An Approach to Genetic Diagnosis for Patients with Developmental Delay

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Genetics and Metabolism Section, Department of Pediatrics
University of Colorado School of Medicine and
Children's Hospital Colorado

Goals for this talk

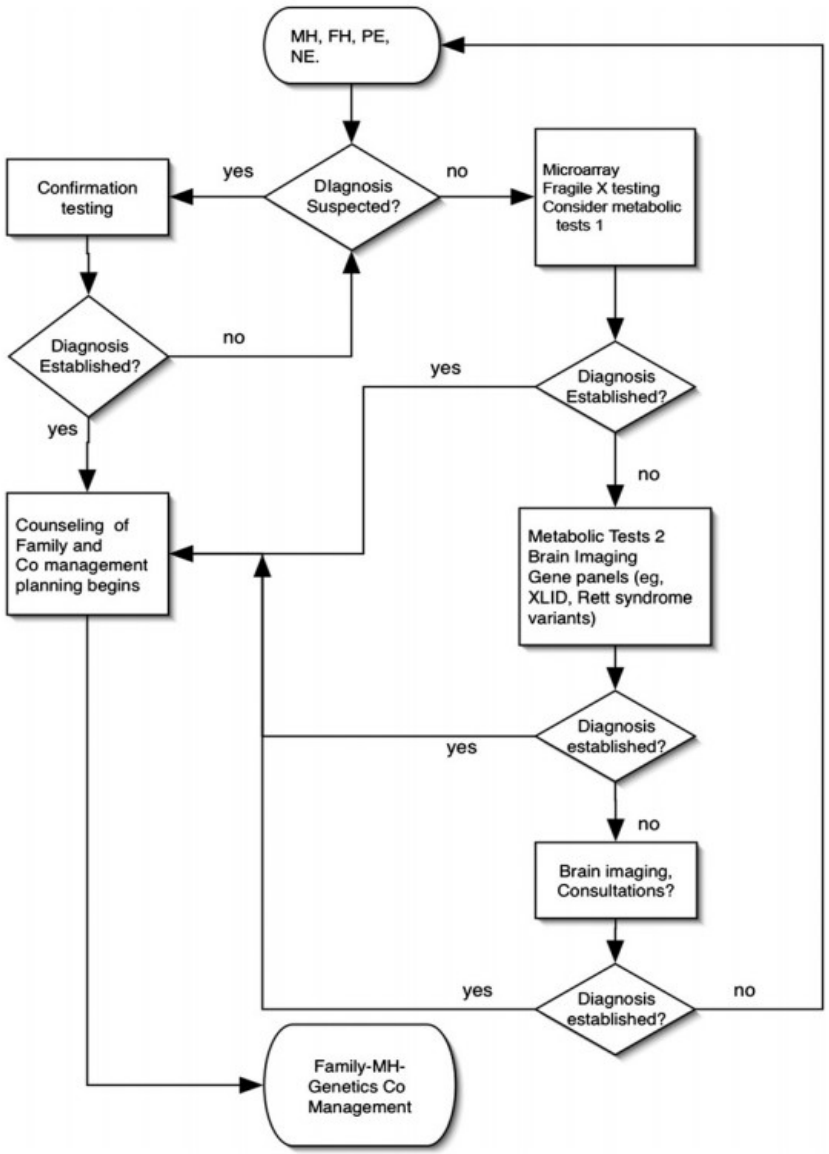
- To review the 2018 “Approach to Genetic Diagnosis in Developmental Delay” position statement released by Mountain States Regional Genetics Network
- To discuss new developments in genetic testing in the last three years
- To explain changes that you have likely already seen and will see in the future in the approach to genetic diagnosis for patients with developmental delay

A step back:
What are we trying to accomplish?

1. Identify patients with treatable conditions and intervene in a timely fashion
2. Resolve diagnostic uncertainty for families and prevent need for additional invasive or expensive diagnostic studies
3. Provide prognostic information to help families plan for the future
4. Help families to understand recurrence risk

Vocabulary

- Microarray – in wide clinical use for about 15 years, detects CNVs only
- CNV – copy number variant (a deletion or duplication of part of a chromosome)
- Exome sequencing – in clinical use for about 5 years; generates sequence data for most genes as well as CNV data
- Genome sequencing – just starting wider clinical use; generates sequence data for almost all genetic material (not just genes); better CNV detection than microarray or exome
- Oligonucleotide repeats – a mechanism of disease that can go undetected by sequencing methods
- Metabolic disease – any condition in which impairment of a biochemical pathway is intrinsic to the mechanism of the disease; most metabolic diseases are not detectable by “metabolic testing”



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FROM THE AMERICAN ACADEMY OF PEDIATRICS

Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays

John B. Moeschler, MD, MS, FAAP, FACMG, Michael Shevell, MDCM, FRCP, and COMMITTEE ON GENETICS

abstract

FREE

Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

Open

Do the data really support ordering fragile X testing as a first-tier test without clinical features?

Veronique Weinstein, MS[1], Pranoot Tanpaiboon, MD[1], Kimberly A. Chapman MD, PhD[1], Nicholas Ah Mew, MD[1] and Sean Hofherr, PhD[2]

Table 3 Comparison of CMA and Fragile X test results between patients with isolated ID/LD and patients with ASD

Population	CMA sensitivity	Fragile X test sensitivity
ID/LD (no ASD)	14.5–29% (28/192–56/192)	2.5% (2/80)
ASD	5–9.5% (5/96–9/96)	0% (0/75)
Total	11.5–22.5% (33/288–65/288)	1.5% (2/155)

ASD, autism spectrum disorder; CMA, chromosome microarray analysis; ID/LD, intellectual disabilities/learning delay.

Table 1 Summary of chromosome microarray analysis results in males with intellectual disability (no autism)

Description	*n* (%)
Total male patients with ID/LD	192
Pathologic or likely pathologic CNV	28 (15)
Likely pathologic CNV but unknown in this phenotype	2 (1)
AOH, no sequencing completed on the autosomal recessive genes in this region	8 (4)
VUS; no parental testing	16 (8)
VUS and AOH; no parental testing, and sequencing not informative	2 (1)

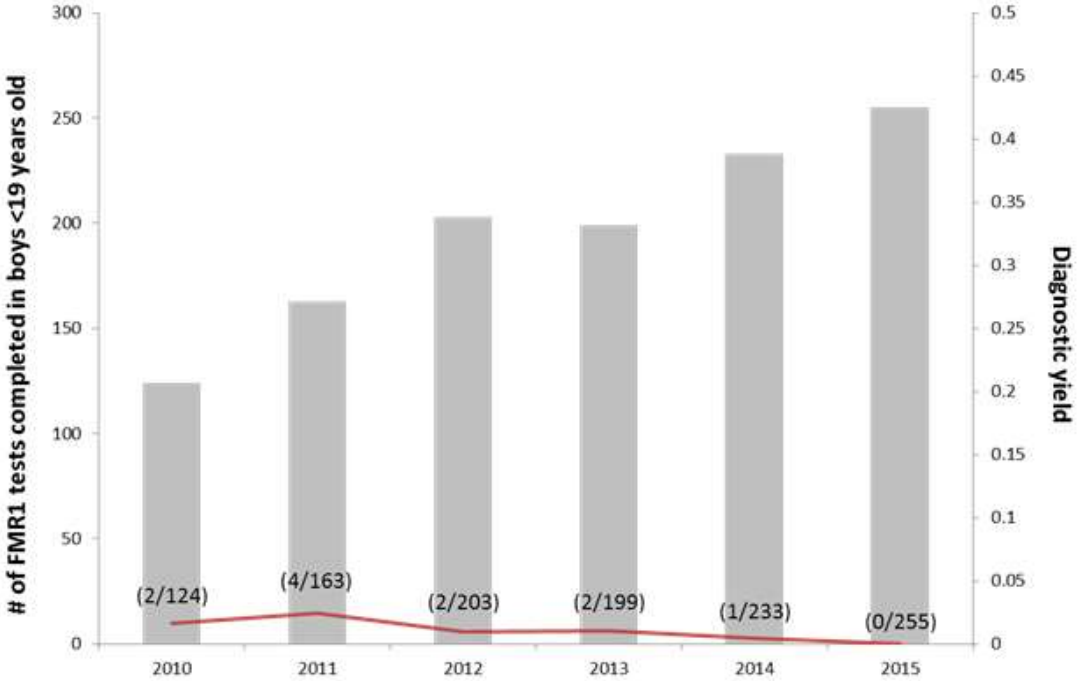
AOH, absence of heterozygosity; CNV, copy-number variant; ID/LD, intellectual disabilities/learning delay; VUS, variant of uncertain significance.

Table 2 Summary of chromosome microarray analysis results in males with ASD

Description	*n* (%)
Total male ASD patients	96
Pathogenic or likely pathogenic CNVs	5 (5)
AOH, but autosomal recessive genes in this region not sequenced	2 (2)
CNVs that were VUS; no parental testing done	2 (2)

ASD, autism spectrum disorder, AOH, absence of heterozygosity; CNV, copy-number variant; VUS, variant of uncertain significance.

Figure 1.



Genetics in Medicine

Letter | Published: 14 September 2017

Letters to the Editor

Fragile X testing as a second-tier test

Taila Hartley, Ryan Potter, Lauren Badalato, Amanda C Smith, Olga Jarinova & Kym M Boycott

Genetics in Medicine **19**, 1380(2017) | Cite this article

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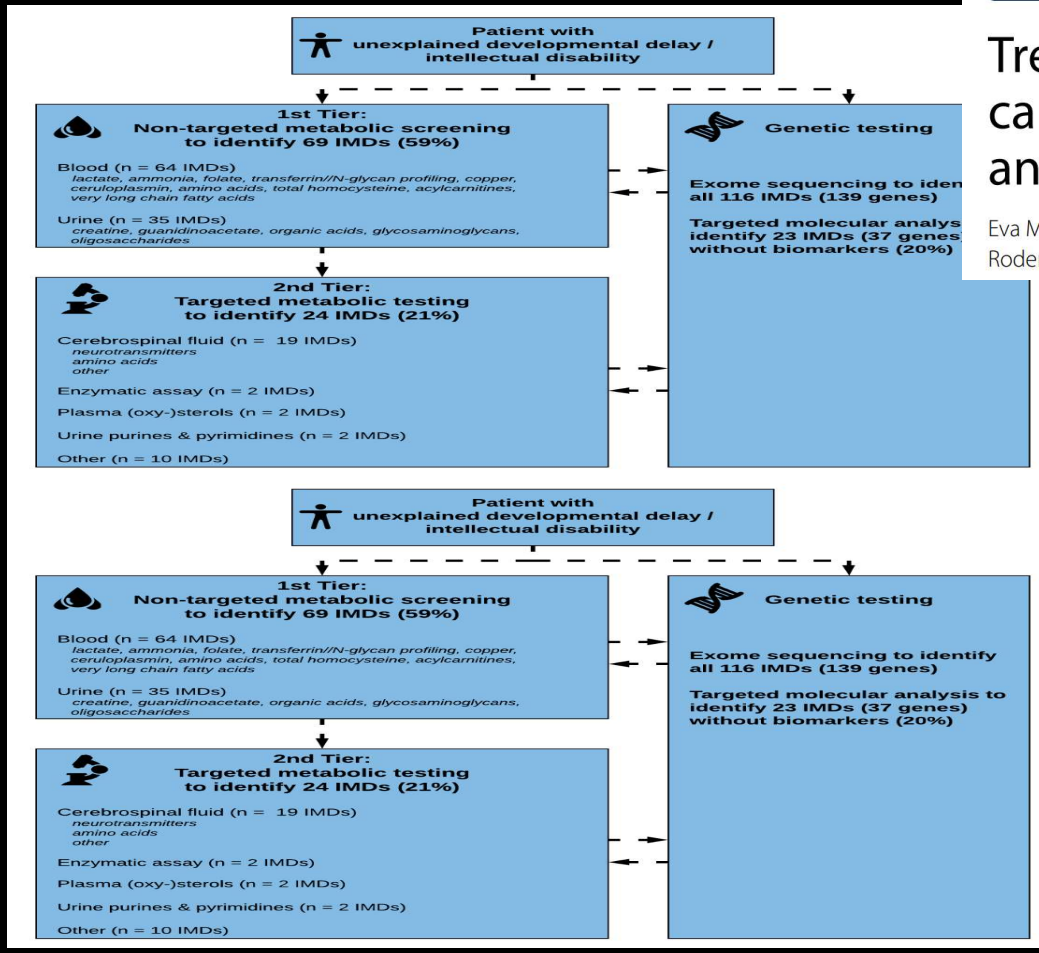
SHARE April 09, 2019; 92 (15 Supplement) MAY 9, 2019

Genetic test results for 523 patients with ASD/ID: The diagnostic yield of multigene analysis (Autism/ID Xpanded test) is higher than conventional first-tier tests, such as FMR1 repeat analysis and chromosomal microarray (P5.6-040)

Anita Shanmugham, Tracy Brandt, Julie Scuffins, Dianalee McKnight

First published April 16, 2019,

Results: Positive *FMR1* full expansions were identified in 0.6% (3/523) of cases and all positive results were identified in males. CMA testing identified causative copy number variants (CNVs) in 5.5% (29/523) of cases. Seventy-two percent of individuals (n=375) proceeded to second-tier testing with the Autism/ID Xpanded panel. The PDR of the panel was 9.6% (36/375). Five positive CMA cases continued with the Xpanded panel; all five CNVs were identified by next-generation sequencing (NGS) along with a second causative variant identified by sequencing in one individual.



Hoytema van Konijnenburg *et al.*
Orphanet J Rare Dis (2021) 16:170
https://doi.org/10.1186/s13023-021-01727-2

Orphanet Journal of Rare Diseases

REVIEW Open Access

Treatable inherited metabolic disorders causing intellectual disability: 2021 review and digital app

Eva M. M. Hoytema van Konijnenburg[1†], Saskia B. Wortmann[2,3,4†], Marina J. Koelewijn[2], Laura A. Tseng[1,4], Roderick Houben[6], Sylvia Stöckler-Ipsiroglu[5], Carlos R. Ferreira[7] and Clara D. M. van Karnebeek[1,2,4,8*]

The exact order of diagnostic tests still depends on local resources and expertise and needs critical appraisal and personalization of the subsequent treatment itself. The diagnostic algorithm as shown in Fig. 1 is our recommendation, based on the yield of metabolic tests combined in the tiers, as well as availability at most if not all metabolic laboratories. The algorithm can be adapted according to the clinician's insights and laboratory specialist's expertise, as well as the patient's clinical phenotype (red flags) along with local laboratory resources.

LETTERS
https://doi.org/10.1038/s41591-020-0966-5
nature medicine
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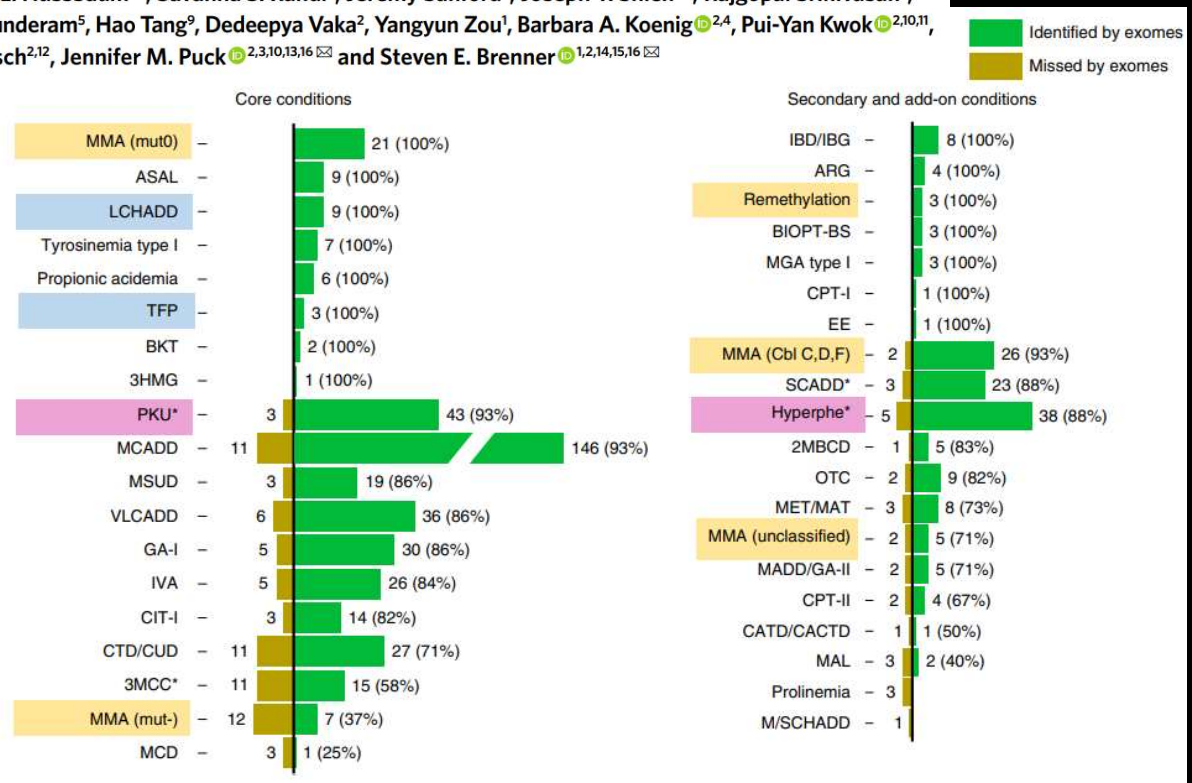
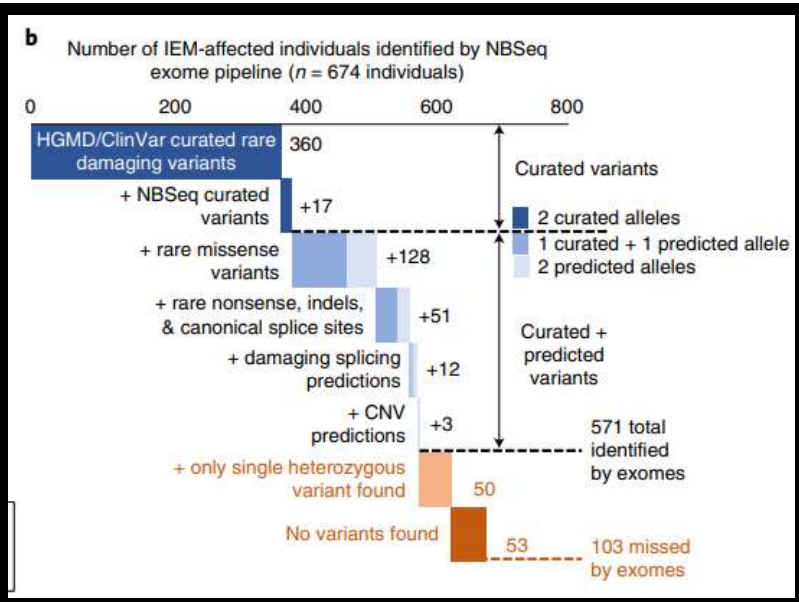
The role of exome sequencing in newborn screening for inborn errors of metabolism

Aashish N. Adhikari[1,2]✉, Renata C. Gallagher[2,3], Yaqiong Wang[1], Robert J. Currier[3], George Amatuni[3], Laia Bassaganyas[2], Flavia Chen[2,4], Kunal Kundu[1,5], Mark Kvale[2], Sean D. Mooney[6], Robert L. Nussbaum[2,7], Savanna S. Randi[8], Jeremy Sanford[8], Joseph T. Shieh[2,3], Rajgopal Srinivasan[5], Uma Sunderam[5], Hao Tang[9], Dedeepya Vaka[2], Yangyun Zou[1], Barbara A. Koenig[2,4], Pui-Yan Kwok[2,10,11], Neil Risch[2,12], Jennifer M. Puck[2,3,10,13,16]✉ and Steven E. Brenner[1,2,14,15,16]✉



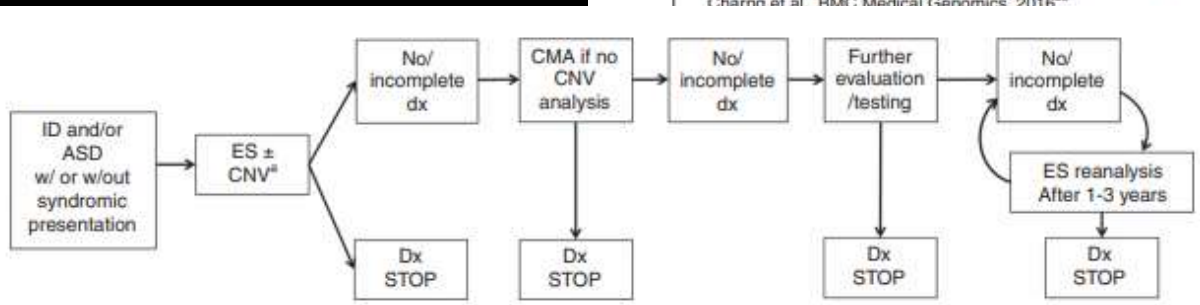


SYSTEMATIC REVIEW | Genetics inMedicine

Open

Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders

Siddharth Srivastava, MD[1], Jamie A. Love-Nichols, MS, MPH[1], Kira A. Dies, ScM[1], David H. Ledbetter, PhD[2], Christa L. Martin, PhD[2], Wendy K. Chung, MD, PhD[3,4], Helen V. Firth, DM, FRCP[5,6], Thomas Frazier, PhD[7], Robin L. Hansen, MD[8], Lisa Prock, MD, MPH[1,9], Han Brunner, MD[10,11,12], Ny Hoang, MS[13,14,15], Stephen W. Scherer, PhD[14,15,16,17], Mustafa Sahin, MD PhD[1], David T. Miller, MD PhD[18] and the NDD Exome Scoping Review Work Group



Conclusion: Our review demonstrates that ES consistently outperforms CMA for evaluation of unexplained NDDs. We propose a diagnostic algorithm placing ES at the beginning of the evaluation of unexplained NDDs.

Rajagopalan *et al. Genome Medicine* (2020) 12:14
https://doi.org/10.1186/s13073-020-0712-0

Genome Medicine

RESEARCH Open Access

A highly sensitive and specific workflow for detecting rare copy-number variants from exome sequencing data

Ramakrishnan Rajagopalan[1,2], Jill R. Murrell[1,3], Minjie Luo[1,3] and Laura K. Conlin[1,3*]

Table 4 Sensitivity of the default and modified ExomeDepth workflow

True-positive rate	Default ExomeDepth workflow		Modified ExomeDepth workflow	
	Deletions	Duplications	Deletions	Duplications
Overall	96% (172/180)	95% (283/299)	98% (163/166)	96% (280/293)
Heterozygous deletions	95% (164/172)		98% (157/160)	
Homozygous deletions	100% (6/6)		100% (4/4)	
Hemizygous deletions	100% (2/2)		100% (2/2)	
Duplications		95% (278/294)		95% (275/288)
Triplications		100% (5/5)		100% (5/5)
Autosomal	96% (165/171)	95% (256/270)	98% (156/159)	95% (254/266)
Chromosome X	78% (7/9)	93% (27/29)	100% (7/7)	96% (26/27)
Clinically reported CNVs	100% (24/24)	100% (17/17)	100% (22/22)	100% (17/17)
CNVs overlapping < 4 exons	86% (31/36)	87% (59/68)	94% (29/31)	87% (58/67)
CNVs overlapping ≥ 4 exons	98% (141/144)	97% (224/231)	99% (134/135)	98% (222/226)

Ultrasound Obstet Gynecol 2021; 57: 43–51
Published online 3 December 2020 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.22072

COngenital heart disease and the Diagnostic yield with Exome sequencing (CODE) study: prospective cohort study and systematic review

F. MONE[1,2], R. Y. EBERHARDT[3], R. K. MORRIS[1,2], M. E. HURLES[3], D. J. MCMULLAN[4], E. R. MAHER[5,6,7], J. LORD[3], L. S. CHITTY[8], J. L. GIORDANO[9,10], R. J. WAPNER[9,10], M. D. KILBY[1,2] and the CODE Study Collaborators

Study or subgroup	ES Events	ES Total	CMA/karyotyping Events	CMA/karyotyping Total	Weight (%)	Risk difference M–H, random, 95% CI
Aarabi (2018)[26]	0	4	0	4	2.3	0.00 (–0.37, 0.37)
Boissel (2018)[20]	3	11	0	11	3.6	0.27 (–0.01, 0.55)
Carss (2014)[21]	3	3	0	3	1.6	1.00 (0.54, 1.46)
Daum (2019)[22]	1	5	0	5	2.0	0.20 (–0.21, 0.61)
de Koning (2019)[30]	2	10	0	10	3.7	0.20 (–0.08, 0.48)
Drury (2015)[23]	1	3	0	3	1.1	0.33 (–0.24, 0.91)
Fu (2018)[24]	7	34	0	34	8.3	0.21 (0.06, 0.35)
Hu (2018)[9]	7	44	0	44	9.8	0.16 (0.05, 0.27)
Leung (2018)[18]	2	7	0	7	2.4	0.29 (–0.08, 0.65)
Lord (2019)[5]	25	197	0	197	13.5	0.13 (0.08, 0.17)
Normand (2018)[28]	11	37	0	37	7.8	0.30 (0.15, 0.45)
Petrovski (2019)[6]	12	143	0	143	13.5	0.08 (0.04, 0.13)
Stals (2018)[25]	2	8	0	8	2.9	0.25 (–0.08, 0.58)
Sun (2019)[11]	20	66	0	66	9.9	0.30 (0.19, 0.42)
Vora (2017)[29]	1	3	0	3	1.1	0.33 (–0.24, 0.91)
Westerfield (2015)[27]	2	5	0	5	1.7	0.40 (–0.05, 0.85)
Westphal (2019)[10]	7	30	0	30	7.5	0.23 (0.08, 0.39)
Yates (2017)[19]	5	26	0	26	7.4	0.19 (0.03, 0.35)
Total (95% CI)		636		636	100.0	0.21 (0.15, 0.27)
Total events	111		0			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 42.57$, 17 d.f. ($P = 0.0006$); $I^2 = 60\%$
Test for overall effect: $Z = 6.70$ ($P < 0.00001$)

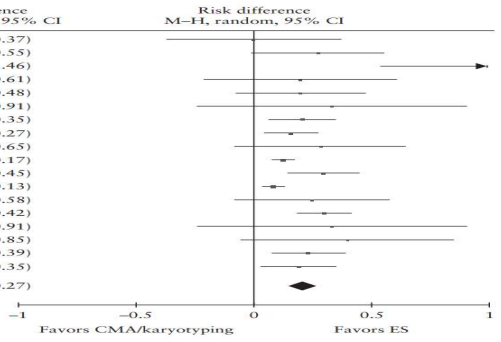


Figure 3 Forest plot showing incremental yield of exome sequencing (ES) over chromosomal microarray analysis (CMA) or karyotyping in fetuses with prenatally detected congenital heart disease overall. Only first author of each study is given. M–H, Mantel–Haenszel.

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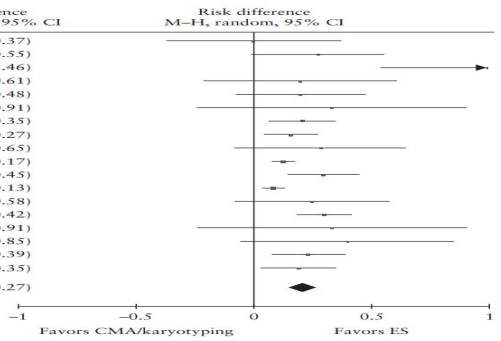

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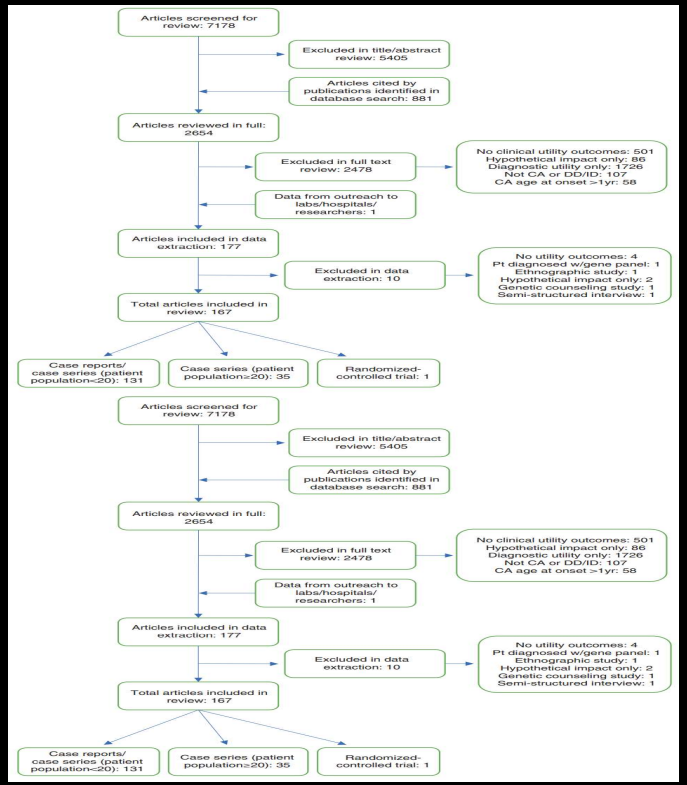
Genetics inMedicine | ACMG SYSTEMATIC EVIDENCE REVIEW

Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability

Jennifer Malinowski, PhD[1], David T. Miller, MD, PhD[2], Laurie Demmer, MD[3], Jennifer Gannon, MD[4,5], Elaine Maria Pereira, MD[6], Molly C. Schroeder, PhD[7], Maren T. Scheuner, MD[8,9], Anne Chun-Hui Tsai, MD[10], Scott E. Hickey, MD[11] and Jun Shen, PhD[12]; on behalf of the ACMG Professional Practice and Guidelines Committee[13]



Articles screened for review: 7178
Excluded in title/abstract review: 5405
Articles cited by publications identified in database search: 881
Articles reviewed in full: 2654
Excluded in full text review: 2478
No clinical utility outcomes: 501
Hypothetical impact only: 86
Diagnostic utility only: 1726
Not CA or DD/ID: 107
CA age at onset >1yr: 58
Data from outreach to labs/hospitals/ researchers: 1
Articles included in data extraction: 177
Excluded in data extraction: 10
No utility outcomes: 4
Pt diagnosed w/gene panel: 1
Ethnographic study: 1
Hypothetical impact only: 2
Genetic counseling study: 1
Semi-structured interview: 1
Total articles included in review: 167
Case reports/ case series (patient population<20): 131
Case series (patient population≥20): 35
Randomized-controlled trial: 1

Conclusion

In summary, we performed a systematic evidence review to characterize the impact of ES/GS in patients with CA/DD/ID on clinical management and health outcomes. We identified one RCT and numerous case series and case reports describing clinical and patient outcomes, for which the overall evidence was limited. However, a change in patient management was observed in nearly all included studies (including case reports), and a substantial number of publications reported a clinical impact on the patient's family members or an impact on reproductive outcomes. Future studies of ES/GS results for patients with CA/DD/ID should explicitly measure patient and family outcomes resulting from testing to better assess the clinical and personal utility of ES/GS.

Genetics inMedicine

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ACMG PRACTICE GUIDELINE

Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

Kandamurugu Manickam[1,2], Monica R. McClain[3], Laurie A. Demmer[4], Sawona Biswas[5], Hutton M. Kearney[6], Jennifer Malinowski[7], Lauren J. Massingham[8,9], Danny Miller[10], Timothy W. Yu[11,12], Fuki M. Hisama[13] and ACMG Board of Directors[14]*

RESULTS: The literature supports the clinical utility and desirable effects of ES/GS on active and long-term clinical management of patients with CA/DD/ID, and on family-focused and reproductive outcomes with relatively few harms. Compared with standard genetic testing, ES/GS has a higher diagnostic yield and may be more cost-effective when ordered early in the diagnostic evaluation.

CONCLUSION: We strongly recommend that ES/GS be considered as a first- or second-tier test for patients with CA/DD/ID.

Cost-effectiveness

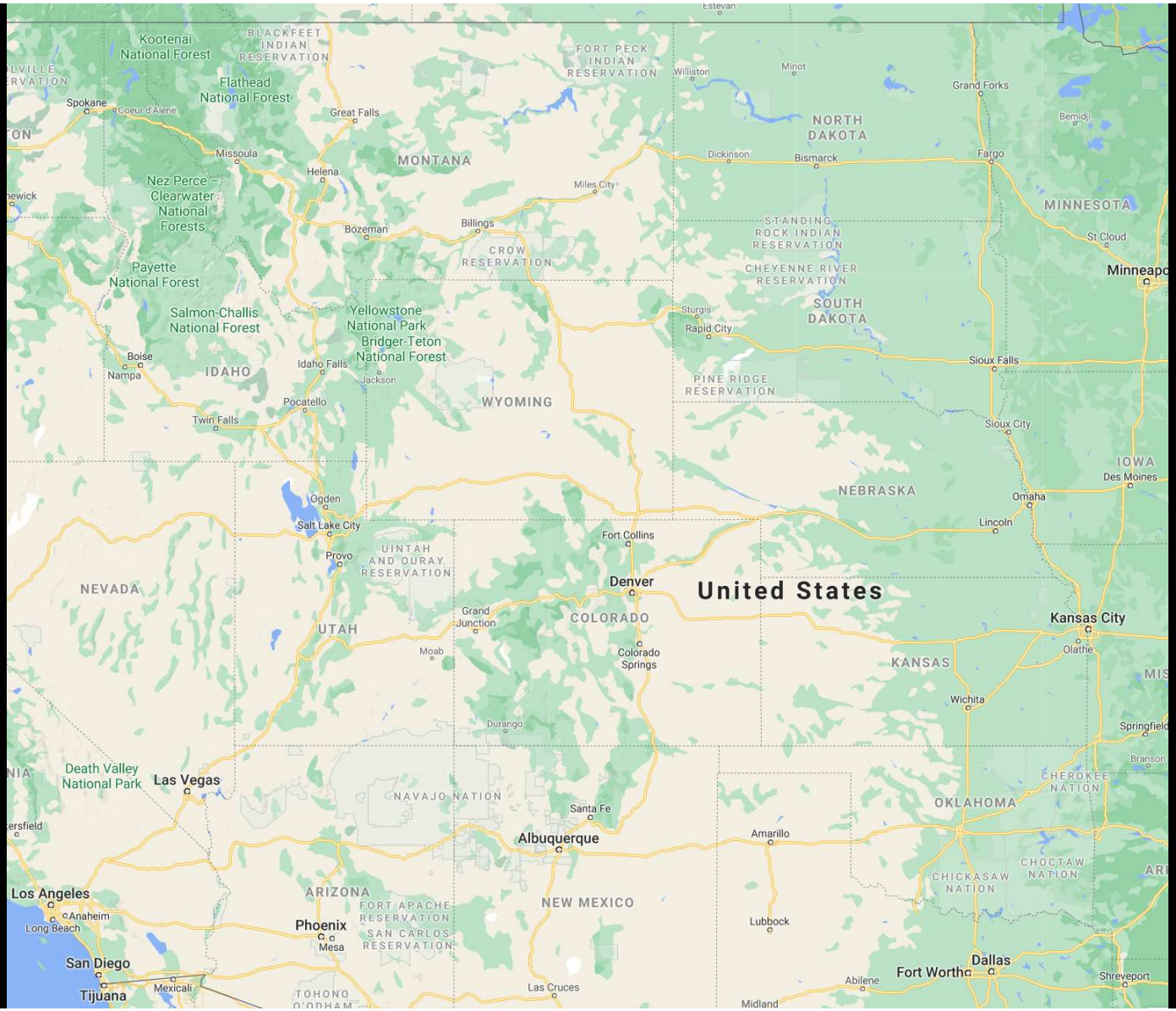
The HTA economic model showed that, overall, ES after standard testing increased the diagnostic yield at an additional cost compared to standard testing alone.[9,82] However, using ES as a first- or second-tier test (e.g., after CMA or targeted testing) yielded more diagnoses at a lower cost than using ES only after extensive standard testing (e.g., large sequencing panels and/or multiple testing approaches) or using standard testing alone. With the anticipated further declines in cost, early use of genome-wide sequencing should continue to enable more timely diagnosis for patients with unexplained DD or multiple CAs.

Equity

In 2016 the Global Burden of Disease Study reported the total number of children under age 5 years with six DDs was 52.9 million, with 50.2 million (94.9%) in low and middle income countries, and 2.7 million (5.1%) in high income countries.[83] There does not appear to be any empirical evidence specifically regarding equity for ES/GS. A PubMed search returned 0 applicable results for "health equity" and the available MESH terms "whole exome sequencing" or "whole genome sequencing." However, it is well-established that minority populations are historically underrepresented in genomic studies.[84] Patients with health insurance and from higher socioeconomic backgrounds are more likely to have access and pursue genetic services. On the other hand, given socioeconomic status–based inequities in access to care, clinical experience suggests that if a diagnosis can be made in fewer visits, increased use of ES/GS should increase equity for patients with genetic disorders.

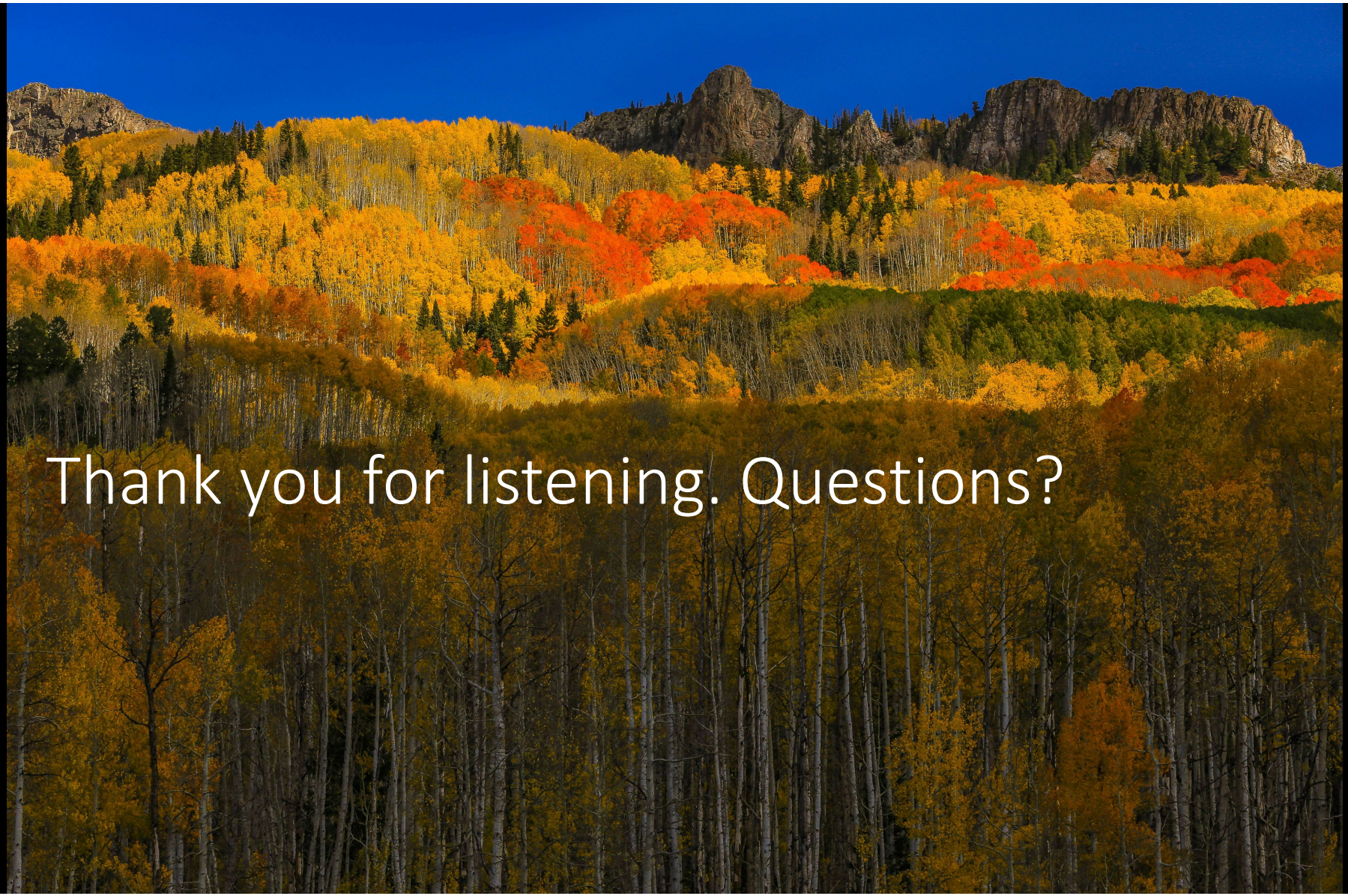
A thought exercise: 100 patients with moderate developmental delay

- Fragile X testing
  - 2 diagnoses @ $250/test = $12,500 per dx
- Metabolic testing
  - 2 diagnoses @ $1,500/evaluation = $75,000 per dx
- Chromosomal microarray
  - 10 diagnoses @ $1,000/test = $10,000 per dx
- Exome sequencing (including CNV diagnoses)
  - 46 dx @ $2,000/test = $4,350 per dx



The value of WES/WGS for rural patients

Significant barriers still exist
- payment
- interpretation
- access to care after diagnosis


Thank you for listening. Questions?