Washington State Health Care Authority

June 14, 2024 Meeting Materials
Health Technology Clinical Committee

Whole genome sequencing

Contents

Health Technology Clinical Committee Application for Membership

Washington State Health Care Authority

1 Contact information

First name: Amy

Middle initial: L

Last name: Yuen

Address:

Phone number:

Best method, time to reach you: email

Email:

Today's date: 02/13/2024

2 Personal information (optional)

Gender:

☐ Male ☑ Female ☐ X/non-binary[1]

Pronouns (select all that apply)

☑ She/her ☐ He/him ☐ They/them ☐ Other (subj./obj.):

Race or Ethnicity

☐ American Indian or Alaska Native

☐ Asian or Pacific Islander American

☐ Black/ African American

☐ Latino, Hispanic, Spanish

☑ White/ Caucasian

☐ Other:

3 Professional training

Education (list degrees): BA, MD, PhD

Health care practitioner licenses: WA state

Professional affiliations: AAP, ACMG

Board certifications, formal training, or other designations: ABP, ABMGG

Current position (title and employer): Physician, Washington Permanente Medical Group

Current practice type and years in practice: Genetics, 2

Total years as an active practitioner: 23

Location of practice (city): Seattle

1 *Non-binary (X) is an umbrella term used to describe those who do not identify as exclusively male or female. This includes but is not limited to people who identify as genderqueer, gender fluid, agender, or bigender.*

4 Experience

Provide a brief explanation (up to 150 words each) addressing the following:

1) Why you would like to serve on the clinical committee;

I have served previously as an invited expert for the WA HTCC for discussion of discussion of whole exome sequencing and for the discussion of genomic microarray. I thoroughly enjoyed these experiences and found them highly educational as I learned a lot about the process by which WA HTCC considers new technologies and the approval process. In addition due to my broad background described in question 3 I believe I can provide great service for the WA HTCC.

2) The value of informing health policy decisions with scientific evidence, including any examples incorporating new evidence into your practice;

Genetics in particular is an area where scientific evidence and guidelines are critical to everyday practice. New information is learned about genes and gene variants essentially every week. In addition, new and revised testing options are frequently launched. It is essential to consider updates in evidence and expert recommendations for each patient that is seen. What may have been the ideal recommendation for a particular patient even a year ago may change and evolve as new evidence is considered.

3) How your training and experience will inform your role on the committee

I believe I can provide great service to the community due to my broad background in genetics as well as prior service in the primary care field of pediatrics. In my current position I care for a wide range of patients from newborns to senior citizens. In my prior position at MultiCare I also had extensive experience with out-patient as well as in-patient care needs encompassing pediatric, intensive care and adult genetic needs.

4) Treating populations that may be underrepresented in clinical trials: women, children, elderly, or people with diverse ethnic and racial backgrounds, including recipients of Medicaid or other social safety net programs?

Consideration of underrepresented populations is a very important consideration in genetics. Historically there has been concern particularly for peoples of diverse ethnic and racial backgrounds that they have been underrepresented in genetic testing. This creates multiple levels of concern. The first level is ensuring these diverse groups are appropriately offered genetic testing and do not experience prohibitive barriers to accepting testing. The second level is that because diverse groups have been less represented in genetic testing, interpreting their genomic variants can be more challenging and these groups may have more uncertain genetic results. The third level is that different groups may have different feelings toward genetic testing, and great care must be taken to acknowledge that and help ensure diverse groups are not exploited in the genetic testing process.

5 Ability to serve

Are you able to participate in all-day meetings, an estimated six times per year? ☐ Yes ☐ No

Are you willing to commit to the responsibilities of a committee member, including:

- Attending meetings prepared for the topics of the day;
- Actively participating in discussions;
- Making decisions based on the evidence presented and the public interest1? ☐ Yes ☐ No

Could you, or any relative, benefit financially from the decisions made by the HTCC? ☐ Yes ☐ No

6 References

Provide three professional references:

1.

First name: Michael
Last name: Raff
Relationship: colleague
Title: Physician
Contact email:
Phone number:

2.

First name: Kathleen
Last name: Leppig
Relationship: colleague
Title: Physician
Contact email:
Phone number:

3.

First name: Jennifer
Last name: Kett
Relationship: colleague
Title: Physician
Contact email:
Phone number:

For your application to be reviewed, please include:

✓ Completed application ✓ curriculum vitae ✓ **conflict of interest disclosure**

Download this form and send the completed version to **shtap@hca.wa.gov**

OR mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

1 *Detailed in Washington Administrative Code (WAC) and committee bylaws*

Health Technology Clinical Committee Conflict of Interest Disclosure

Washington State Health Care Authority

Instructions

This conflict of interest (COI) form must be completed by an applicant for appointment to the state of Washington Health Technology Clinical Committee (HTCC) or clinical expert serving in a temporary capacity on the HTCC, as well as appointment to any of its subcommittees or work groups.
Those wishing to provide public comment at HTCC meetings are also requested to complete this COI form, but are not required to do so.

Instructions specific to HTCC applicants

As stewards of public funds, the practicing clinicians who serve (or apply to serve) on the Committee strive to uphold the highest standards of transparency and impartiality. Identifying financial, professional, and other interests contributes to the effective management of perceived, potential, and/or real conflicts of interest/bias that could affect Committee determinations (WAC 182-55). Management of potential conflicts of interest on specific topics are addressed in committee bylaws.

1 Applicant information

First name: Amy

Middle initial: L

Last name: Yuen

Phone number: [redacted]

Email: [redacted]

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.
List amounts totaling $1,000 or more from a single source.
Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.
Indicate the source and date of the financial interest. For each chosen category, include date and if your activities are ongoing.
Indicate the recipient. Family: spouse, domestic partner, child, stepchild, parent, sibling (his/her spouse or domestic partner) currently living in your home.

Financial interest categories

Use these categories to indicate the nature of the financial interest:

A. Payment from parties with a financial or political interest in the outcome of work as part of your appointment or activity.
B. Employment including work as an independent contractor, consultant, whether written or unwritten.
C. Ownership or owning stock (stock, options, warrants) or holding debt or other significant proprietary interests or investments in any third party that could be affected.
D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.
E. Participating on a company's proprietary governing boards.
F. Participating in a speakers bureau.
G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures None apply

Category (A-G)	Source of income and date	Amount	Recipient	
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

No

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

No

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying HTA program staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership (*applies to HTCC committee only*).

To sign this request, do not use the "Fill & Sign" function; instead, simply click in the signature field to add your signature.

Signature

Date

02/09/2024

Download this form and send the completed version to shtap@hca.wa.gov.

Or mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

AMY LAWSON YUEN, MD, PhD

PROFILE

Physician board certified in both clinical genetics and pediatrics.

LICENSE AND CERTIFICATIONS

AMERICAN BOARD OF PEDIATRICS
Initial certification 2004, meeting requirements for continuous maintenance of certification (MOC)

AMERICAN BOARD OF MEDICAL GENETICS AND GENOMICS
Initial certification 2007, meeting requirements for continuous maintenance of certification (MOC)

WASHINGTON STATE MEDICAL LICENSE
2007 – current

EXPERIENCE

KAISER PERMANENTE WASHINGTON
August 2021 – current
Clinical genetics.

CLINICAL GENETICS - MULTICARE HEALTH SYSTEM/MARY BRIDGE CHILDREN'S HOSPITAL, TACOMA, WA
June 2013 – August 2021
Clinical genetics.
Medical director July 2018-August 2021.

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 – August 2021
Scientific member of the MultiCare IRB.

MEDICAL ADVISOR, SYNDROMES WITHOUT A NAME (SWAN)
http://www.undiagnosed-usa.org
May 2013 – 2018
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.

INVITED EXPERT

INVITED CLINICAL EXPERT for the Health Technology Clinical Committee of the Health Technology Authority of Washington State for the discussion of whole exome sequencing. November 22, 2019

INVITED CLINICAL EXPERT for the Health Technology Clinical Committee of the Health Technology Authority of Washington State for the discussion of Genomic microarray.
January 19, 2018

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

2020 MultiCare President's Award for Excellence in Clinical Outcomes and Quality for establishing the SMA (Spinal Muscular Atrophy) Multidisciplinary Treatment Clinic.

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

PUBLICATIONS

Mapping variants in thyroid hormone transporter MCT8 to disease manifestations and severity by genomic, phenotypic, functional, structural and deep learning integration. Multiple authors, submitted to Nature Medicine, under review.

Synchronized long-read genome, methylome, epigenome, and transcriptome for resolving a Mendelian condition. Multiple authors, submitted, under review Nature Genetics.

Long-term efficacy of T3 analogue Triac in children and adults with MCT8 deficiency: a real-life cohort study. Ferdy S van Geest, Stefan Groeneweg, Erica L T van den Akker, Iuliu Bacos, Diana Barca, Sjoerd A A van den Berg, Enrico Bertini, Doris Brunner, Nicola Brunetti-Pierri, Marco Cappa, Gerarda Cappuccio, Krishna Chatterjee, Alexander D Chesover, Peter Christian, Régis Coutant, Dana Craiu, Patricia Crock, Cheyenne Dewey, Alice Dica, Paul Dimitri, Rachana Dubey, Anina Enderli, Jan Fairchild, Jonathan Gallichan, Luigi R Garibaldi, Belinda George, Annette Hackenberg, Bianka Heinrich, Tony Huynh, Anna Kłosowska, **Amy Lawson-Yuen**, Michaela Linder-Lucht, Greta Lyons, Felipe Monti Lora, Carla Moran, Katalin E Müller, Laura Paone, Praveen G Paul, Michel Polak, Francesco Porta, Christina Reinauer, Yolanda B de Rijke, Rowen Seckold, Tuba Seven Menevşe, Peter Simm, Anna Simon, Marco Spada, Athanasia Stoupa, Lilla Szeifert, Davide Tonduti, Hans van Toor, Serap Turan, Joel Vanderniet, Monique

de Waart, Ronald van der Wal, Adri van der Walt, Anne-Marie van Wermeskerken, Jolanta Wierzba, Federica Zibordi, Amnon Zung, Robin P Peeters, W Edward Visser. J Clin Endocrinol Metab. 2022 Feb 17;107(3):e1136-e1147.

Disease characteristics of MCT8 deficiency: an international, retrospective, multicenter cohort study. Stefan Groeneweg, Ferdy S van Geest, Ayhan Abacı, Alberto Alcantud, Gautem P Ambegaonkar, Christine M Armour, Priyanka Bakhtiani, Diana Barca, Enrico S Bertini, Ingrid M van Beynum, Nicola Brunetti-Pierri, Marianna Bugiani, Marco Cappa, Gerarda Cappuccio, Barbara Castellotti, Claudia Castiglioni, Krishna Chatterjee, Irenaeus F M de Coo, Régis Coutant, Dana Craiu, Patricia Crock, Christian DeGoede, Korcan Demir, Alice Dica, Paul Dimitri, Anna Dolcetta-Capuzzo, Marjolein H G Dremmen, Rachana Dubey, Anina Enderli, Jan Fairchild, Jonathan Gallichan, Belinda George, Evelien F Gevers, Annette Hackenberg , Zita Halász, Bianka Heinrich, Tony Huynh, Anna Kłosowska, Marjo S van der Knaap, Marieke M van der Knoop, Daniel Konrad, David A Koolen, Heiko Krude, **Amy Lawson-Yuen**, Jan Lebl, Michaela Linder-Lucht, Cláudia F Lorea, Charles M Lourenço, Roelineke J Lunsing, Greta Lyons, Jana Malikova, Edna E Mancilla, Anne McGowan, Veronica Mericq, Felipe M Lora, Carla Moran, Katalin E Müller, Isabelle Oliver-Petit, Laura Paone, Praveen G Paul, Michel Polak, Francesco Porta, Fabiano O Poswar, Christina Reinauer, Klara Rozenkova, Tuba S Menevse, Peter Simm, Anna Simon, Yogen Singh, Marco Spada, Jet van der Spek, Milou A M Stals, Athanasia Stoupa, Gopinath M Subramanian, Davide Tonduti, Serap Turan, Corstiaan A den Uil, Joel Vanderniet, Adri van der Walt, Jean-Louis Wémeau, Jolante Wierzba, Marie-Claire Y de Wit, Nicole I Wolf, Michael Wurm, Federica Zibordi, Amnon Zung, Nitash Zwaveling-Soonawala, W Edward Visser. The Lancet Diabetes & Endocrinology, 2020 Jul;8(7):594-605.

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**. Clin Case Rep. 2019 Sep 30;7(12):2311-2315.

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.

WHOLE GENOME SEQUENCING

Heather Schultz, MD, MHA
Associate Medical Director
Health Care Authority

Washington State Health Care Authority

Background: Whole Genome Sequencing (WGS)

Laboratory procedure that sequences the entire genome

Varied clinical uses to aid diagnosis and targeted treatment at the individual, tumor tissue, microorganism level

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Background: WGS compared to other genetic testing

- WGS expands the range of genetic variants that can be identified
  - WGS doesn't require a prespecified set of genes
  - WGS results can be reanalyzed after new gene-disease associations are made
  - WGS detects structural variants that other gene testing cannot

Scope of WGS literature review

EXCLUDED: Testing in inpatient hospital settings and non-clinical research settings

Population: Children or adults suspected of a genetic disorder in an outpatient setting

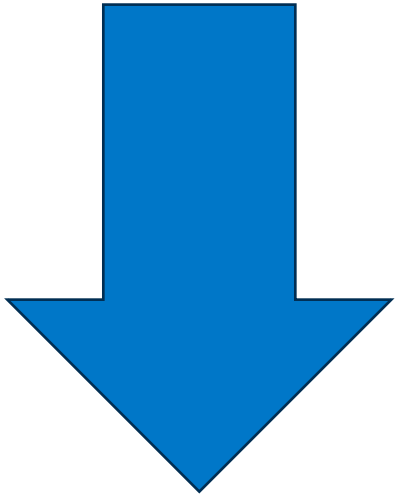
Intervention: Whole genome sequencing in a clinical setting

Comparator: Usual care

Outcomes: clinical utility, health, non-health, cost, harms

Clinical phenotypes evaluated in the evidence report

Broad clinical categories



Individual diseases

Any suspected genetic conditions
Rare diseases
Neurodevelopmental disorders
Global developmental delay
Intellectual disability
Epilepsy
Ataxia
Oculocutaneous albinism
Hypertrophic cardiomyopathy

Agency Medical Director Concerns

Efficacy	Medium concern
Safety	Low concern
Cost	Medium concern

Evidence Report Key Questions

Efficacy What is the efficacy of WGS for use in diagnosing possible genetic disorders?

Safety What are the harms associated with its use?

Cost Effectiveness What is the cost effectiveness of its use?

Efficacy Considerations

What are the potential benefits?

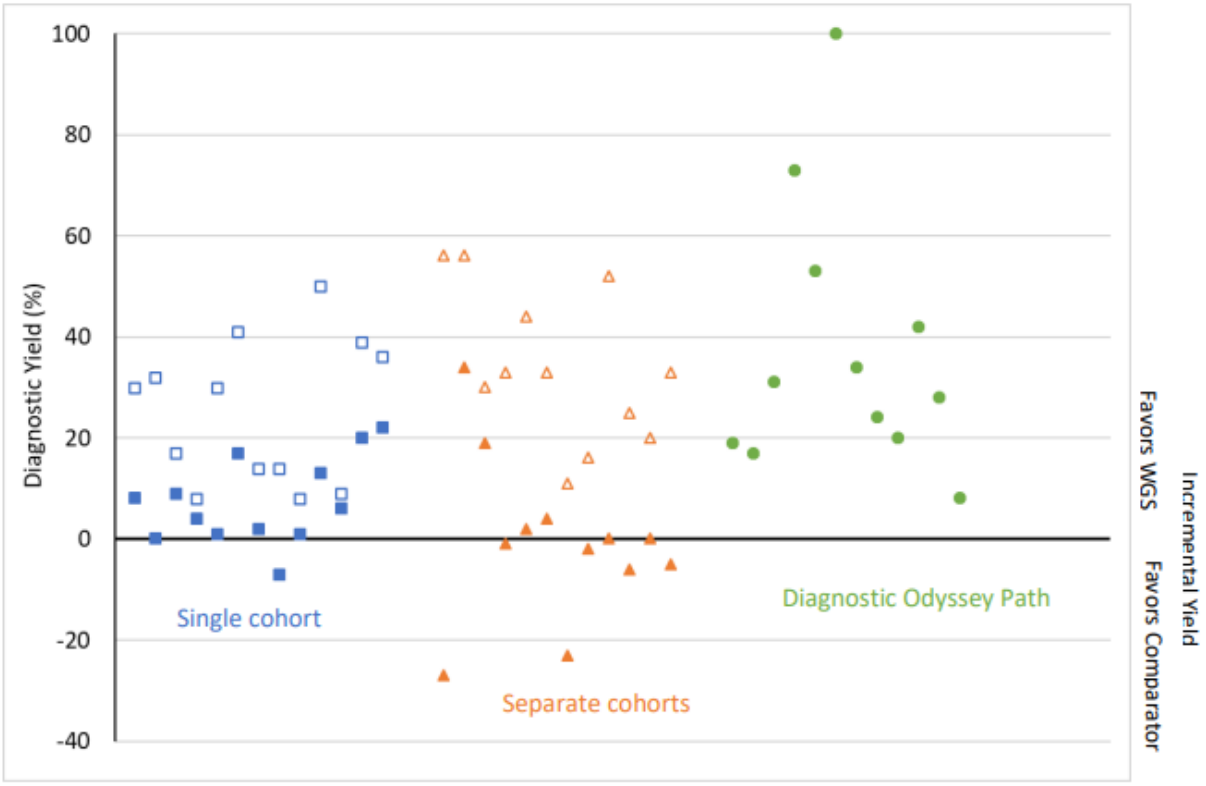
- Increase diagnostic yield
  - Reduce diagnostic odyssey burden
  - Alter treatment/surveillance plan
  - Qualitative benefits

What alternatives exist?

- Lab, imaging and targeted gene testing for some populations

Diagnostic Yield Evidence Across All Studies

Figure 5. Diagnostic Yield Among All Included Studies



Efficacy Considerations: 2 Randomized Controlled Trials

- Both studies were separate cohort studies:
  - Brockman: SOC* vs SOC + WGS
  - Vanderver: SOC + immediate WGS vs SOC + late WGS
- Both studies had elements of single cohort with individual patients serving as their own control
- Both showed increased diagnostic yield for WGS compared to other diagnostic methods

* SOC = standard of care

Brockman RCT

- Included adults and children enrolled at time of clinical genetics evaluation
- SOC defined by ordering clinician
- Variety of genetic clinics: cardiovascular, medical, ataxia, GI cancer, endocrine tumor, pulmonary
- 99 patients in each cohort
- Similar identification efficacy of diagnosis between cohorts (19 diagnoses in 18 individuals in SOC, 24 diagnoses in 20 individuals in WGS)

Brockman RCT

- **In the SOC +WGS cohort, 9 additional diagnoses made by WGS out of 24**
- 4/9 related to primary phenotype and 5/9 related to nonprimary phenotype and family history
- Referring clinicians reported plan to change medical management or pursue additional workup for WGS variants of unknown significance

Vanderver RCT

- Included 34 pediatric patients with leukoencephalopathy diagnoses (32 analyzed)
- Randomized to SOC + immediate WGS or SOC for 4 months followed by WGS
- SOC defined by the ordering clinician: primarily involved targeted gene panels
- Diagnostic efficacy was 59% for WGS vs 16% for SOC (19/32 vs 5/32)

Vanderver RCT

- **Study design changed at interim analysis because of the benefit of treatment to the patients in immediate WGS**
- No individuals in the immediate WGS cohort received a diagnosis by SOC
- 5 individuals in the late WGS cohort received a diagnosis by SOC vs 14 individuals diagnosed by WGS
- Diagnosis led to changes in clinical management:
  - Additional warranted subspecialty follow up, initiation of disease specific therapy, prognostic counseling

Safety/Harm Considerations

Variants of unknown significance

Secondary findings

Rescinded diagnoses

Safety/Harm Considerations: 2 Trials

- **Limited concern for safety/harm and limited evidence investigating safety/harm**
- One study looked at VUS frequency:
  - Lower rate of VUS from WES and WGS compared to multigene panels
  - No difference between WES and WGS
- Second study looked at rescinded diagnoses after WES or WGS
  - 1.9% rescinded diagnosis rate (4/214)

Cost Considerations

WGS testing costs continues to decline

Duo or trio testing increases diagnostic yield and cost

WGS costs could reduce or replace alternative testing costs

Downstream savings difficult to estimate

Cost Considerations: 2 Trials

- Two studies reported cost-effectiveness outcomes for WGS testing compared to other tests using decision analysis models
- Both models compared first line WGS to SOC followed by WGS
- **Conflicting findings:**
  - One study reported WGS testing cost less and identified more diagnoses
  - Second study reported higher cost for WGS compared to SOC and WES

Related HTCC Decision: Whole Exome Sequencing (WES)

Whole exome sequencing (WES) was selected for review in 2019

Health Technology Assessment was completed in 2020

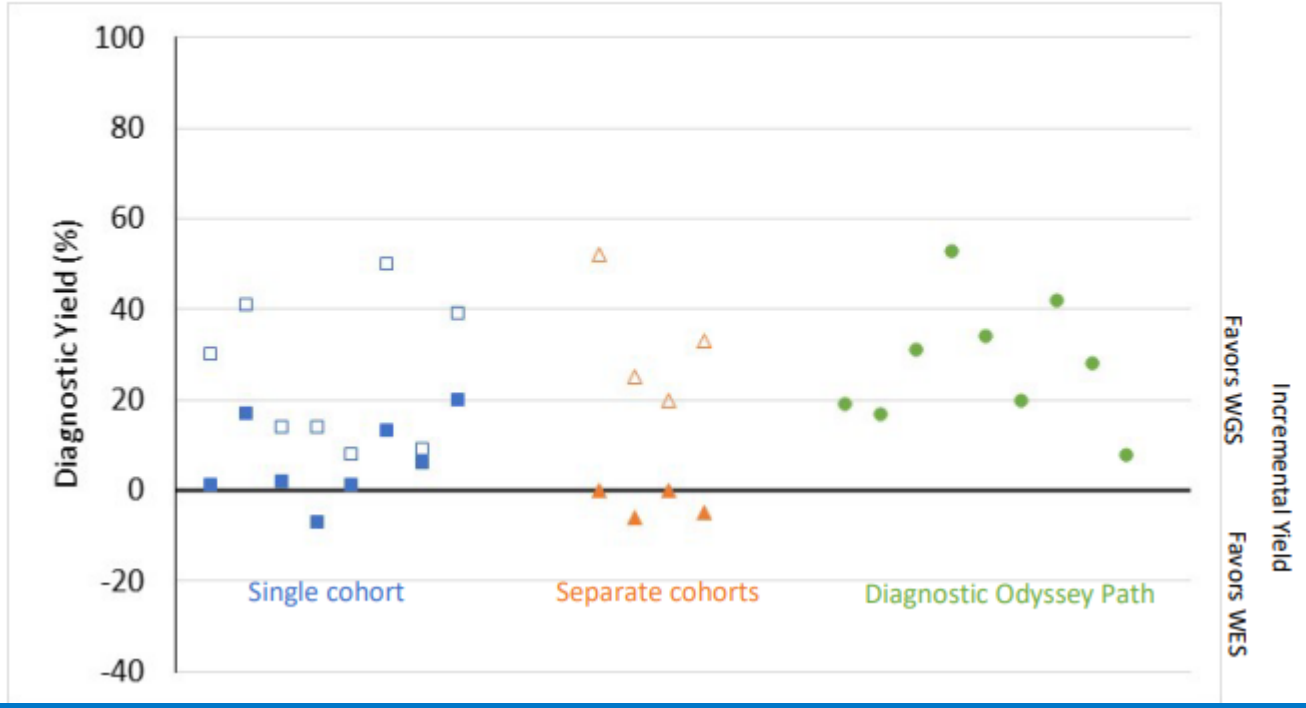
2020 HTCC decision: WES is currently a covered benefit with conditions

WGS vs WES

- Same next generation sequencing technology used
- Both used when more targeted genetic testing unrevealing or no target known
- WES sequences the protein coding portion of the genome
- WGS sequences the entire genome including non-protein coding portion
- WGS has better ability to detect structural variants
- Similar PICO used for WGS and WES health technology assessment reviews

Diagnostic Yield WGS vs WES

Figure 6. Diagnostic Yield, WGS vs. WES Strategies



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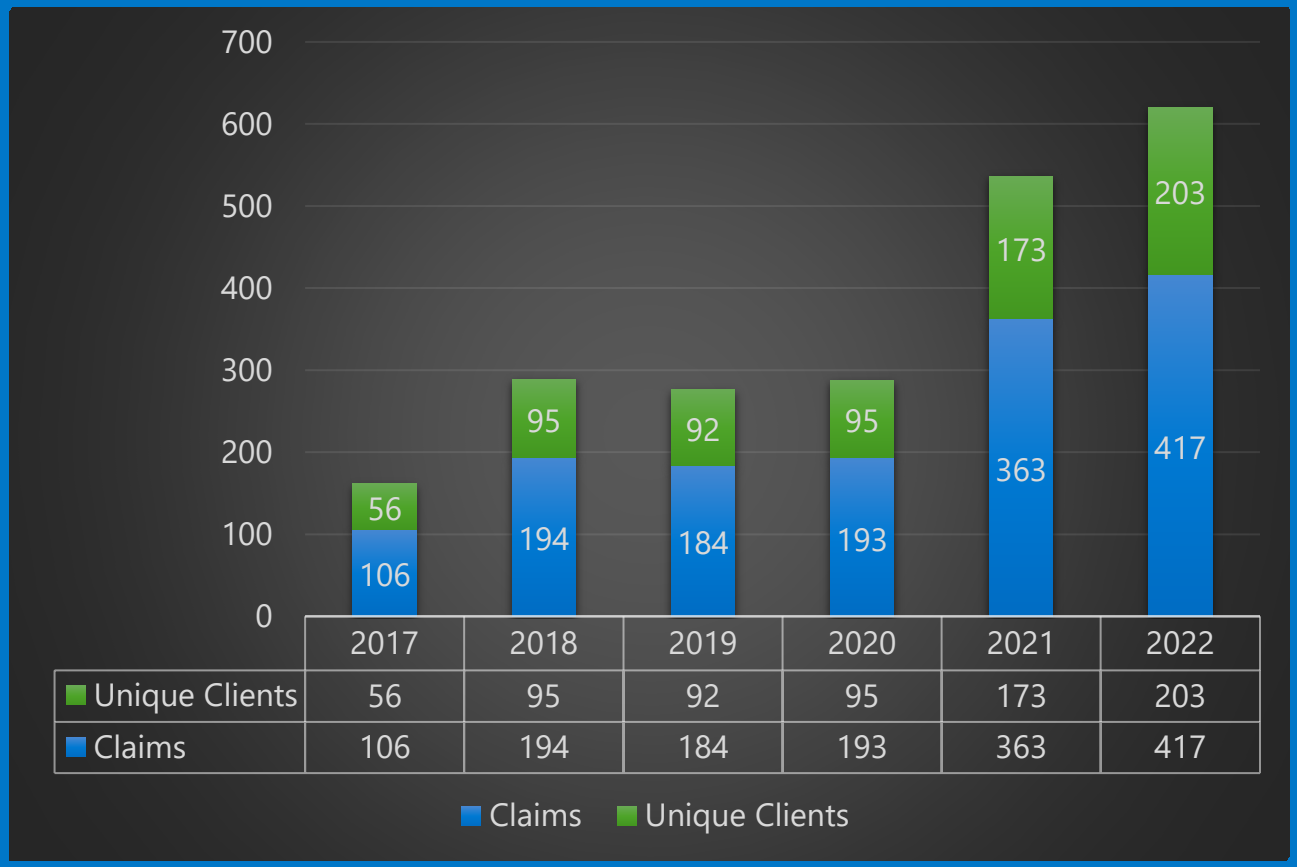
Current Utilization of WES Medicaid



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Current WGS State Agency Coverage Policies

- Health Care Authority
  - PEBB and SEBB (Public and School Employee Benefits Boards/UMP Plans) **Considered investigational**
  - Apple Health (Medicaid) **Reviewed for medical necessity**
- Labor and Industries **Not covered (not relevant to job related illness or injury**)

Current utilization of WGS

	2021	2022	2023
FFS Medicaid	NR	NR	NR
Managed Care Medicaid	NR	25	71
Total payment		$16,797	$87,821
Payment per individual		$672	$1237
PEBB/SEBB	NR	NR	NR
LNI	NA	NA	NA

NR= not reported, small numbers suppressed to protect patient privacy

NA = not applicable

Selected Coverage Policies

COVERED

- Cigna
- United Healthcare

NOT COVERED

- Aetna
- Humana
- Kaiser Permanente
- Premera
- Regence

Clinical Practice Guidelines

- Guidelines with recommendations have a broad range of specificity
- Recommendations vary regarding first line use or sequential
- 2021 American College of Medical Genetics and Genomics (ACMG) guideline offers the most detailed recommendations
- ACMG guidelines strongly recommended ES or GS as first or second tier test guided by clinical judgement/after focused testing in patients with congenital anomalies, development delay, intellectual disability

ACMG 2021 WES/WGS Guideline

- Based on systematic review of 167 studies evaluating WES and WGS
- Strongly recommended WES or WGS as first or second tier test guided by clinical judgement/after focused testing in patients with congenital anomalies, developmental delay, intellectual disability
  - Considered certainty of evidence, benefit/harm, patient values and resource utilization
  - Noted increasing emerging evidence of therapeutic benefit
  - Found limited negative outcomes
  - Advised not for use in patients with clinical presentations highly suggestive of a specific genetic diagnosis

AMDG Evidence Considerations

- Genetic diseases are rare and heterogenous making large RCTs evidence base challenging
- Higher incremental diagnostic yields were seen across all study types for WGS
- Clinician preference for testing strategy in separate cohort designed studies likely produced biased estimates against WGS
- Studies that used individuals as their own controls support the use of WGS to increase diagnostic yield for rare genetic diseases
- WES currently covered with criteria and WGS demonstrated increased incremental yield compared to WES

AMDG Recommendation: Coverage with criteria that aligns with WES

- Limited to congenital anomalies, intellectual disability and developmental delay with moderate to severe findings
- Ordered by a geneticist after genetic counseling
- Alternative non-genetic causes ruled out
- Diagnosis not reached with targeted testing

Questions?

Heather Schultz, MD, MHA

heather.schultz@hca.wa.gov

WES HTCC Coverage Determination

Limitations of coverage:

Whole exome sequencing (WES) is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorders in a phenotypically affected individual when ALL of the following criteria are met:

1. A board-certified or board-eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), who is not employed by a commercial genetic testing laboratory, has evaluated the patient and family history, and recommends and/or orders the test; and

WES HTCC Coverage Determination

1. 2. A genetic etiology is considered the most likely explanation for the phenotype, based on EITHER of the following; and
    1. Multiple abnormalities affecting unrelated organ systems, (e.g. multiple congenital anomalies); or
    2. TWO of the following criteria are met:
        1. — Significant abnormality affecting at minimum, a single organ system,
        2. — Profound global developmental delay, or intellectual disability as defined below,
        3. — Family history strongly suggestive of a genetic etiology, including consanguinity,
        4. — Period of unexplained developmental regression (unrelated to autism or epilepsy),
        5. — Biochemical findings suggestive of an inborn error of metabolism where targeted testing is not available;

WES HTCC Coverage Determination

3. Other circumstances (e.g. environmental exposures, injury, infection) do not reasonably explain the constellation of symptoms; and

4. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing (e.g., comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available; and

5. The differential diagnosis list and/or phenotype warrant testing of multiple genes and ONE of the following:

- WES is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity); or
- WES results may preclude the need for multiple invasive procedures or screening that would be recommended in the absence of testing (e.g. muscle biopsy); and

WES HTCC Coverage Determination

6. A standard clinical work-up has been conducted and did not lead to a diagnosis; and

7. Results will impact clinical decision-making for the individual being tested; and

8. Pre- and post-test counseling is performed by an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor.

WES HTCC Coverage Determination

Non-covered indicators:

WES is not covered for:

- Uncomplicated autism spectrum disorder, developmental delay, mild to moderate global developmental delay.
- Other circumstances (e.g. environmental exposures, injury, infection) that reasonably explain the constellation of symptoms.
- Carrier testing for “at risk” relatives.
- Prenatal or pre-implantation testing

WES HTCC Coverage Determination

Definitions:

Global developmental delay (GDD) is used to categorize children who are younger than five years of age. GDD is defined as a significant delay in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of ID. Such delays require accurate documentation by using normreferenced and age appropriate standardized measures of development administered by experienced developmental specialists, or documentation of profound delays based on age appropriate developmental milestones are present.

Reference: Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays Pediatrics 2014;134:e903–e918. Page e905 (Reaffirmed by American Academy of Pediatrics in 2020)

Significant delay is typically defined as performance two standard deviations or more below the mean on age-appropriate, standardized, normal-referenced testing.

WES HTCC Coverage Determination

Definitions:

Intellectual disability (ID) is a life-long disability diagnosed at or after age five when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-V), defines patients with ID as having an IQ

less than 70, onset during childhood, and dysfunction or impairment in more than two areas of adaptive behavior or systems of support.

Washington State Health Care Authority

Whole genome sequencing

Order of scheduled presentations:

	Name
1	**Seattle Children's Hospital** • Abbey Scott, CGC • Jamie Love-Nichols, CGC • Tara Wenger • Katrina Dipple, MD • Michael Bamshad, MD
2	Ashley Arthur, Head of Market Access – GeneDx
3	Max Brown, Vice President of Public Affairs – NW Rare Disease Coalition
4	**Patient-centered Laboratory Utilization Guidance Services (PLUGS)** • Sarah Clowes Candadai, CGC • Jessie Conta, CGC

Health Technology Clinical Committee Conflict of Interest Disclosure

Washington State Health Care Authority

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1 Applicant information

First name: Katrina

Middle initial: M

Last name: Dipple

Phone number: [redacted]

Email: [redacted]

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

Indicate the source and date of the financial interest. For each chosen category, include date and if your activities are ongoing.

Indicate the recipient. Family: spouse, domestic partner, child, stepchild, parent, sibling (his/her spouse or domestic partner) currently living in your home.

Financial interest categories

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B. Employment including work as an independent contractor, consultant, whether written or unwritten.

C. Ownership or owning stock (stock, options, warrants) or holding debt or other significant proprietary interests or investments in any third party that could be affected.

D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.

E. Participating on a company's proprietary governing boards.

F. Participating in a speakers bureau.

G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

Yes. I am a clinical geneticist in academic medicine. I have published academic articles which use genome sequencing for diagnosis of patients and gene discovery.

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

No

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying HTA program staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership (*applies to HTCC committee only*).

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Signature

[redacted]

Date

5/28/2024

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1 Applicant information

First name: Abbey

Middle initial: A

Last name: Scott

Phone number: [redacted]

Email: [redacted]

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

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D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.
E. Participating on a company's proprietary governing boards.
F. Participating in a speakers bureau.
G. Receiving honoraria.

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			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

I was the first author on a poster at an academic meeting that detailed exome and genome diagnostic rates for our inpatient service at Seattle Children's Hospital within the last few years, but otherwise no.

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

It is possible that I could be involved in policy positions and/or clinical guidelines within Seattle Children's Hospital.

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

Not that I am aware of.

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying HTA program staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership (*applies to HTCC committee only*).

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Signature

Date

05/23/2024

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1 Applicant information

First name: Ashley

Middle initial: L

Last name: Arthur

Phone number:

Email:

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

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			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

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Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

Yes, publically provided opinion for WGS Coverage in multiple states promoting access to testing

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

No

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

No

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Signature

[redacted]on to shtap@hca.wa.gov.

Date

5/24/24

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1 Applicant information

First name: Michael

Middle initial: J

Last name: Bamshad

Phone number: [redacted]

Email: [redacted]

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

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G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
D	GeneDx	[redacted]	X Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

Yes, I am a scientist and clinical geneticist who studies the use of whole genome sequencing in clinical settings.

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

no

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

no

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Date 5/28/2024

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1 Applicant information

First name: Sarah

Middle initial:

Last name: Clowes Candadai

Phone number: [redacted]

Email: [redacted]

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

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			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

Yes - my organzation, PLUGS, is a non profit collaborative network that advocates to improve access, ordering, interpretation and fair payment of clinical lab testing for patients, including for genome sequencing. I contributed opinions for HTCC's exome sequencing review.

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

PLUGS is an academic collaborative - I've contributed to coverage policy recommendations and to hospital policies regarding genome sequencing access for patents.

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

Yes, if the HTCC does not recommend genome sequencing coverage by Medicaid it would be in conflict with policies I promote. Coverage decisions being in conflict with standard of care testing is normative for a variety of lab testing.

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1 Applicant information

First name: Jessie

Middle initial: H

Last name: Conta

Phone number:

Email:

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.
List amounts totaling $1,000 or more from a single source.
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B, G	Seattle Children's Hospital Jan 2023 - present		✓ Self	Family
B	Columbia University Feb 2024 - present		✓ Self	Family
B	Exact Sciences Nov 2023 - present		✓ Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

No

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

Create and review medical coverage policies for health insurers related to genomic testing (including whole genome sequencing).

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

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Whole Genome Sequencing

Health Technology Assessment
Washington State Health Care Authority

Contributors:

Lead Investigator: Leila Kahwati, MD, MPH
Co-Investigators: Heidi Cope, MS, CGC, Ana Forsythe, MS
Clinical Advisor: Elizabeth Heise, MS, CGC
Project Coordinator: Sara Kennedy, MPH
Scientific Reviewer: Meera Viswanathan, PhD
Information Specialist: Mark Howell, MLS
Editorial Support: Mary Gendron, BA, Michelle Bogus

Presented by:
Leila Kahwati, MD MPH

June 14, 2024

Lkahwati@rti.org

Overview of Presentation

- Background
- Methods
- Results
- Discussion
- Conclusions

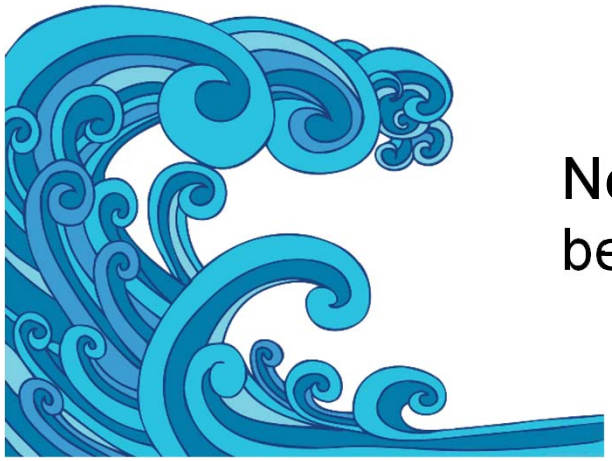
Abbreviations

ACMG	**American College of Medical Genetics and Genomics**
AGREE II	Appraisal of Guidelines for Research & Evaluation II
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMA	chromosomal microarray
CMS	Centers for Medicare & Medicaid Services
COE	certainty of evidence
CQ	cost question
EQ	efficacy question
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCA	Health Care Authority
HTA	health technology assessment
LDT	Laboratory-developed tests
NGS	next-generation sequencing
NSRI	nonrandomized studies of interventions
RCT	randomized controlled trial
RoB	risk of bias
SNV	single nucleotide variant
SOC	standard of care
SQ	safety question
UDN	Undiagnosed Diseases Network
VUS	variants of unknown significance
WES	whole exome sequencing
WGS	whole genome sequencing

Background

Genetic and Rare Disorders-Burden of Disease

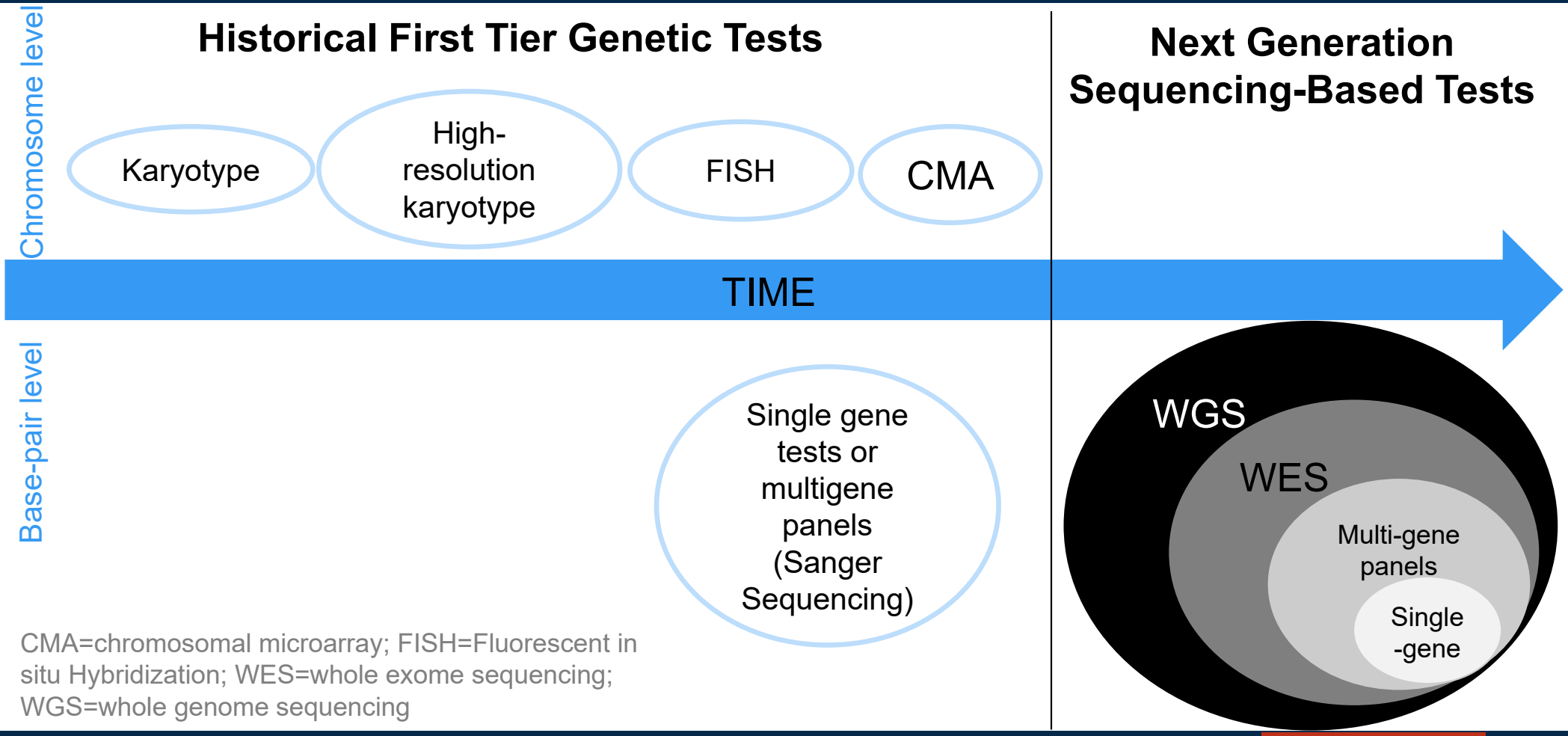
- 7,000 rare disorders affecting 6% to 8% of the US population
  - More than a third have a genetic origin
  - Treatment available for 600 to 700 of them



Source: FreePNGimg.com Creative Commons (CC BY-NC 4.0)

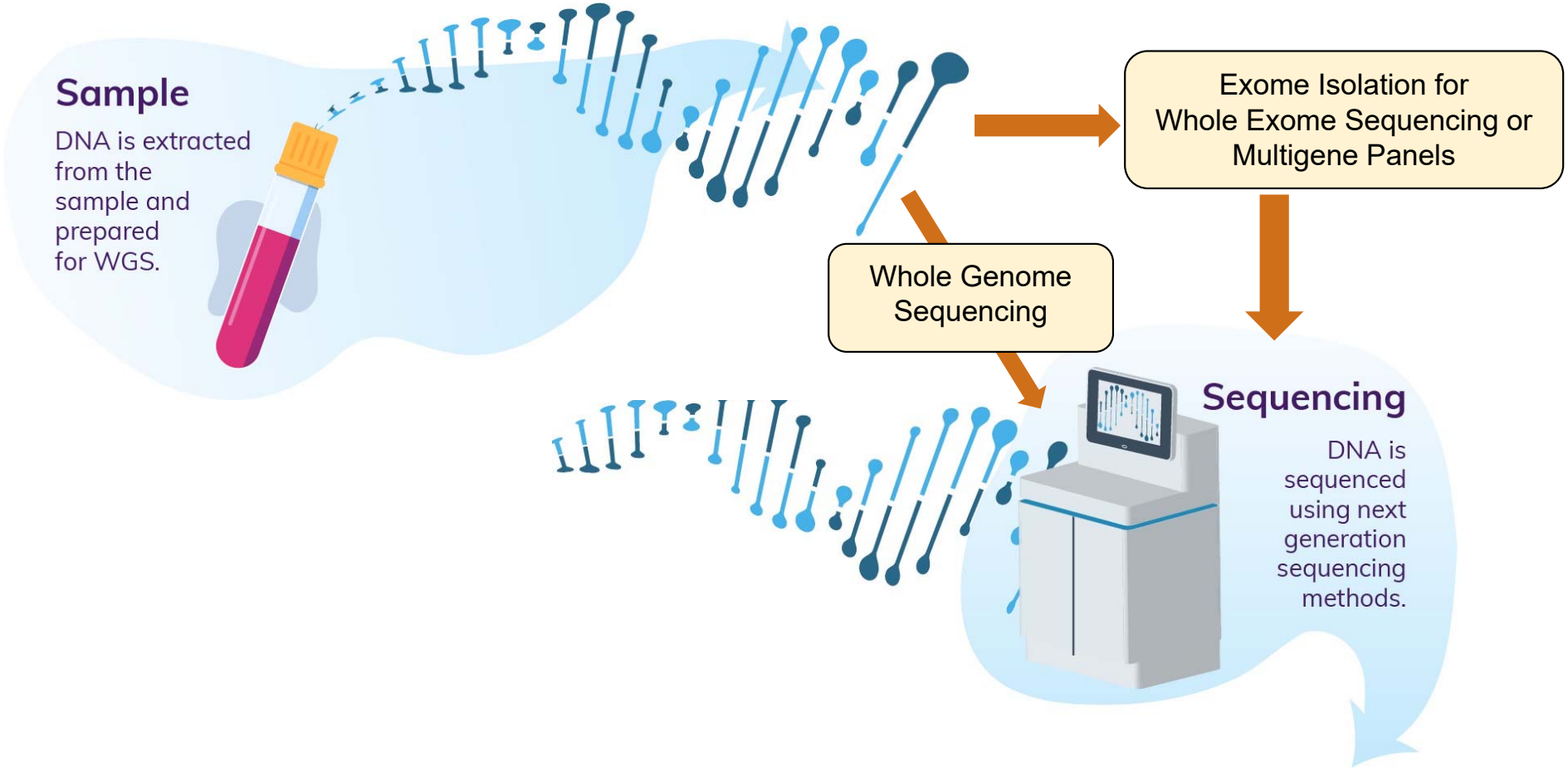
Nearly 250 disease-gene relationships are being identified each year

Genetic Tests



CMA=chromosomal microarray; FISH=Fluorescent in situ Hybridization; WES=whole exome sequencing; WGS=whole genome sequencing

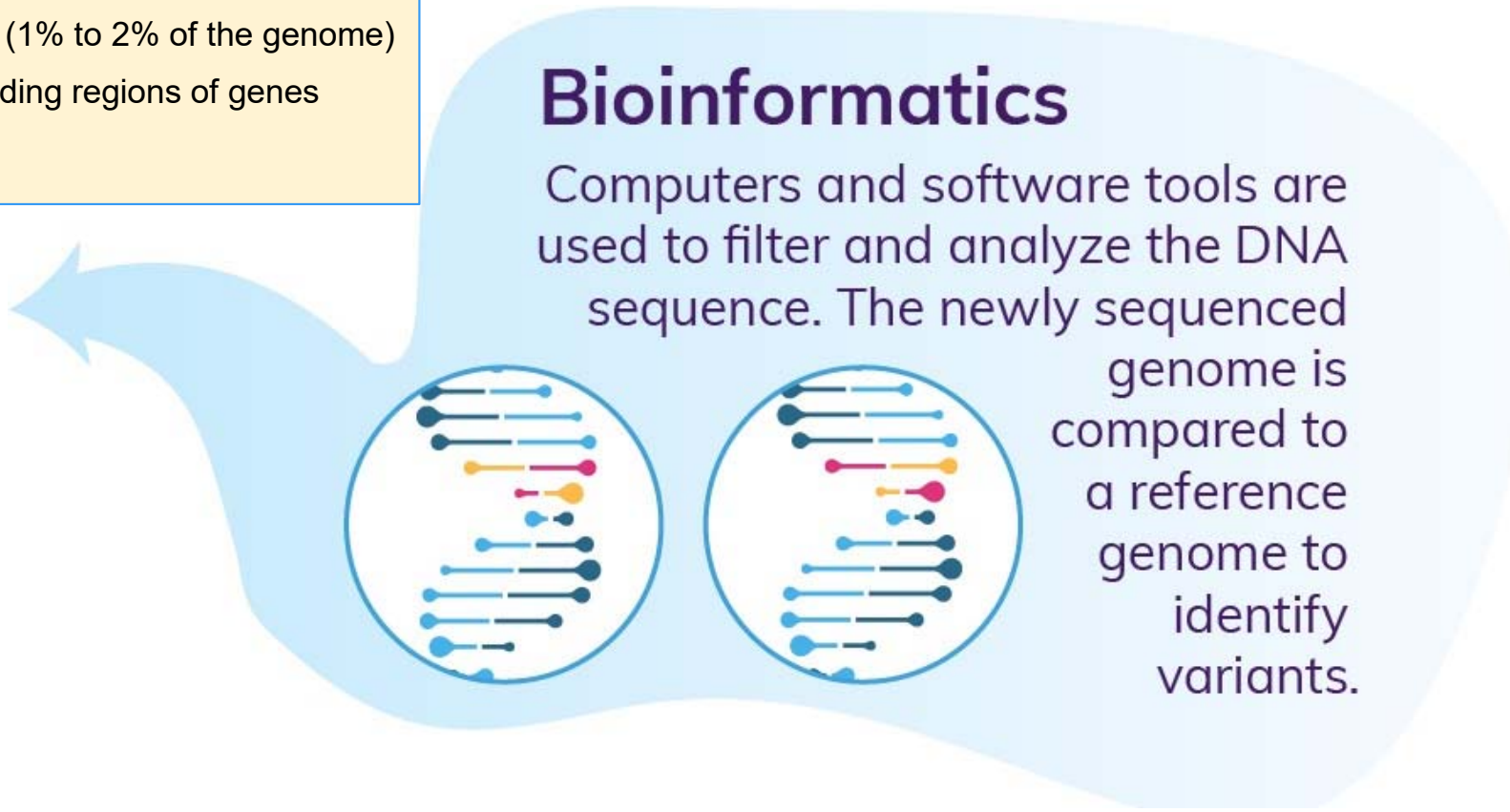
Whole Genome Sequencing-Description 1



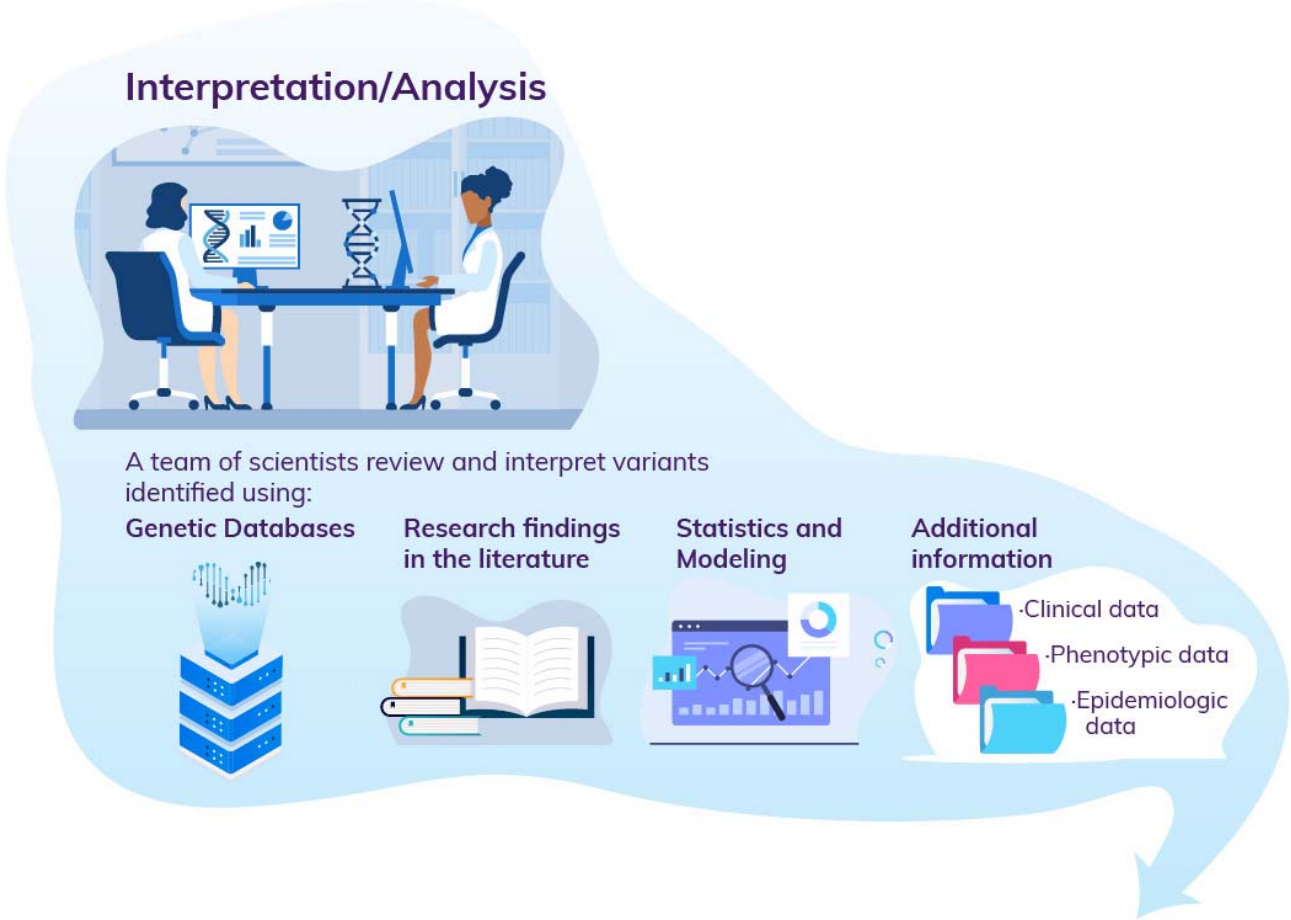
Whole Genome Sequencing-Description 2

Bioinformatics and analysis depends on which NGS test

- WGS entire genome
- WES protein coding regions (1% to 2% of the genome)
- Multigene panels: protein coding regions of genes specific to the panel



Whole Genome Sequencing-Description 3



Whole Genome Sequencing-Description 4

Whole Genome Sequencing-Description 5

Types of WGS-1

- Clinical WGS
  - Conducted in a clinical diagnostic laboratory, ordered by a provider in the context of a patient-provider relationship
- Research WGS
  - Conducted by an academic or research laboratory, ordered as part of study participation

Types of WGS-2

- Relatives may be sequenced to interpret variants in the patient
  - Trio testing: patient and both parents (preferred)
  - Duo testing: patient and 1 parent or sibling
  - Singleton: patient alone

- Standard WGS
- Rapid WGS

Regulatory Status

- **Food and Drug Administration (FDA)**
  - Authority to regulate the safety and effectiveness of in vitro diagnostics
    - Debate over whether WGS is a test or a clinical service

- **Clinical Laboratory Improvement Amendments (CLIA) governed by CMS**
  - Regulates laboratory developed tests used in clinical care (*analytic validity)*
  - No regulation of *clinical validity* or *clinical utility,* or research use of tests
  - FDA announced a final rule on April 29, 2024 that clarifies its authority to regulate laboratory developed tests as medical devices

Rationale for Use of WGS for Diagnosis

- WGS could potentially
  - Avoid or shorten diagnostic odysseys
  - Speed the time to appropriate intervention
  - Guide disease management
  - Alleviate patient and family burden

Same as rationale for use of WES

- WGS identifies:
  - Single nucleotide variants with high accuracy (similar to WES)
  - Indels and copy number variants more accurately than WES
  - Structural variations, variants in intronic regions (e.g., in promoters, regulatory elements, or SNVs that alter splicing) and repeat expansions (as compared with WES)

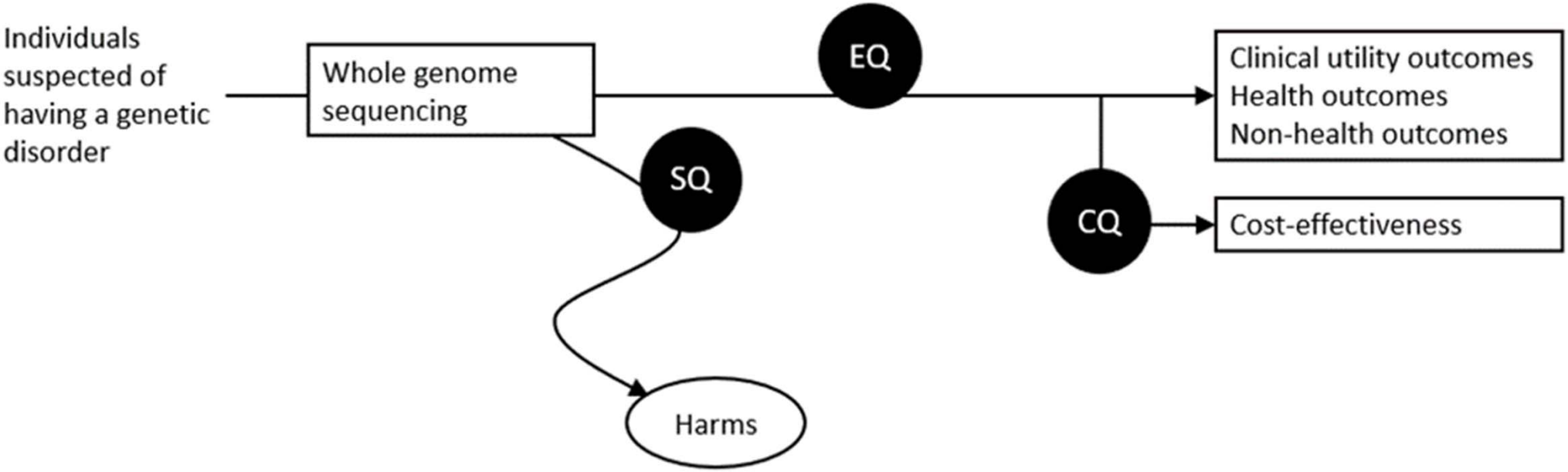
- As knowledge of disease-gene associations have increased and NGS technology has improved and dropped in price, WGS has become more practical and offers a more efficient workflow as compared to WES

Policy Context

- In November 2019, the Health Technology Clinical Committee approved **WES** as a covered benefit with conditions
- At that time, **WGS** was not in widespread clinical use and was not reviewed
- The State of Washington Health Care Authority has now selected **WGS** used in outpatient settings for an HTA because of:
  - High concerns for safety and cost
  - Medium concerns for efficacy
- **WGS** used in critically ill patients in acute settings such as the NICU/PICU is a covered benefit under inpatient prospective payment systems

Methods

Analytic Framework



Abbreviations: CQ = cost question; EQ = efficacy question; SQ = safety question

Key Questions

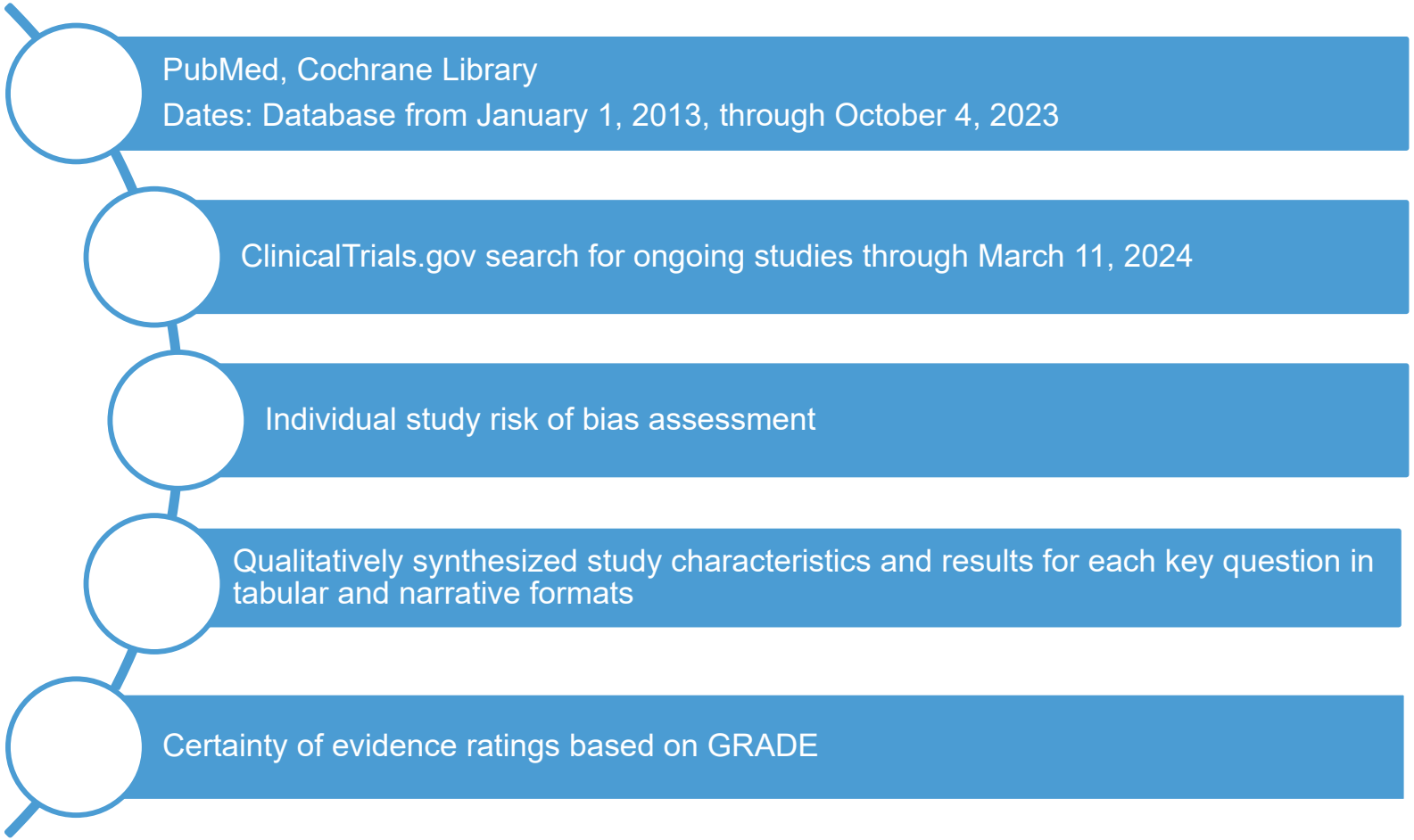
- **Efficacy Question (EQ).** What is the efficacy of WGS in diagnosing possible genetic disorders?
- **Safety Question (SQ).** What are the harms of WGS in diagnosing possible genetic disorders?
- **Cost Question (CQ 1).** What is the cost-effectiveness of WGS in diagnosing possible genetic disorders?
- **Contextual Question.** What is the diagnostic yield of WGS sequencing reported in systematic reviews published in the past 4 years?

Inclusion Criteria

Domain	Summary
Population	Infants, children, or adults with suspected genetic disorder
Intervention	Standard or rapid WGS alone or with other tests, WGS reanalysis
Comparator	• Usual diagnostic care (e.g., clinical, laboratory, or imaging evaluation; single gene testing; multigene panel testing; chromosomal microarray; WES) • Alternative test results in the same participant, including reanalysis
Outcomes	• **Clinical utility**: diagnostic yield; secondary findings; time to diagnosis; changes in care; at-risk relative identification • **Health**: mortality, survival, morbidity • **Non-health**: personal utility; psychosocial outcomes; patient experience • **Cost**: cost-effectiveness measured using U.S.-based costs • **Harms**: any outcome or other findings that suggest a harm
Setting	Outpatient setting in highly developed countries
Study Design	Trials, comparative cohort studies (single arm for harms), cost-effectiveness analyses
Other	English language, published in 2013 or later

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

Search and Assessment Methods

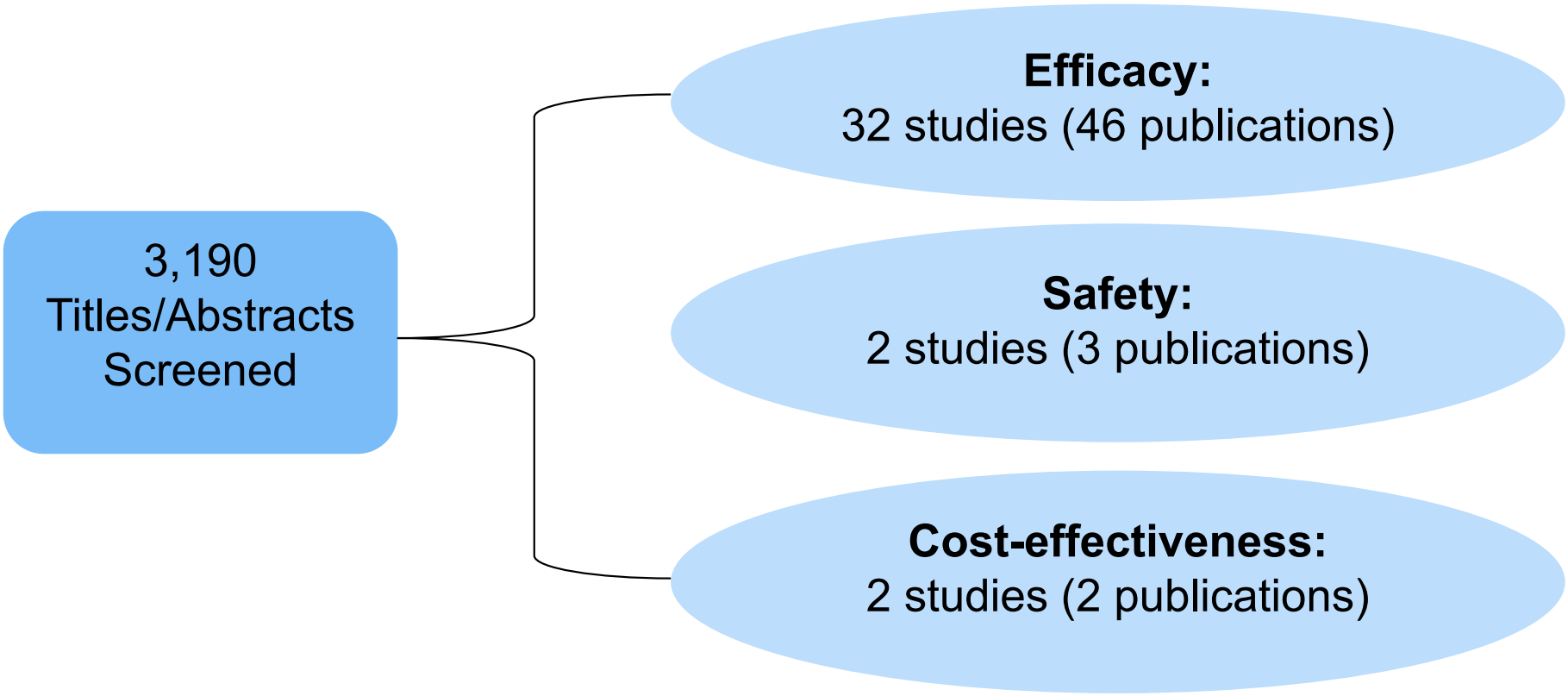


GRADE

Certainty of Evidence	**Outcomes:** diagnostic yield, other clinical utility, health outcomes, secondary findings, safety, cost-effectiveness
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 no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.** No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

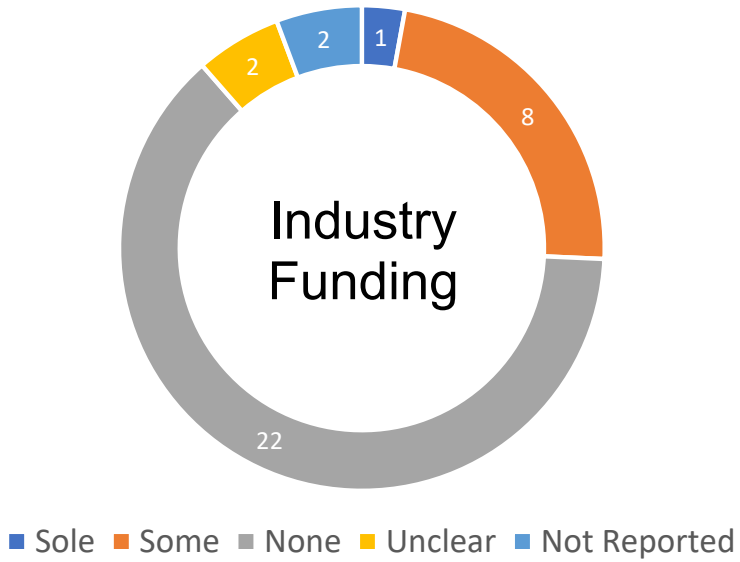
Findings

Search Yield

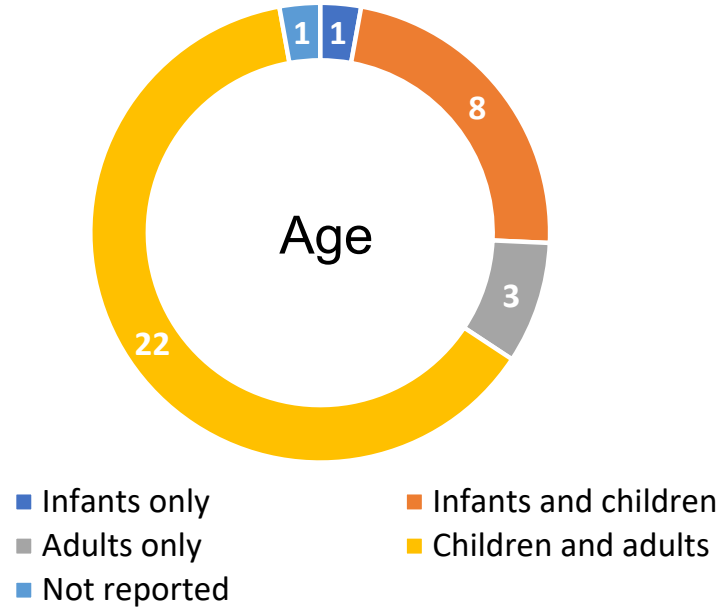


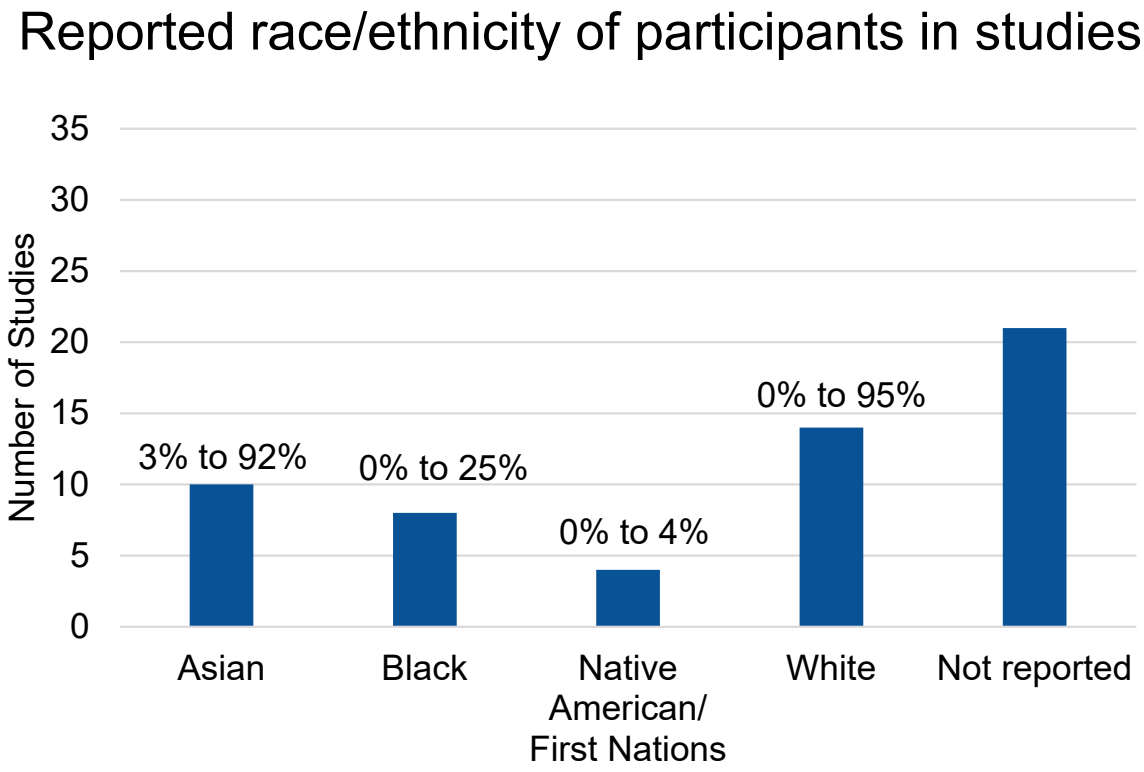
Study and Population Characteristics-1

Number of Studies



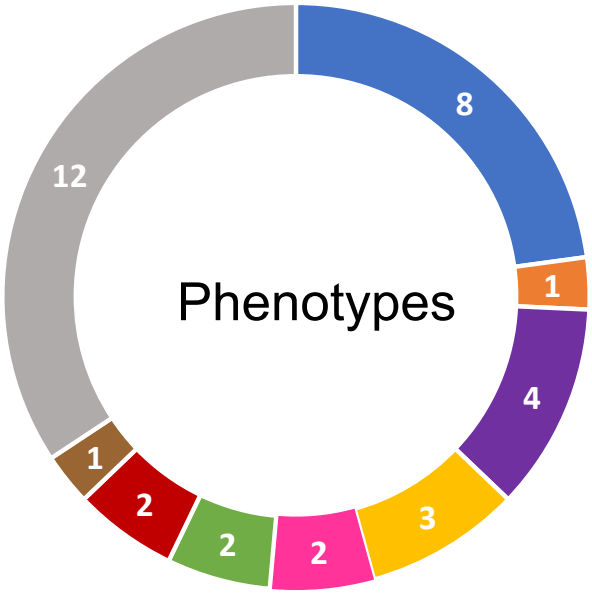
Study and Population Characteristics-2

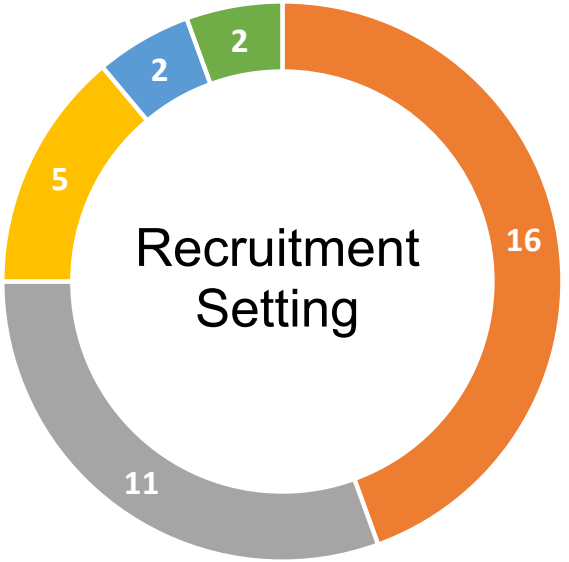




% Female: range 13% to 64%

Study and Population Characteristics-3

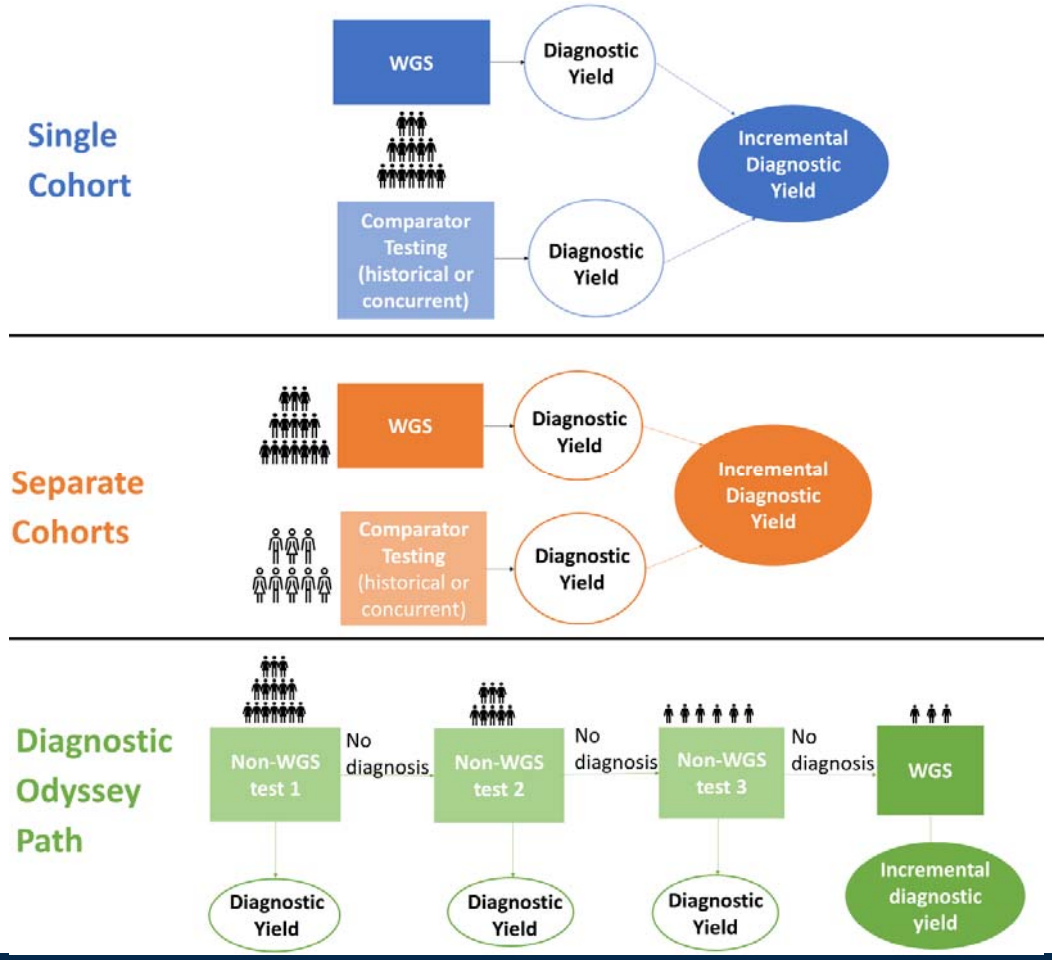




- Neurodevelopmental (DD/ID)
- Autism
- Epilepsy
- Neurologic (abnormal white matter)
- Neurologic (ataxia)
- Neurologic (heterogeneous)
- Vision
- Cardiomyopathy
- Not specific

- Primary care
- Genetics clinic
- Speciality clinics
- Tertiary medical centers
- Clinical lab or registry
- Unclear/Not reported

Study and Population Characteristics-4



11 studies

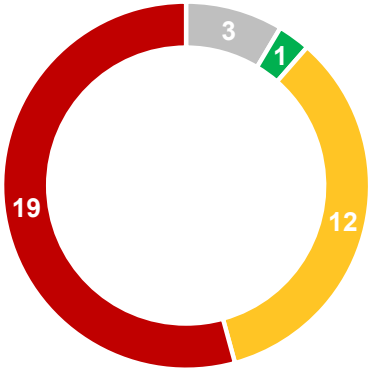
11 studies

11 studies

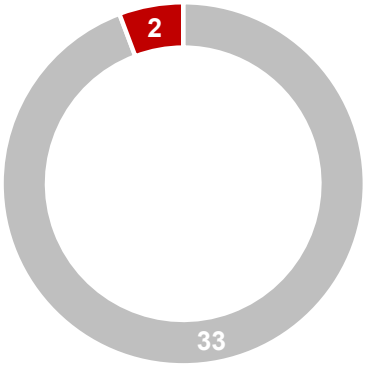
2 Cost-effectiveness Studies

Risk of bias

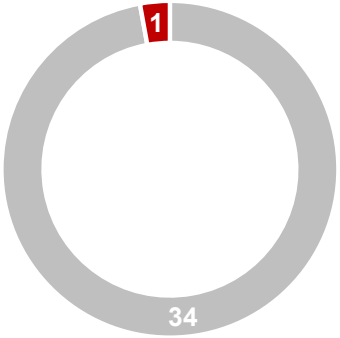
Clinical Utility Outcomes



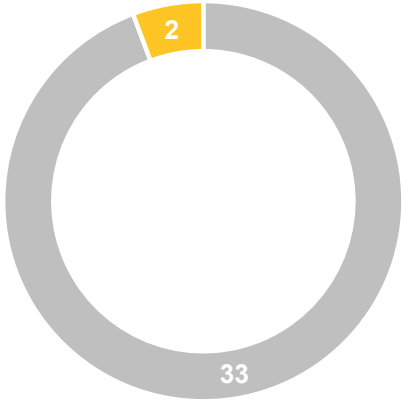
Safety Outcomes



Health Outcomes



Cost Outcomes



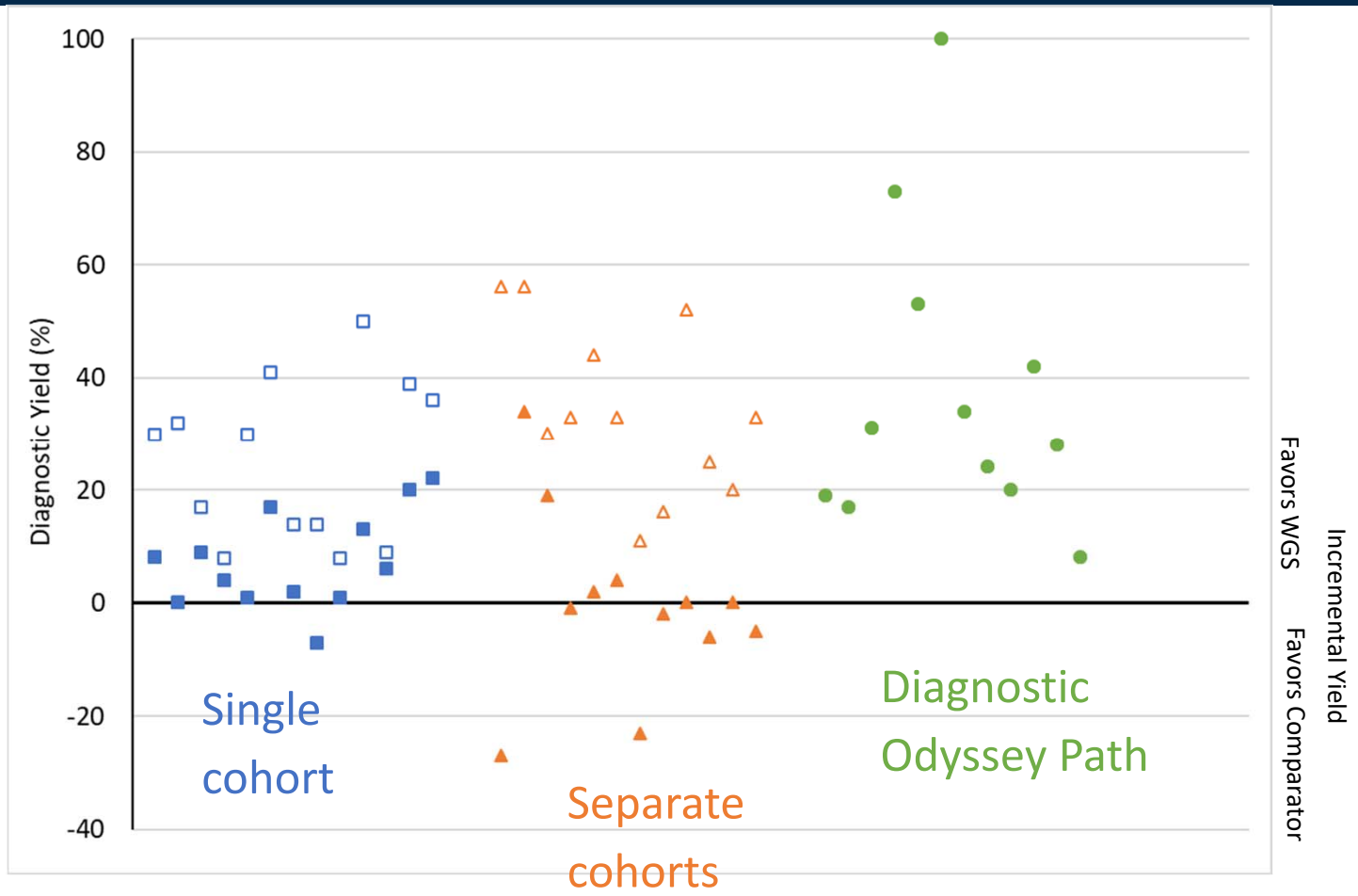
Not applicable Low risk of bias Some risk of bias High risk of bias

Sources of variation across studies

- Type of lab used (research vs. clinical)
- Year of testing
- Reference genome used
- Use of singleton, duo, or trio testing
- Definition of a ‘positive’ test
  - For example, whether variants of unknown significance are included
  - Use of ACMG criteria for classifying variants
- Extent of pre-WGS testing and evaluation

Findings: Diagnostic Yield

Diagnostic Yield: WGS vs all comparators



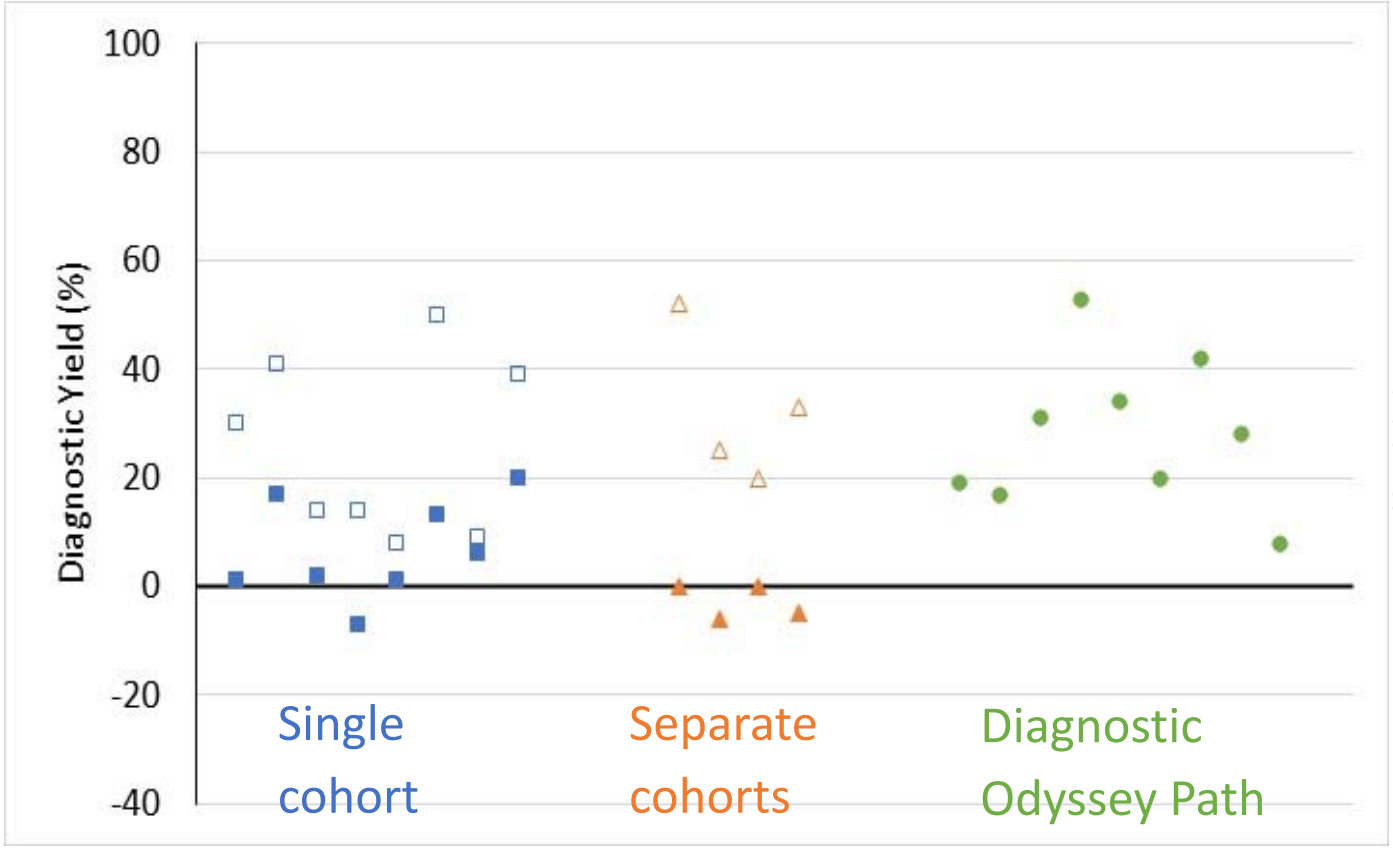
32 studies reporting 37 comparisons

Legend:

Open symbols (e.g., □, △) depict absolute yield of WGS

Solid symbols (e.g., ■, ▲, ●) depict incremental yield

Diagnostic Yield: WGS vs. WES



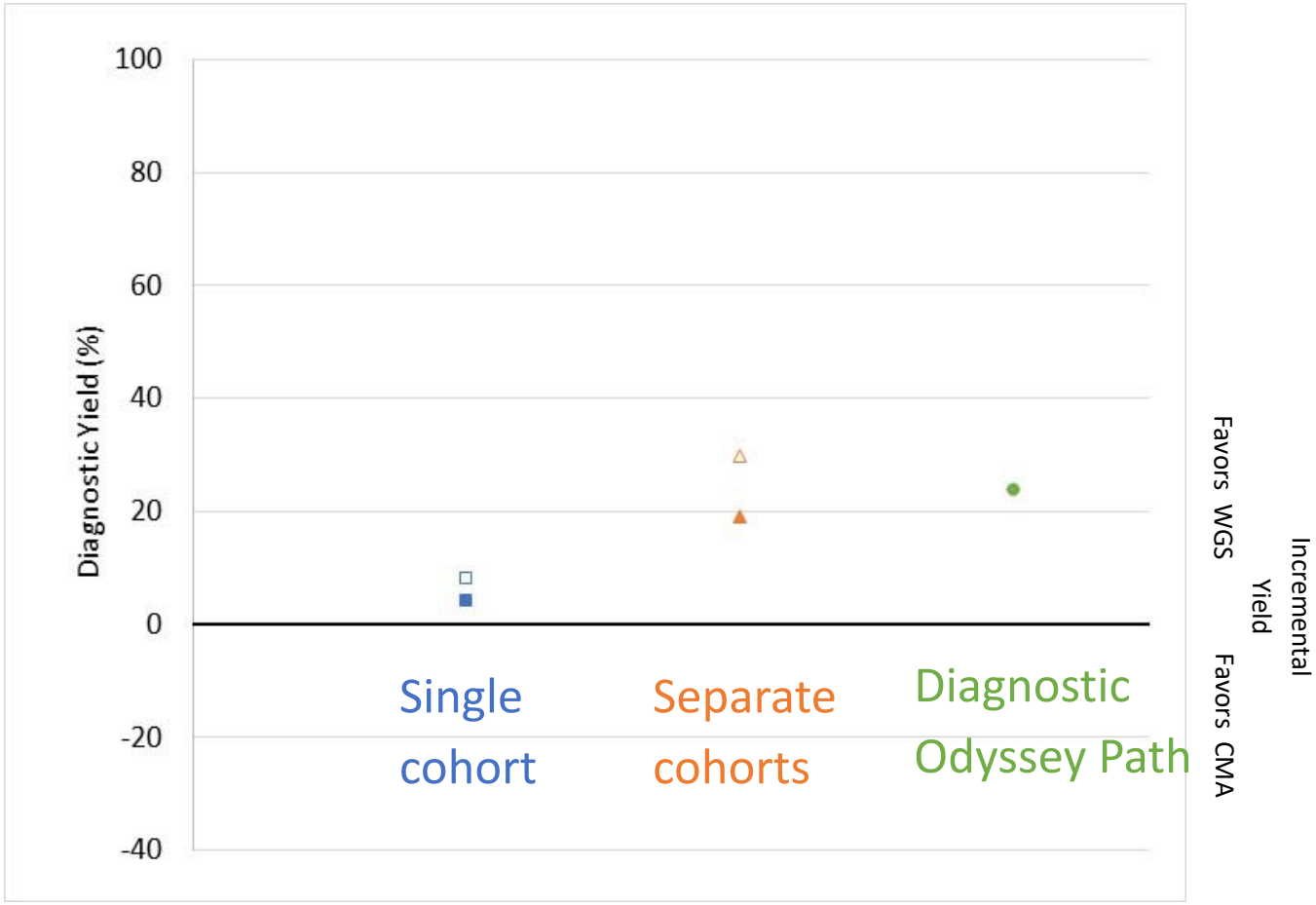
19 studies reporting 21 comparisons

Legend:

Open symbols (e.g., □, △) depict absolute yield of WGS

Solid symbols (e.g., ■, ▲, ●) depict incremental yield

Diagnostic Yield: WGS vs. CMA



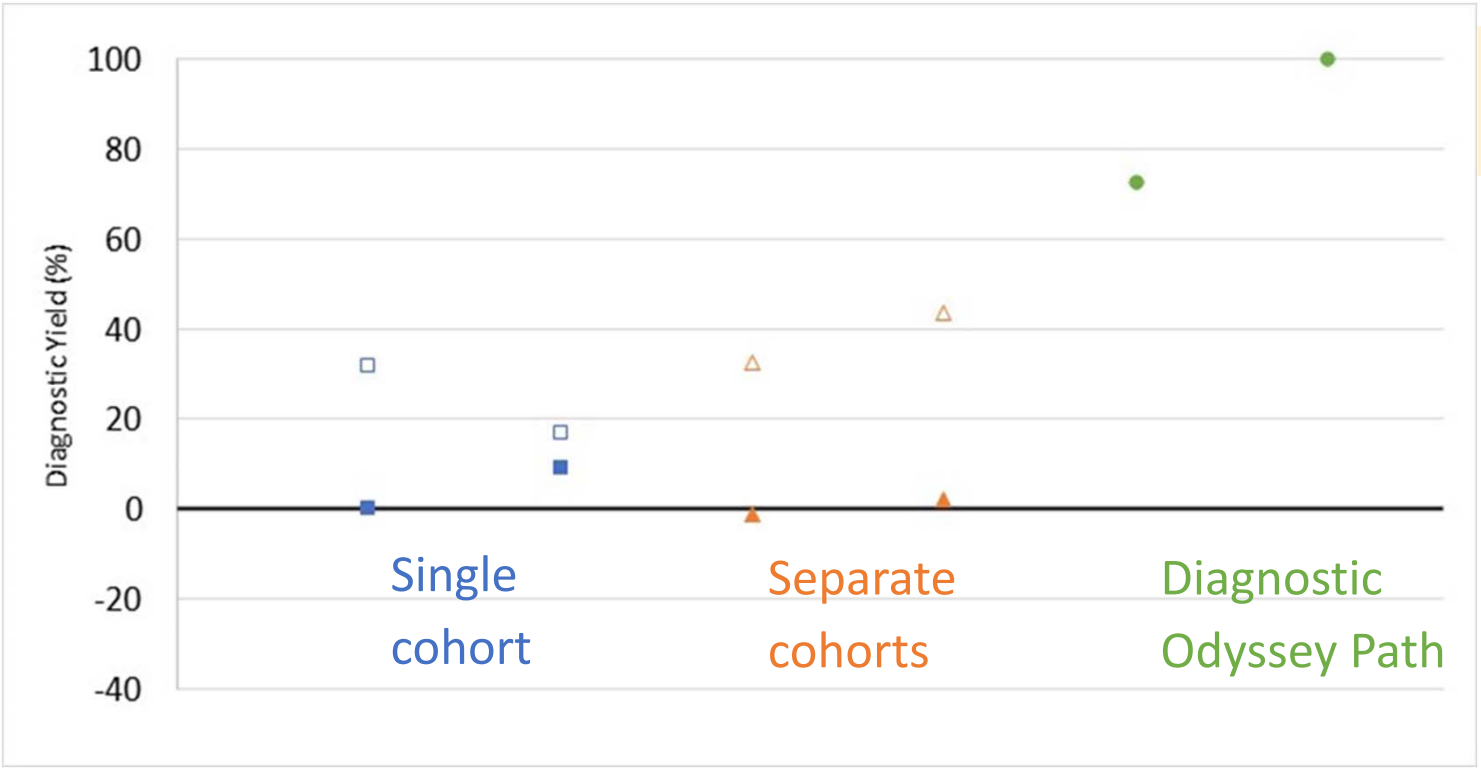
3 studies reporting 3 comparisons

Legend:

Open symbols (e.g., □, △) depict absolute yield of WGS

Solid symbols (e.g., ■, ▲, ●) depict incremental yield

Diagnostic Yield: WGS vs. Multigene Panels



6 studies reporting 6 comparisons

Legend:

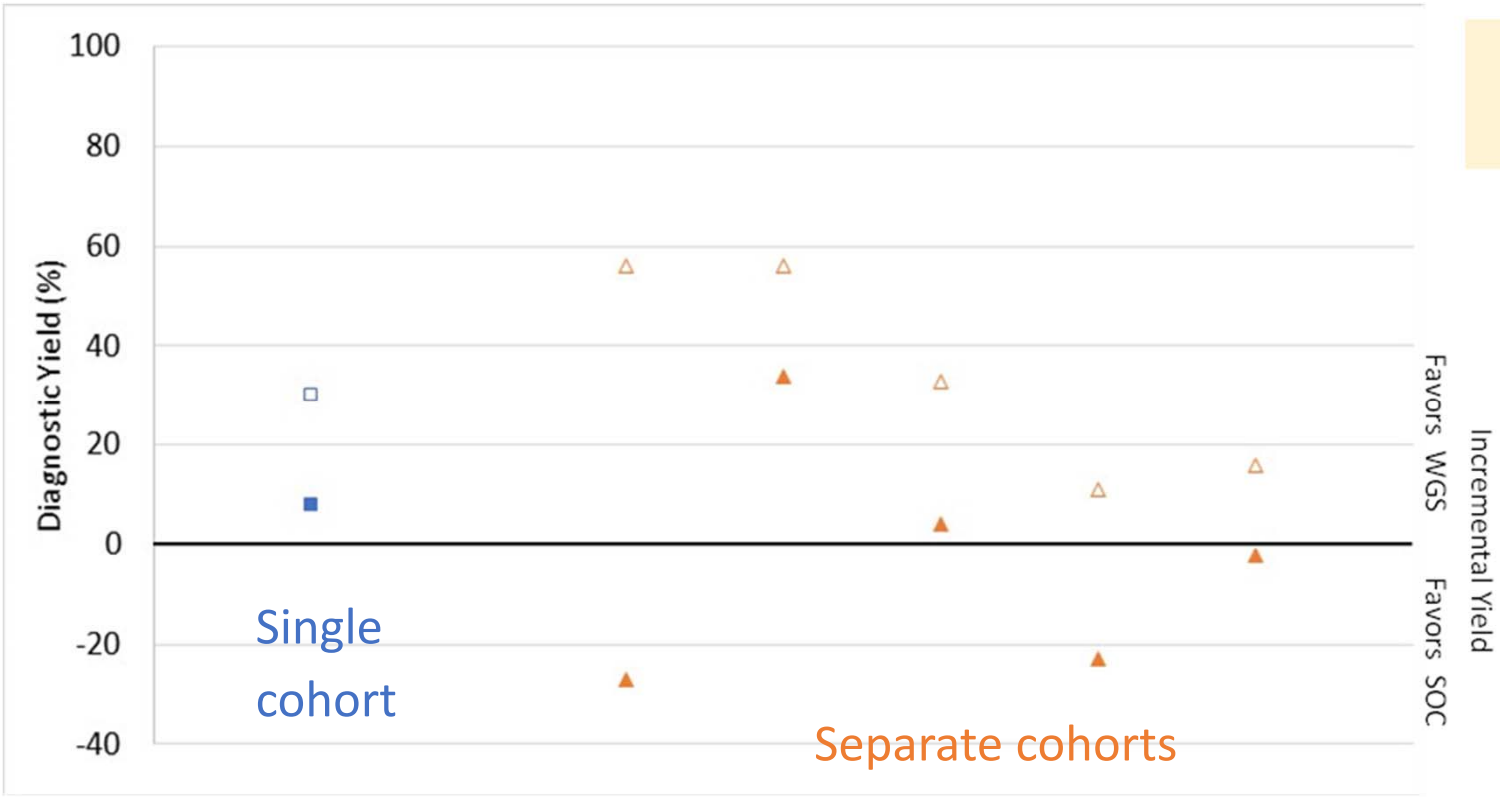
Open symbols (e.g., □, △) depict absolute yield of WGS

Solid symbols (e.g., ■, ▲, ●) depict incremental yield

Legend: open symbols depict absolute yield of WGS, solid symbols represent incremental yield

Legend: open symbols depict absolute yield of WGS, solid symbols represent incremental yield

Diagnostic Yield: WGS vs. Standard of Care Genetic Testing



5 studies reporting 6 comparisons

Legend:

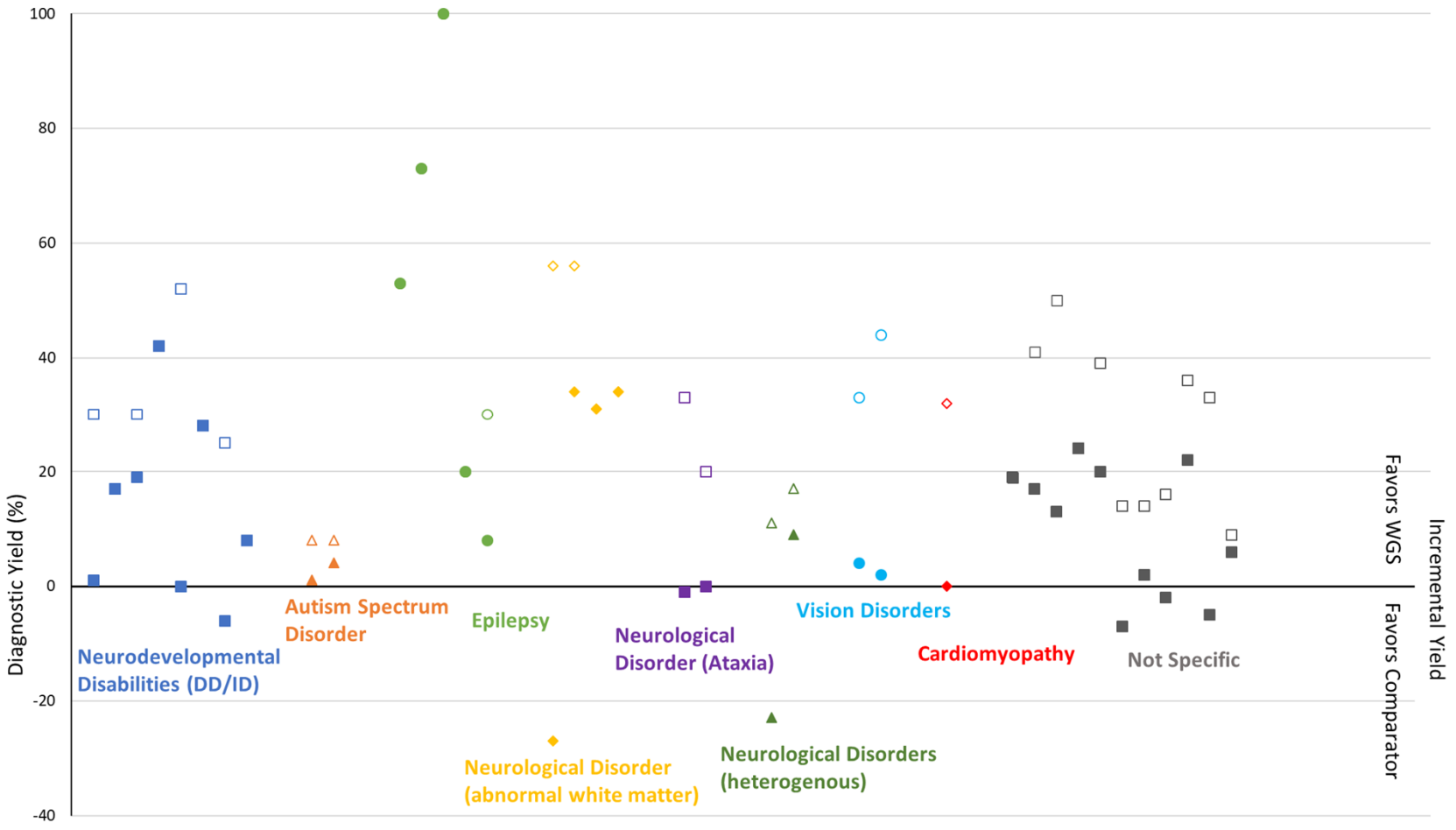
Open symbols (e.g., □, △) depict absolute yield of WGS

Solid symbols (e.g., ■, ▲, ●) depict incremental yield

Diagnostic Yield: WGS reanalysis vs. WGS

- 1 study conducted among 22 children and adults with suspected genetic disorders from a single clinic
  - *Initial WGS*: 3 of 22 diagnosed (14%)
  - *Cumulative diagnoses after reanalysis*: 8 of 22 diagnosed (36%)
  - ***Incremental yield*: 5 additional diagnoses (22%)**

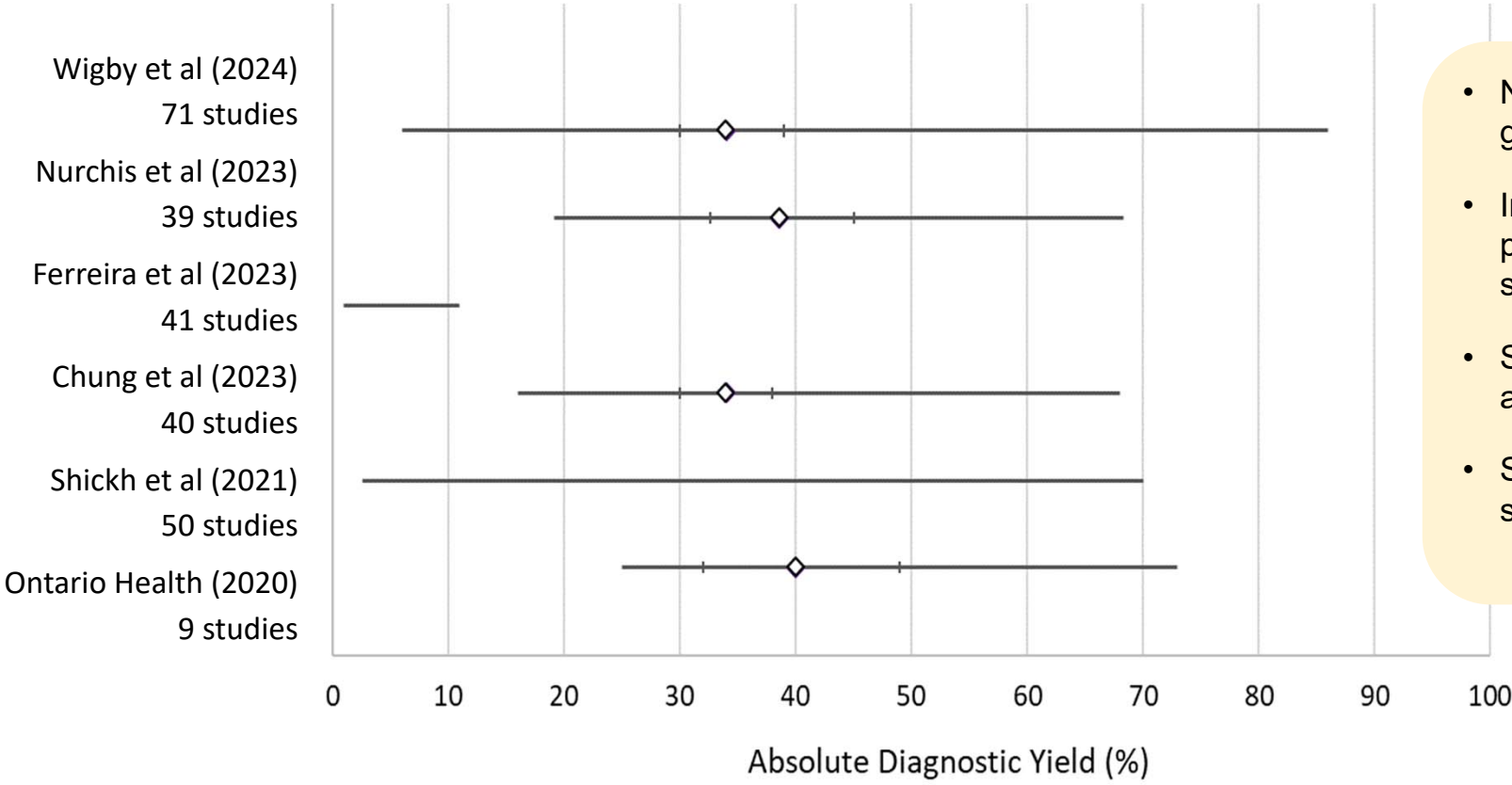
Diagnostic Yield by Phenotype



Legend:
Open symbols (e.g., □) depict absolute yield of WGS

Solid symbols (e.g., ■) depict incremental yield

Contextual Question: Diagnostic Yield from Recent SRs



- No comparator group required;
- Included critically ill patients in inpatient settings
- Some excluded adults
- Some focused on specific phenotypes

Notes: Lines on graph represent the range of diagnostic yield; pooled estimates (when available) are indicated by the diamond marker (◊) and tick marks (95% confidence intervals)

Other Clinical Utility Outcomes

- 14 studies reporting
- Limited interpretation due to variability in measures reported, ascertainment methods, risk of bias, and available comparator data.

Among the 8 *some* risk of bias studies:
12% to 65% of patients/families had a change in treatment, evaluation, management, or surveillance

In 1 RCT, time to diagnosis was significantly shorter with first-line WGS vs. standard of care plus delayed WGS
(100% vs. 22.8% diagnosed within 5 weeks, P=0.04)
(Vanderver et al)

Example of Clinical Utility Outcomes Reported

- WGS plus SOC testing vs SOC in children and adults with suspected genetic conditions
  - 25% of those with a diagnosis required additional workup because of uncertainty as to whether the molecular diagnosis from WGS explained clinical features

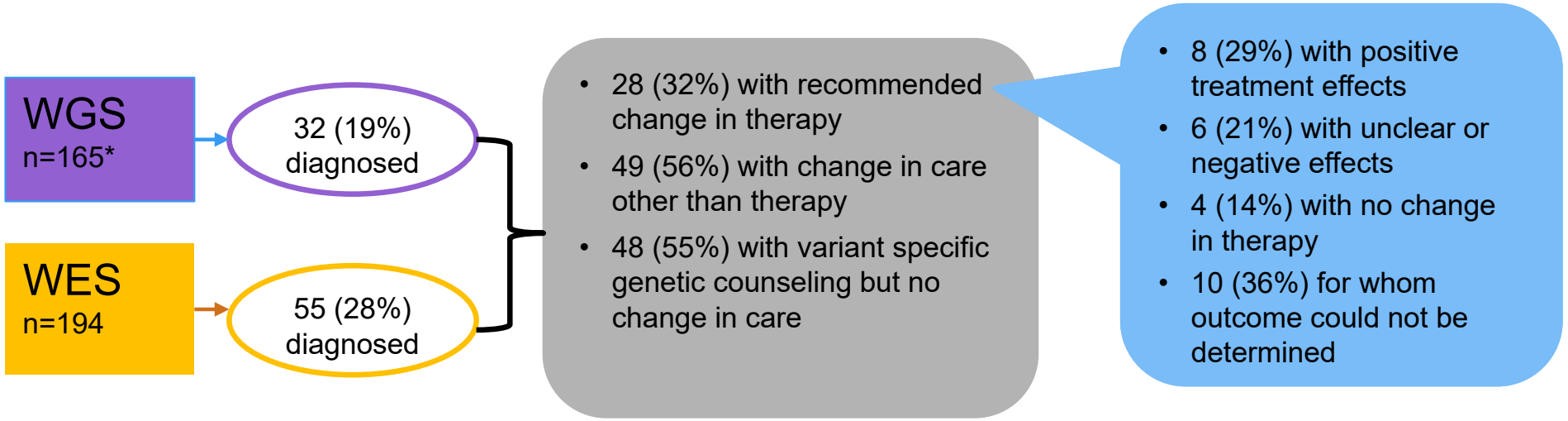
  Brockman et al.

- WGS vs. SOC testing in infants with new onset epilepsy
  - 48% of those tested had results (positive or negative) that influenced changes to medical care, further evaluation, or referral of at-risk relatives
    - 30% in those with a diagnostic result

  D'Gama et al.

Health Outcomes

- One cohort study (N=357) from the Undiagnosed Diseases Network among children and adults with undiagnosed conditions despite thorough clinical evaluation



*Includes participants with and without prior WES testing

Secondary Findings

- Medically actionable variants in 1 or more genes not related to primary indication for testing
- Reported by 9 studies
  - 5 studies reported findings from genes on the ACMG's recommended list
    - Range: 0% to 12.5% of participants
  - 5 studies reported a broader set of findings, including and beyond the ACMG list
    - Range in 3 studies: 4% to 9%
    - Mean number of findings 2.05/person in 1 study and 1.86 findings/person in 1 study

Findings: Safety

Safety: Frequency of VUS Findings

- 1 study conducted among 1.5 million tests from 19 clinical laboratories in North America
  - VUS are reported for all tests based on NGS platforms
  - Represent a potential harm as they can result in patient and provider uncertainty and downstream costs due to additional surveillance or testing.
  - Rate of VUS
    - Multigene Panels: 32.6%
    - WES/WGS: 22.5%;
      - Trio WES/WGS: 18.9%
      - Non-trio WES/WGS: 27.6%; P<0.0001
    - WES (22.6%) vs. WGS (22.2%); P NS

Safety: Rescinded Diagnoses

- 1 single cohort study conducted among 500 individuals younger than 19 years (mean age 8 years) with suspected genetic condition but who remained undiagnosed after standard genetic evaluations
  - Diagnostic Yield
    - Trio WES: 217 / 415 (52%)
    - Trio WGS: 44 /85 (52%)
  - Rescinded diagnoses:
    - 4/261 (1.5%)
      - 3: followup exams or tests were not consistent with the molecular diagnosis
      - 1: a different variant was reinterpreted as probably disease-causing and was a better fit with the patient's phenotype

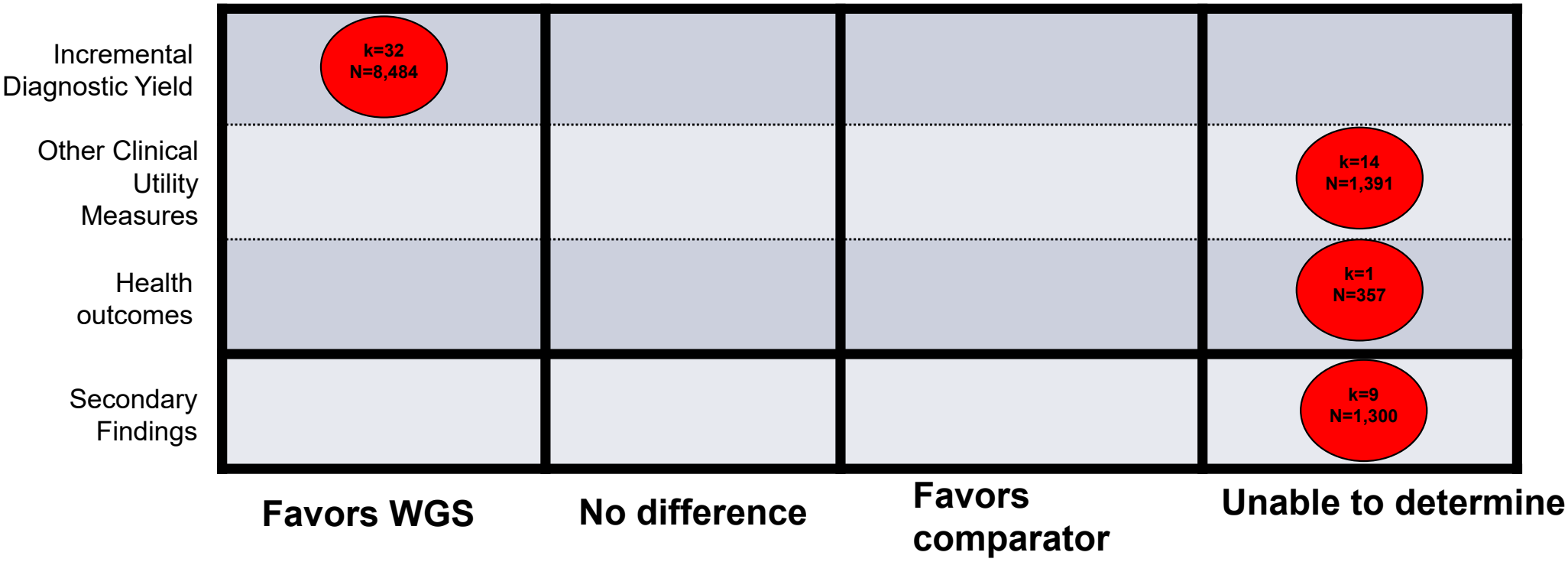
Findings: Cost-effectiveness

Cost-effectiveness From Decision Analyses (Modeling)

Author, Year RoB`	Population	Testing Approaches	Perspective and Costs	Brief Results
Incerti et al., (2021)[2] Some concerns	Noncritically ill children younger than age 18 years with suspected genetic disease	1. SOC genetic testing (single gene and multigene panels, "other tests") 2. Trio WGS 3. SOC → trio WGS	Payor; Medicare Clinical Laboratory Fee Schedule, microcosting studies, cost of WGS assumed to included labor, supplies, bioinformatics, equipment, and confirmatory testing	Cost per additional diagnosis (2020 USD) • WGS has more diagnoses and lower costs vs. SOC • SOC →WGS: $24,178 vs. SOC
Lavelle et al. (2022)[3] Some concerns	Noncritically ill children younger than age 18 years with undiagnosed suspected genetic conditions and moderate disability	1. SOC testing (single gene, multigene panels, CMA, karyotype) 2. First-line trio WES 3. SOC →WES 4. First-line trio WGS 5. SOC →WGS 6. WES →WGS 7. SOC →WES →WGS	Payor; CMS rates or from applying cost-to-charge ratios to list prices from major U.S. testing labs	Cost per additional diagnosis (2019 USD) • First-line trio WGS: $27,349 vs. SOC • First-line trio WES: $28,822 vs. SOC • First-line WGS with reanalysis at 1 year: $30,078 vs. SOC • Singleton WGS: $3,076 vs. singleton WES All other strategies cost more and had fewer diagnoses compared to alternative strategies.

Discussion

Evidence Map: Effectiveness



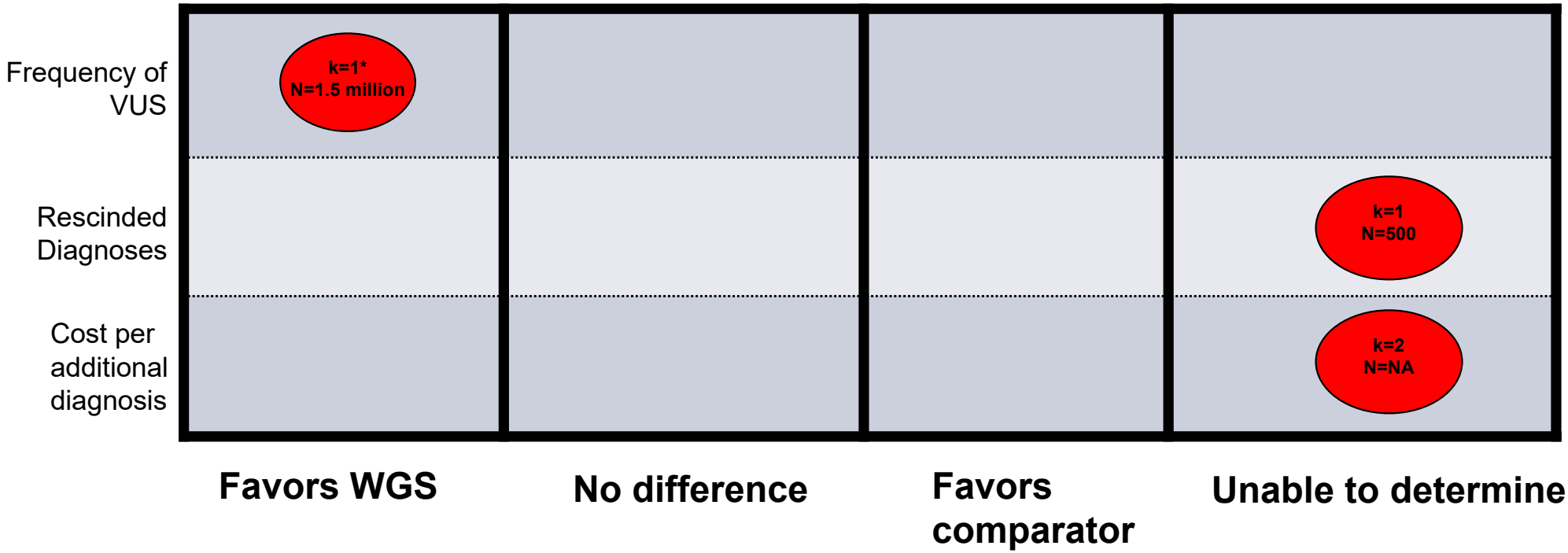
Legend

GRADE Certainty of Evidence

Very low | Low | Moderate | High

K=number of studies
N=total number of participants

Evidence Map: Safety and Cost



Legend

GRADE Certainty of Evidence

Very low | Low | Moderate | High

K=number of studies
N=total number of participants
NA=not applicable, modeled

* Versus comparator of singleton WGS

Limitations of the Evidence-1

- Limited information on clinical utility and health outcomes
- No information on psychosocial or personal utility, particularly those related to patient and family experience with diagnostic odyssey
- Versions of NGS-based tests (WGS and comparators, WES, MGP) are likely already obsolete
- Extreme clinical and methodologic heterogeneity in this evidence base; **this will be applicable for any genetic test that is applied to the entire exome or genome**

Limitations of the Evidence-2

National Academies of Sciences, Engineering, and Medicine acknowledged in 2017 the challenges of making evidence-based decisions about the use of genetic tests because the clinical value of genetic testing is generally based on lower-quality evidence, and because of the accelerated development of the technology

Clinical Practice Guidelines - 1

Medical Genome Initiative [Academic-Industry Consortium] (2024): Use of first-line genome sequencing to diagnose rare genetic disorders

- Recommended as first line test for pediatric patients who have an unexplained illness with a suspected genetic etiology,
- Recommended to be included alongside sequential genetic tests for patients with features indicating a genetic cause
- Recommended if panel testing does not include all variants known to be causative of a disorder,
- If clinical course or response to therapy for a nongenetic condition is better explained by a rare genetic diagnosis.

National Society of Genetic Counselors (2023): Genetic testing and counseling for the unexplained epilepsies

- First tier options for unexplained epilepsy at any age: WGS, WES, or multigene panel plus CMA.

Clinical Practice Guidelines - 2

NICE(2022): Epilepsies in Children, Young People, and Adult

- Consider WGS for epilepsy of unknown cause younger than 2 years or have clinical features suggestive of a specific genetic epilepsy syndrome or have additional clinical features that meet the eligibility criteria

- Consider WGS for epilepsy of unknown cause between ages 2 and 3 years when epilepsy started if clinically agreed by a specialist multidisciplinary team

EuroGentest: Recommendations for WGS in Diagnostics for Rare Diseases (2022)

- Recommended when it is a relevant improvement on quality, efficiency, and/or diagnostic yield

Clinical Practice Guidelines - 3

ACMG (2021): Exome and Genome Sequencing for Pediatric Patients with Congenital Anomalies or Intellectual Disability Evidence-based Guideline

- Recommends exome and genome sequencing as first-tier or second-tier tests for patients with 1 or more congenital anomalies prior to age 1 or with developmental delay and intellectual disability with onset prior to age 18

Canadian College of Medical Geneticists (2015): The Clinical Application of Genome-wide Sequencing for Monogenic Diseases in Canada

- Genome-wide sequencing appropriate for suspected monogenic disease associated with genetic heterogeneity or who has had previous genetic tests that have failed to provide a diagnosis

Payor Coverage Policies - 1

Medicare	Aetna	Cigna	Humana	Kaiser Permanente	Premera Blue Cross	Regence Blue Shield	TRICARE	United-Healthcare
—	X	✓[a]	X	X	X	X	—[b]	✓[a]

Coverage conditions required by Cigna and United Healthcare are detailed in the full report and summarized in slides at the back of the slide deck.

Notes: ✓ = covered; X = not covered; — no policy identified

[a] covered with conditions

[b] We did not identify a TRICARE coverage policy specific to WGS. The TRICARE web page indicates that TRICARE may cover genetic testing when medically necessary.

Future Research

Studies registered on ClinicalTrials.gov

Not Yet Recruiting	Active Not Recruiting	Completed Not Yet Published	Unknown	Total
11	2	6	4	23

Challenges:

- Genomic heterogeneity within phenotypes
  - Patients should serve as their own controls with respect to evaluating diagnostic yield from alternative tests
- Technology and associated knowledge bases are continually evolving
  - Standardize approach and measures for evaluating diagnostic yield, clinical utility, harms, and impact on diagnostic odyssey
- Need long-term funding and support to measure meaningful health and cost outcomes, but is this even feasible given the volume and diversity of phenotypes and known (and unknown) genetic conditions?

Limitations of the HTA

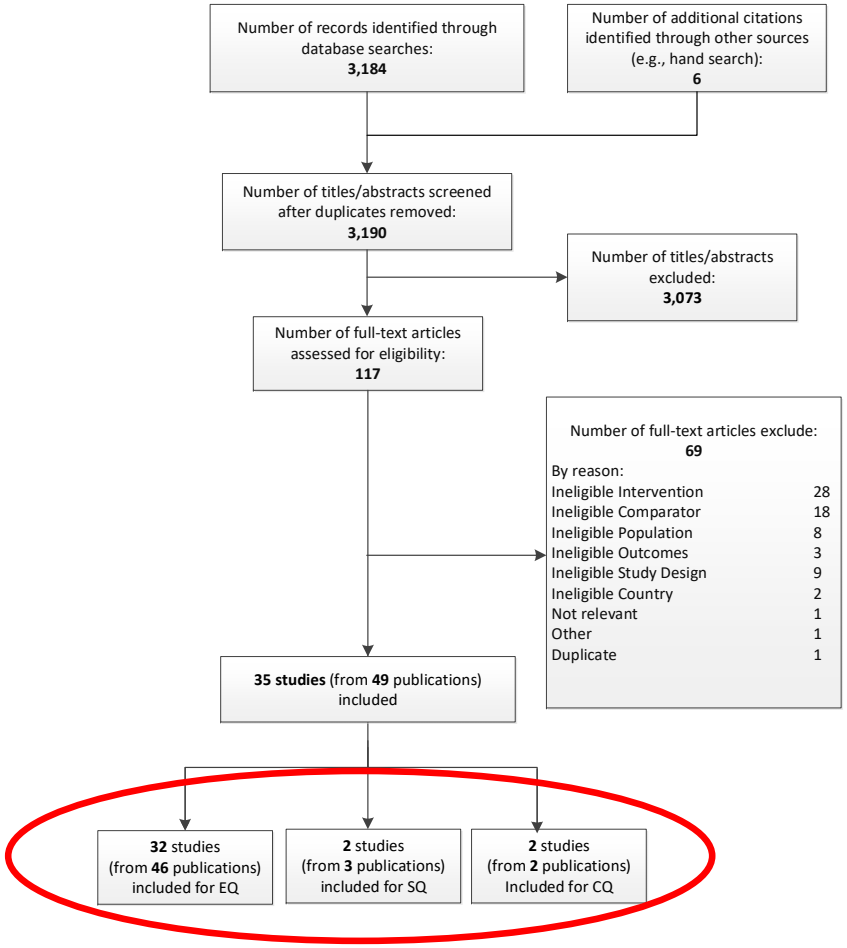
- English language only
- Excluded studies from non-very highly developed countries
- Required a comparator test (except for harms)
- Excluded WGS used in inpatient settings

Conclusions

- WGS may increase the yield of molecular diagnoses in people with suspected genetic conditions as compared with alternative testing strategies (*very low certainty*).
- The evidence for changes in management and health outcomes resulting from WGS is limited (*very low certainty*).
- The incidence of actionable secondary findings from WGS ranges from 0% to 12.5% (*very low certainty*).
- Few studies report outcomes related to safety (*very low certainty*).
- Limited data on cost-effectiveness exists (*very low certainty*).

Questions?

Search Yield



Payor Coverage Policies - 2

Cigna

- WES or WGS is considered medically necessary when a recommendation for testing is confirmed by a provider with specific expertise in genetics, the condition, and who is not employed by a commercial genetic testing laboratory
- ALL of the following criteria are met:
  - Evaluated by a geneticist or specialist physician with specific expertise in the conditions
  - Testing results will directly impact clinical decision-making and/or clinical outcome
  - No other causative circumstances (e.g., environmental exposures, injury, prematurity, infection) can explain symptoms
  - Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available
  - The differential diagnosis list and/or phenotype warrant testing of multiple genes and WES or WGS is more practical than the separate single-gene tests or panels or may preclude the need for multiple and/or invasive procedures
- ANY of the following clinical scenarios when ALL of the general criteria listed above are also met:
  - Phenotype suspicious for a genetic diagnosis
  - Epilepsy
  - Hearing loss
  - Global developmental delay
  - Intellectual disability
  - Fetal testing (when additional criteria met)

Payor Coverage Policies - 3

United Health

WGS is medically necessary for the diagnosing or evaluating a genetic disorder when the results are expected to directly influence medical management and clinical outcomes AND ALL the following criteria are met:

- Neither CMA nor WES have been performed and no specific or targeted gene test is available
- WGS is ordered by a medical geneticist, neonatologist, neurologist, or developmental pediatrician; AND 1 of the following:
  - Clinical history strongly suggests a genetic cause and one or more of the following features are present:
    - Multiple congenital anomalies (must affect different organ systems)
    - Moderate, severe, or profound Intellectual Disability diagnosed by 18 years of age
    - Global Developmental Delay
    - Epileptic encephalopathy with onset before three years of age; or
  - Clinical history strongly suggests a genetic cause AND 2 OR MORE of the following features are present:
    - Congenital anomaly; Significant hearing or visual impairment diagnosed by 18 years of age; Laboratory abnormalities suggestive of an Inborn errors of metabolism; Autism spectrum disorder; Neuropsychiatric condition; Hypotonia or hypertonia in infancy; Dystonia, ataxia, hemiplegia, neuromuscular disorder, movement disorder, or other neurologic abnormality; Unexplained developmental regression, unrelated to autism or epilepsy; Growth abnormality (e.g., failure to thrive, short stature, microcephaly, macrocephaly, or overgrowth); Persistent and severe immunologic or hematologic disorder; Dysmorphic features ; Consanguinity; Other first- or second-degree family member(s) with similar clinical features
  - Comparator (e.g., parents or siblings) WGS for evaluating a genetic disorder when the above criteria have been met and WGS is performed concurrently or has been previously performed on the member
  - WGS is not medically necessary for any other clinical situation due to the availability of clinically equivalent diagnostic tests.

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.

Based on Legislative mandate: RCW 70.14.100(2).

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

- 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.
- 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
Variants of unknown significance		
Incorrect diagnosis		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Diagnostic yield		
Other clinical utility outcomes		
Health outcomes		
Medically actionable variants		

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost-effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Sex		
Comorbidity		
Adolescents		
Pregnant individuals		

For safety:

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

No relevant studies	Low Risk Safe	Moderate Risk	High Risk Unsafe
	Confidence: Low Medium High	Confidence: Low Medium High	Confidence: Low Medium High

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care compared to the evidence-based alternative(s)?

No relevant studies	Less Less effective	Equivocal	More More effective at least in some
	Confidence: Low Medium High	Confidence: Low Medium High	Confidence: Low Medium High

For cost outcomes/ cost-effectiveness:

Is there an accepted scale for cost effectiveness for treatments for this disease? If so, how does this treatment compare with evidence-based alternatives?

No relevant studies	**Less** Less cost effective	**Equivocal**	**More** More cost effective at least in some
	Confidence: Low Medium High	Confidence: Low Medium High	Confidence: Low Medium High

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 with conditions**

Discussion item

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

The report "identified no Medicare national coverage determination on the use of SBRT or any local coverage determinations that apply to the state of Washington."

Medicare Coverage

[see page ES-14 of final report]

There is no current National Coverage Determination of Whole Genome Sequencing specifically.

Clinical Practice Guidelines

[see page 35 – 37 of final report]

Title	Year	AGREE-II Rating	Summary of Recommendation(s)
Medical Genome Initiative (MGI): Evidence review and consideration for use of first-line genome sequencing to diagnose rare genetic disorders[79] (MGI is an academic-industry consortium)	2024	6	• For pediatric patients who have an unexplained illness with a suspected genetic etiology, WGS is recommended as a first-line genetic test. • For patients with features indicating a likely genetic cause, WGS is recommended to be included alongside sequential genetic tests. • If panel testing does not include all variants known to be causative of a disorder, WGS is recommended. • For patients undergoing treatment for a nongenetic condition, WGS is recommended if they have a clinical course or response to therapy that is better explained by a rare genetic diagnosis. • The group supports targeted tested as an alternative to WGS when the clinician determines this testing will likely identify the disorders and the patient's features suggest a single recognizable genetic disorder.
National Society of Genetic Counselors (NSGC): Genetic testing and counseling for the unexplained epilepsies: an evidence-based practice guideline[82]	2023	6	The recommendations are relevant to genetic testing and counseling for individuals with unexplained epilepsies. • NSGC strongly recommends that individuals with unexplained epilepsy be offered genetic testing without limitation of age. • First-tier testing includes WGS, WES and/or a multigene panel followed by CMA. • NSGC additionally recommends in the setting of appropriate pre-test and post-test genetic counseling for genetic tests to be selected, ordered, and interpreted by a qualified health care provider.
National Institute of Health and Care Excellence (NICE): Epilepsies in children, young people, and adults[83]	2022	5	• WGS should be considered for people with epilepsy of unknown cause who are younger than 2 years when epilepsy started or have clinical features suggestive of a specific genetic epilepsy syndrome or have additional clinical features that meet the eligibility criteria set by the NHS National Genomic Test Directory. • If clinically agreed by a specialist multidisciplinary team, NICE recommends the consideration of WGS for people with epilepsy of unknown cause who were between ages 2 and 3 years when epilepsy started.
EuroGentest: Recommendations for WGS in diagnostics for rare diseases[84] (EuroGentest is an initiative initially funded by European governments but also involves industry.)	2022	5	• WGS is recommended when it is a relevant improvement on quality, efficiency, and/or diagnostic yield. • Diagnostic WGS should only be performed in accredited laboratories for rare disease and cancer. • Acceptable validation tests for NGS are needed prior to the use of NGS in a clinical practice. • In a research setting, the confirmation, interpretation, and communication of results to the patient should be done after retesting by a diagnostic laboratory.

Title	Year	AGREE-II Rating	Summary of Recommendation(s)
American College of Medical Genetics and Genomics (ACMG): Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability evidence-based guideline[68]	2021	7	Recommends the use of exome sequencing and genome sequencing as first-tier or second-tier tests for patients who meet the following criteria: 1 or more congenital anomalies prior to age 1 year or for patients with developmental delay and intellectual disability with onset prior to age 18 years.
Canadian College of Medical Geneticists: The clinical application of genome-wide sequencing for monogenic diseases in Canada[85]	2015	6	• For the diagnostic assessment, the use of clinical genome-wide sequencing (including WES and WGS) is appropriate for a patient with a suspected monogenic disease associated with genetic heterogeneity or who has had previous genetic tests that have failed to provide a diagnosis. Prior to undertaking clinical genome-wide sequencing, genetic counseling should be provided and informed consent obtained from the patient. Clinical WGS may be used to detect CNV and structural variation in addition to sequence variants, though it is not currently a first-tier test for such analyses • The group does not recommend the use of intentional clinical analysis of disease-associated genes (i.e., secondary findings) other than those linked to the primary indication until the benefits of reporting incidental findings are established.

Abbreviations: AGREE = Appraisal of Guidelines for Research & Evaluation II instrument; ACMG = American College of Medical Genetics and Genomics; NGS = next-generation sequencing; NHS = National Health Survey; NICE = National Institute of Health and Care Excellence; NSGC = National Society of Genetic Counselors; WES = whole exome sequencing; WGS = whole genome sequencing.

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 unclear (i.e., tie), outcome chair will lead discussion to determine next steps.

Washington State Health Care Authority

Final Key Questions and Background

Whole Genome Sequencing

November 15, 2023

Background

There are approximately 7,000 rare disorders that affect 6% to 8% of the US population[1], a substantial portion of which have genetic origin. In addition to the clinical burden associated with these illnesses, patients and families often experience delays in diagnosis and encounter diagnostic odysseys that can introduce delays in diagnosis, substantial psychosocial costs and potentially preventable use of health care resources.[2-5]

Whole genome sequencing (WGS; also called genome sequencing or full genome sequencing) is a laboratory procedure for determining an organism's entire DNA sequence in one procedure. In contrast to whole exome sequencing, which identifies only the exome – the 1%-2% of the genome that code for proteins – genome sequencing focuses on nearly all of the genome.

In the context of genetic disease diagnosis, WGS could potentially avoid or shorten diagnostic odysseys, speed the time to appropriate intervention, guide disease management, and alleviate and patient and family burden. Use of whole genome sequencing could aid in diagnosing a wide array of genetic diseases. However, questions remain about the clinical utility of genome sequencing compared to WES or traditional approaches. Evidence about the clinical utility of WGS in providing accurate diagnosis that guides clinical management and improve patient outcomes could guide assessments of appropriate use of WGS in clinical settings.[5] However, any benefits must be weighed against its potential harms and costs.

The purpose of this health technology assessment (HTA) on the efficacy, safety, and cost-effectiveness of the clinical use of whole genome sequencing (WGS) for diagnosis of suspected genetic disorders.

Policy context

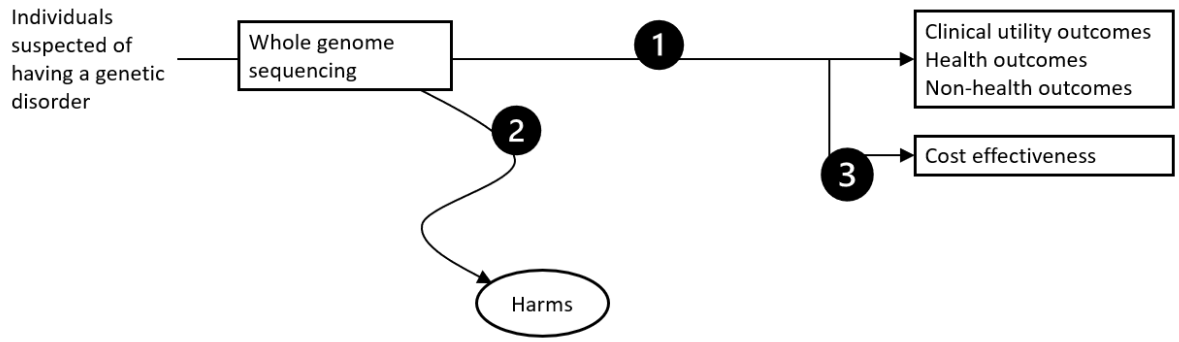
The State of Washington Health Care Authority selected WGS for a health technology assessment (HTA) because of high concerns for safety, medium concerns for efficacy, and high concerns for cost.

Scope of this HTA

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

Washington State Health Care Authority

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



Research Questions

Efficacy Question 1. What is the efficacy of whole genome sequencing for use in diagnosing possible genetic disorders?

Safety Question 2. What are the harms associated with whole genome sequencing for use in diagnosing possible genetic disorders?

Cost Question 3. What is the cost-effectiveness of whole genome sequencing for use in diagnosing possible genetic disorders?

Study Selection Criteria

Table 1 provides the study selection criteria we will use to include studies in the HTA and are organized by population, intervention, comparator, outcomes, timing, setting, and study design (PICOTS) criteria.

Table 1. Proposed Population, Intervention, Comparator, Outcome, Timing, and Setting for Health Technology Assessment

Domain	Included	Excluded
Population	Children or adults, with or without a clinical diagnosis, suspected of genetic disorder	• Embryos and fetuses • Persons with nonsyndromic cancer or infections, where WGS is being used to characterize the tumor or microbe • Deceased persons • Healthy persons
Intervention	Diagnostic standard or rapid genome sequencing, alone or as part of a testing pathway including clinical, laboratory and imaging evaluation	• Single gene sequencing • Multi-gene panels • Mitochondrial sequencing • Genome-wide association studies • Exome sequencing • WGS for purposes other than diagnosis (e.g. pharmacogenetic; screening or risk

Domain	Included	Excluded
		assessment; characterization of tumors or infectious agents; research) • Long-read WGS
Comparator	Usual care (e.g. clinical, laboratory, or imaging evaluation; exome sequencing; single gene testing; and/or multigene panel testing; chromosomal microarray) Alternative test results in same participant, including reanalysis (diagnostic yield outcomes only) Single arm studies (harms outcomes only)	Literature-based outcome estimates (e.g. diagnostic yield from previously published papers)
Outcomes	Clinical utility: diagnostic yield for initial and/or subsequent reanalysis, including uncertain or secondary actionable findings; time to diagnosis; clinician referral and treatment selection or other changes in care; at-risk relative identification. Health: (mortality, survival, morbidity) Non-health: (e.g., personal utility; psychosocial outcomes; patient experience related to diagnostic odyssey) measured with a validated scale where possible. Cost: Cost-effectiveness Harms: any clinical utility, health, or non-health outcome or other findings that suggest harm (e.g., psychosocial distress; false negative or false positive results)	• Health outcomes related to secondary findings • Hypothetical patient, family, or provider preferences • Non-U.S. costs
Setting	Any outpatient setting in countries categorized as 'very high'[a] on the UN Human Development Index 2021	Inpatient hospital settings[a] Non-clinical settings Countries categorized as other than 'very high'[b] on the UN Human Development Index 2021
Study Design	Study designs • Randomized controlled trial; controlled clinical trial; comparative cohort studies (non-comparative studies for harm outcomes only) • Cost utility analysis, cost-effectiveness analysis performed from societal or payor perspective	• Editorials, commentaries, narrative reviews, or letters; conference abstracts; case reports or case series; case-control studies; other observational study designs with comparator group specified • Relevant systematic reviews and meta-analyses will be excluded but may be hand searched to identify potentially eligible studies. • Qualitative studies
Language and Time Period	• English • 2013 or later	• Any language other than English

Abbreviations: WGS=whole genome sequencing; UN=United Nations; US = United States
Notes: [a] Studies that take place in inpatient hospital settings, such as intensive care units, are excluded. Though rapid genome sequencing may be used in these settings, this use is not within the scope of this HTA. This is because such testing would be part of the care and services attributed to billing codes covering inpatient care.
[b] Countries identified as very high with the 2021 UN Human Development Index: Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Belarus, Belgium, Brunei, Canada, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Montenegro, Netherlands, New Zealand, Norway, Oman, Panama, Poland, Portugal, Qatar, Romania, Russian Federation, San Marino, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Trinidad And Tobago, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay.

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