost

4a: What is the cost of WES testing?

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

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

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

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GRADE interpretation

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

67 Page in Report: 13, Table 2

Systematic Reviews

Author (Year)	Inclusion Criteria	Number of Studies; Total Patients	Diagnostic Yield
Schwarze (2018)	• Any age group or phenotype • Studied cost (main focus), clinical utility, diagnostic yield or health outcomes	WES: 27; NR WGS: 3; NR	Range: 3% (colorectal cancer) to 79% (childhood-onset muscle disorders)
Sanchez (2019)	• WES, CMA, Epilepsy panel (EP) • Any age group • Phenotype of epilepsy	Any genetic test: 20, NR WES: 6; 1,193 CMA: 8; 2,341 EP: 9; 2,341	Pooled estimates: WES: 45% (95% CI, 33% to 57%) CMA: 8% (95% CI, 6% to 12%) EP: 23% (95% CI, 18% to 29%)
Clark (2018)	• Children • Any phenotype • Studied diagnostic yield	WES: 26; 9,014 CMA: 13; 1,1429 WGS: 7; 374	Pooled estimates: WES:36% (95% CI, 33% to 40%) CMA: 10% (95% CI, 8% to 12%) WGS: 41% (95% CI, 34% to 48%)
Alam (2019	• Children • Any phenotype • Studied cost	WES: 11, NR	Range: 16% to 79%
This review	• Any age group or phenotype	WES: 99; 22,460	WES: 38% (95% CI, 35.7% to 40.6%)

68 Page in Report: 15, Table 3

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.

[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

- 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.
- 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

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

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:

- 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
Misdiagnosis		
Psychosocial harms		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Change in management		
Change in medications		
Mortality		
Improved seizure control		

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Race		
Gender		
Ethnicity		

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 (yes)

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 (yes)

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 (yes)

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 Coverage and Guidelines

[From page ES-12/13 of Final Evidence Report]

ES 4.4 Selected Payer Coverage Policies

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

ES 4.3 Clinical Practice Guidelines and Related Health Technology Assessments

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

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

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

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

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

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

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

Washington State Health Care Authority

FINAL Key Questions and Background

Whole Exome Sequencing

Background

Whole exome sequencing (WES) may be applicable to testing for a wide range of genetic disease. It is most commonly used when a disorder is suspected to be genetic but is not recognizable clinically or when the patient's symptoms are consistent with a wide range of genetic disorders. Experts recommend a family physician consider that a condition may be genetic when a patient has any of the following: dysmorphic features, multiple anomalies, unexplained neurocognitive impairment, or a family history suggestive of a genetic disease.[1] Other signs of a potential genetic disorder include a much earlier onset of symptoms than is common, a multifocal presentation (i.e., bilateral cataracts, many colon polyps, etc.; or an unusual combination of symptoms).[2] Some conditions with pediatric onset may not be diagnosed in childhood, leading to adult patients who may present with a confusing mix of symptoms.[3]

WES identifies the DNA base pair sequence of the protein coding regions of the genome, including proximal regulatory segments and the splicing junctions.[4] WES is primarily used to identify small changes in base pair sequences that disrupt protein function and cause disease, but new bioinformatics software has increased the ability to identify chromosomal copy number variants (i.e., larger deletions or duplications involving larger stretches of DNA) from sequenced data. WES may be done for clinical or research purposes. Diagnostic WES testing is ordered by a physician or other health care professional and is conducted in a clinical diagnostic laboratory to aid in the diagnosis of a patient. The proband's parents or siblings may be sequenced to help interpret identified variants. Research WES testing is used to identify and characterize a common disease gene or genes among multiple families or patients with a similar phenotype.

WES uses next generation sequencing (NGS) technologies, which makes many copies of the target genome, cuts them into random sequences, and then simultaneously sequences the resulting fragments. WES requires multiple layers of bioinformatics analysis, often referred to as the analysis pipeline.[5] This pipeline includes identifying variants in the sequenced genome against a reference genome, identifying the gene in which the variant occurs and its function, classifying variants as pathogenic (or not) in relationship to the patient's clinical phenotype, and reporting all variants identified that are associated with the clinical phenotype along with other American College of Medical Genetics and Genomics (ACMG)-defined medically actionable findings in genes not associated with the patient's clinical phenotype. Most laboratories allow patients to opt-out of receiving medically actionable findings or other secondary findings.

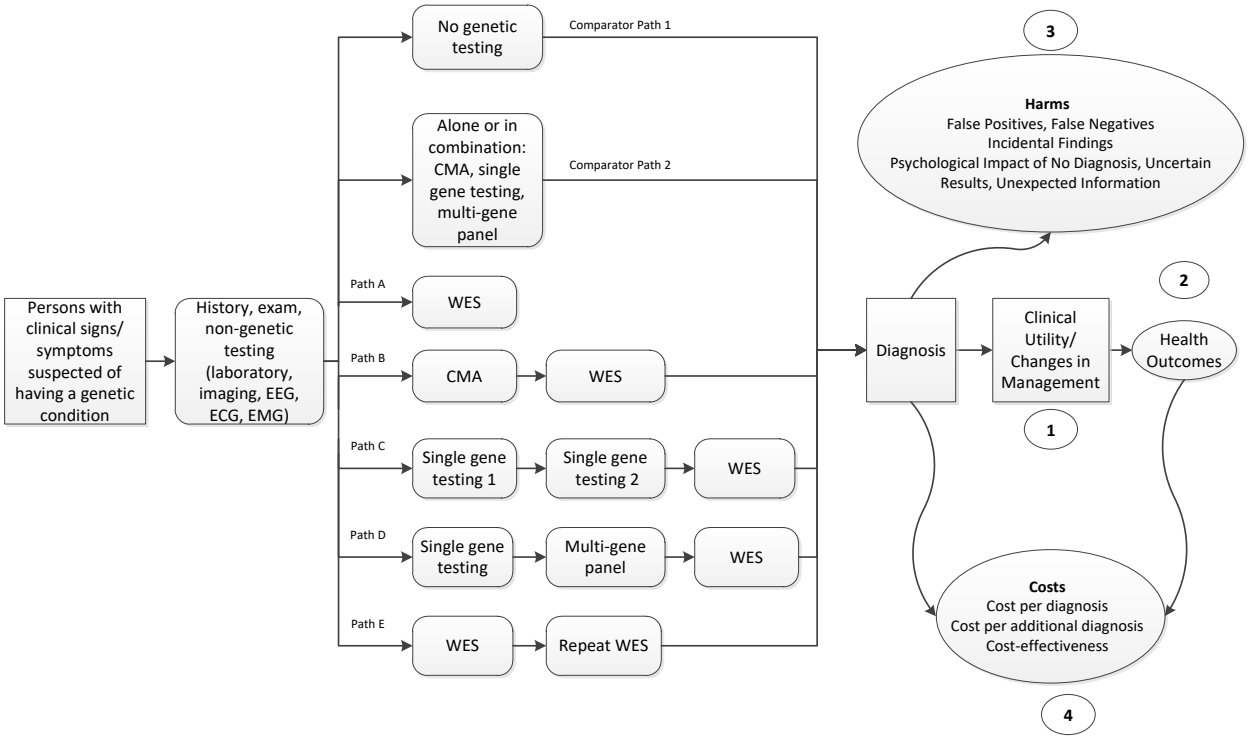
Policy Context

The State of Washington Health Care Authority selected WES as a topic for a health technology assessment because of high concerns for safety and medium concerns for efficacy, and cost.

Scope of this HTA

The analytic framework (***Figure 1***), research questions, and study selection criteria are listed in this section.

Figure 1. Analytic Framework Depicting Scope of Proposed Health Technology Assessment



Key Question 1: Effectiveness (Clinical Utility)

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

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

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

Key Question 2: Effectiveness (Health Outcomes)

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

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

Final

Key Question 3: Safety and Harms

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

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

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

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

Key Question 4: Cost

4a: What is the cost of WES testing?

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

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

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

Contextual questions will not be systematically reviewed and are not shown in the analytic framework. To address contextual questions, we will rely on recent systematic reviews and/or a subset of the largest, most recent primary research articles identified through our search.

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

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

Table 1 provides the study selection criteria we will use to select studies for inclusion in this HTA; these criteria are organized by population, intervention, comparator, outcomes, timing, setting, and study design and risk of bias criteria.

Table 1. Proposed Population, Intervention, Comparator, Outcome, Timing, and Setting for HTA on Whole Exome Sequencing

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

Outcomes	• Clinical utility
	  ○ Results from WES could be or are used for medical management (e.g. therapy, further diagnostic testing, monitoring), reproductive counseling, or risk counseling for other family members
	• Health outcomes
	  ○ Mortality, length of survival
	  ○ Morbidity, cognitive ability, functional outcomes
	• Safety
		• Outcome differences due only to different genetic defects
		• Clinical utility and health outcomes related to incidental findings
		• Cost of testing from studies performed in non-U.S. countries
		• Cost of testing from studies performed in the U.S. but that are older than 2 years.

Final

Domain	Included	Excluded
	○ Misdiagnosis (false positives, false negatives) ○ Proportion of patients with ACMG-defined medically actionable variants ○ Psychosocial harms (e.g., anxiety, family stress, depression, distress, financial consequences) to proband and family from testing related to lack of diagnosis, uncertain findings, incidental findings, and unexpected information (e.g., carrier status, non-paternity) ○ Employment or insurance Discrimination • Costs ○ Cost of testing (U.S. based studies from previous 2 years only) ○ Cost per diagnosis ○ Cost per additional diagnosis ○ Cost-effectiveness	
Setting	Any outpatient or inpatient clinical setting in countries categorized as 'very high' on the UN Human Development Index	Non-clinical settings, countries categorized other than 'very high' on the UN Human Development Index
Study Design and Risk of Bias Rating	Study designs[6] • Clinical trial (single group or controlled) • Cohort (single group of more than 10 participants or families or controlled) • Case-control • Cross-sectional • Case series (between 5 to 10 participants or families) • Cost analyses, cost-benefit analysis, cost utility analysis, cost-effectiveness analysis • Modeling studies (for clinical utility, health outcomes, and cost outcomes only) • Qualitative study designs (for safety outcomes only) Risk of Bias Rating • Any	• Case reports (fewer than 5 participants) • Narrative reviews • Editorials and commentary • Letters to the editor
Language and Time Period	• English • 2010 or later	• Any language other than English • Studies published prior to 2010

Abbreviations: CMA=chromosomal microarray analysis; HTA=health technology assessment; WES=whole exome sequencing; UN=United Nations

Notes: [a]Andorra, Argentina, Australia, Austria, Bahrain, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg,

Malta, Montenegro, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States.

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Public comment and response

See **Draft key questions: Comment and response** document published separately.

Final