Financial Disclosure

I have financial relationships to report within the past 24 months with ACCME defined ineligible companies.

Name of Company	Nature of Relationship
GeneDx, LLC	Employee, Shareholder

Unlabeled/Investigational Uses

I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals during this presentation.



Factors influencing molecular diagnostic yield in a clinical autism exome sequencing cohort of over 100,000 individuals

Presenting author: Kendall King, Ph.D., GeneDx

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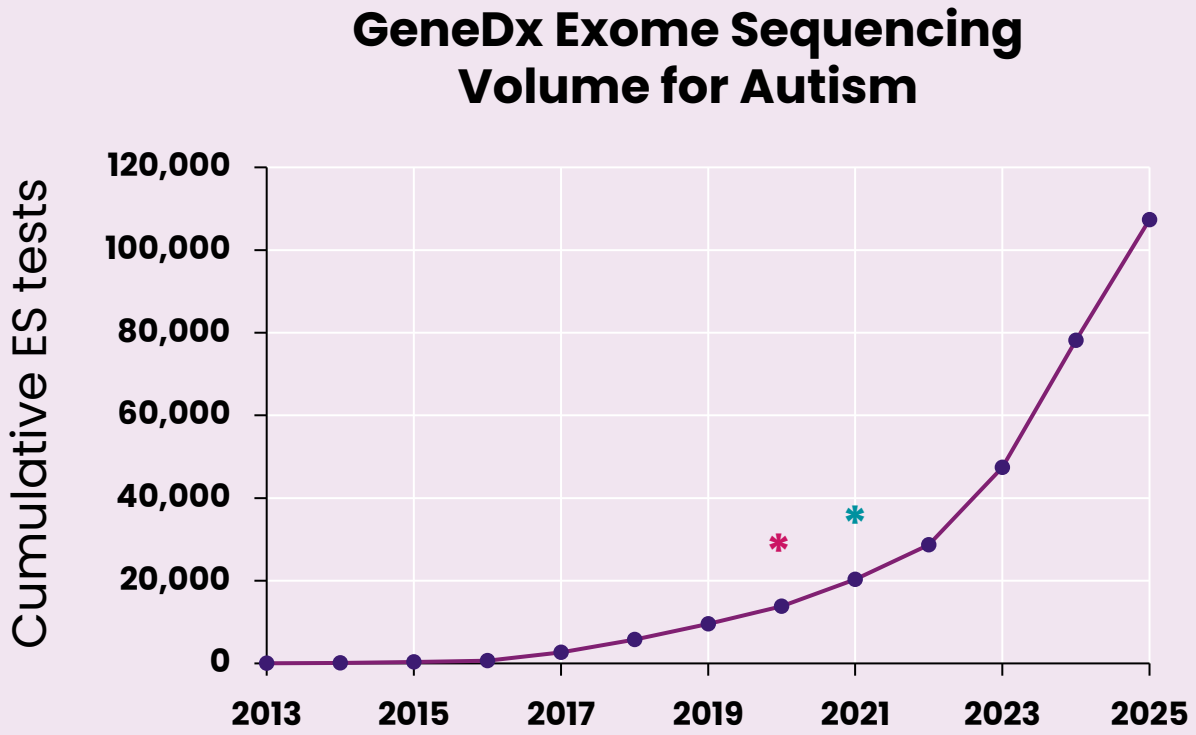
Genetic testing in autism

Evidence supports that ASD is…

genetic [1, 2]

heterogeneous [1, 3-5]

- ES testing well-suited for heterogeneous disorders
- Not routinely a first-tier test for autism



* [6]The AAP recommends children between 18 and 24 months are screened for ASD along with ongoing developmental and behavioral surveillance at 9, 18, and 30 months

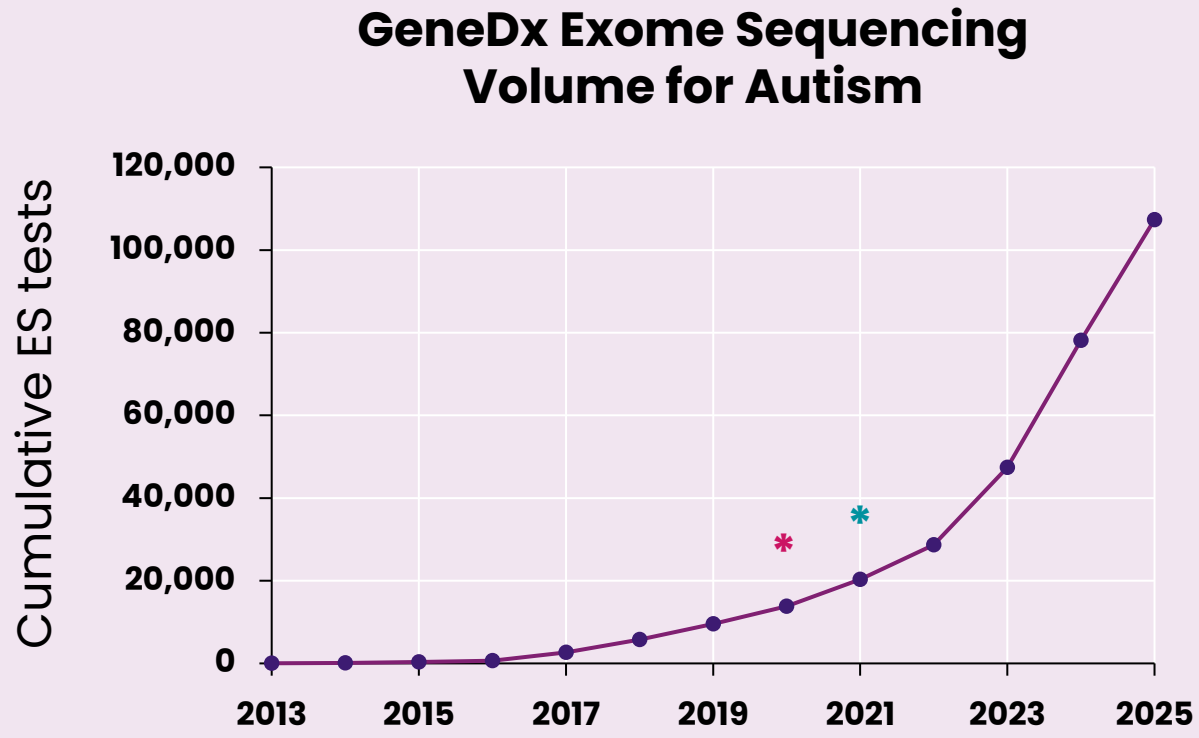
* [7]ACMG recommends ES/GS for pediatric patients with congenital anomalies, developmental delay or intellectual disability

[1]Bai et al, 2019; [2]Qiu et al, 2022; [3]Winder et al, 2017; [4]Antaki et al, 2020; [5]Litman et al, 2025. [6]Hyman et al. 2020, [7]Manickam et al. 2021

Genetic testing in autism

Study Goal

What demographic, clinical, and genetic factors are associated with ES diagnostic yield?



* [6]The AAP recommends children between 18 and 24 months are screened for ASD along with ongoing developmental and behavioral surveillance at 9, 18, and 30 months

* [7]ACMG recommends ES/GS for pediatric patients with congenital anomalies, developmental delay or intellectual disability

Autism cohort definitions

Individuals met the following criteria

Autism indicated or suspected at time of testing

HP:0000717 “Autism” or HP:0000729 “Autistic behavior”

Received clinical Exome Sequencing (ES)

rapid and standard turn around-time

ES from March 2013 – May 2026

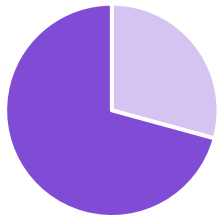
Minimum age at testing: 2 years

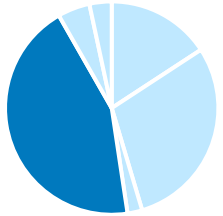
Unrelated probands

Final analytic cohort: 102,006 individuals

All individuals had appropriate clinical consent for inclusion in de-identified research

Characteristic		%
Sex at Birth	**Male**	**70.7**
	Female	29.3
Genetic Ancestry [1]	**European (EUR)**	**44.1**
	Admixed American (AMR)	29.6
	African (AFR)	15.8
	Middle Eastern (MDE)	4.9
	South Asian (SAS)	3.4
	East Asian (EAS)	2.2
Age at Testing	**2-5 years**	**44.5**
	6-9 years	25.1
	10-13 years	13.7
	14-17 years	9.4
	18+ years	7.3







[1] Inferred based on principal component analysis with 1000 Genomes Reference Populations and 1 internally developed reference population (MDE)

Diagnostic categories

Overall Diagnostic Yield

proportion of cases that have a definitive or possible diagnostic finding

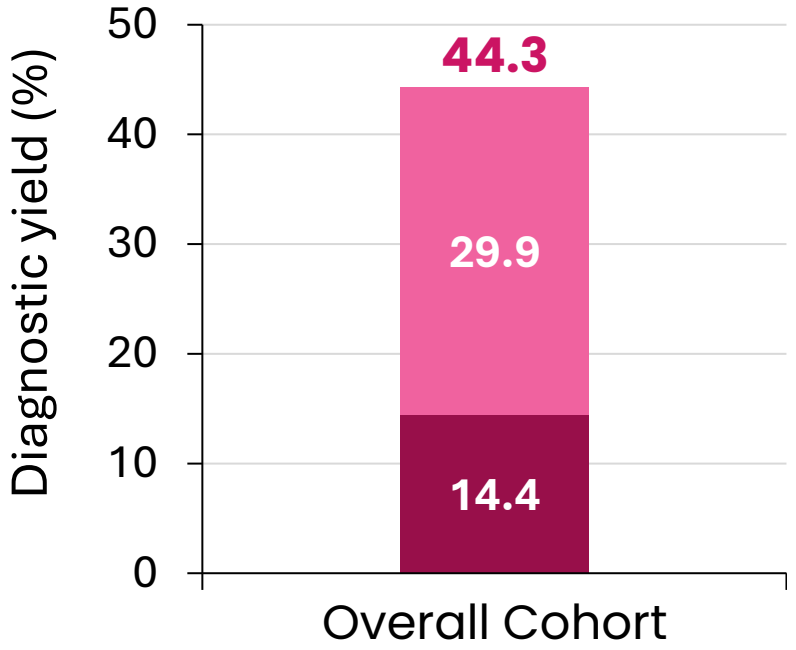
Definitive

P/LP variants associated with reported phenotype and expected inheritance pattern

+

Possible

P/LP/VUS possibly associated with reported phenotype



CMA [1-3]

6% – 10%

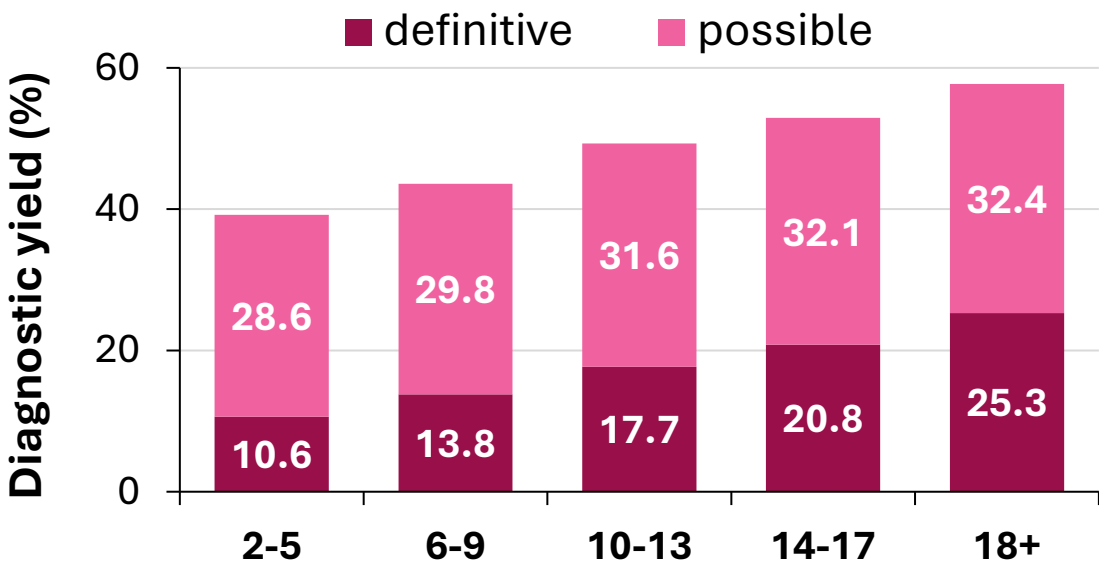
Fragile X [1-3]

0.4% – 5%

[1]Harrington et al. 2025; [2]Harris et al. 2020; [3]Shaefer et al. 2023

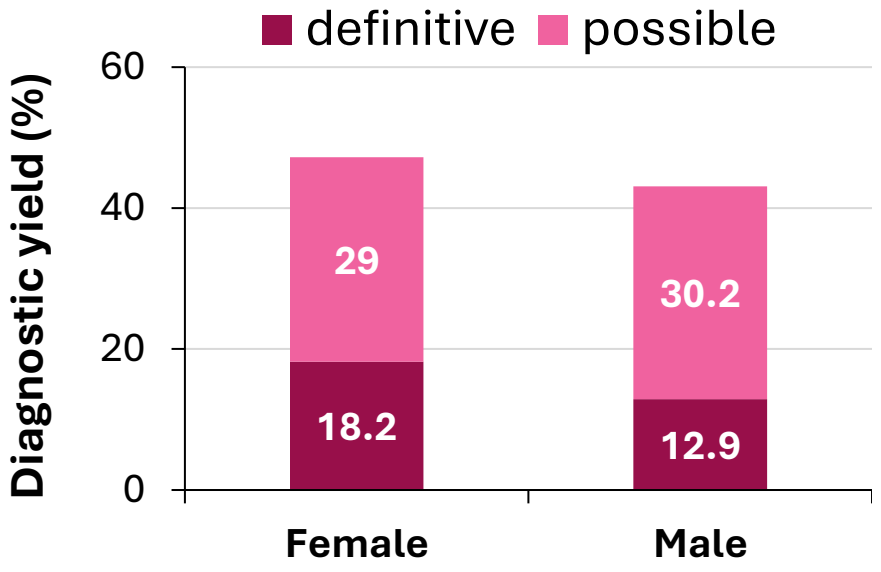
Diagnostic yield by demographic groups

Yield (%) increased with age at testing



	2-5	6-9	10-13	14-17	18+
N	45,434	25,553	13,962	9,604	7,453
%	44.5	25.1	13.7	9.4	7.3
Dx Yield	**39.2**	**43.6**	**49.3**	**52.9**	**57.7**

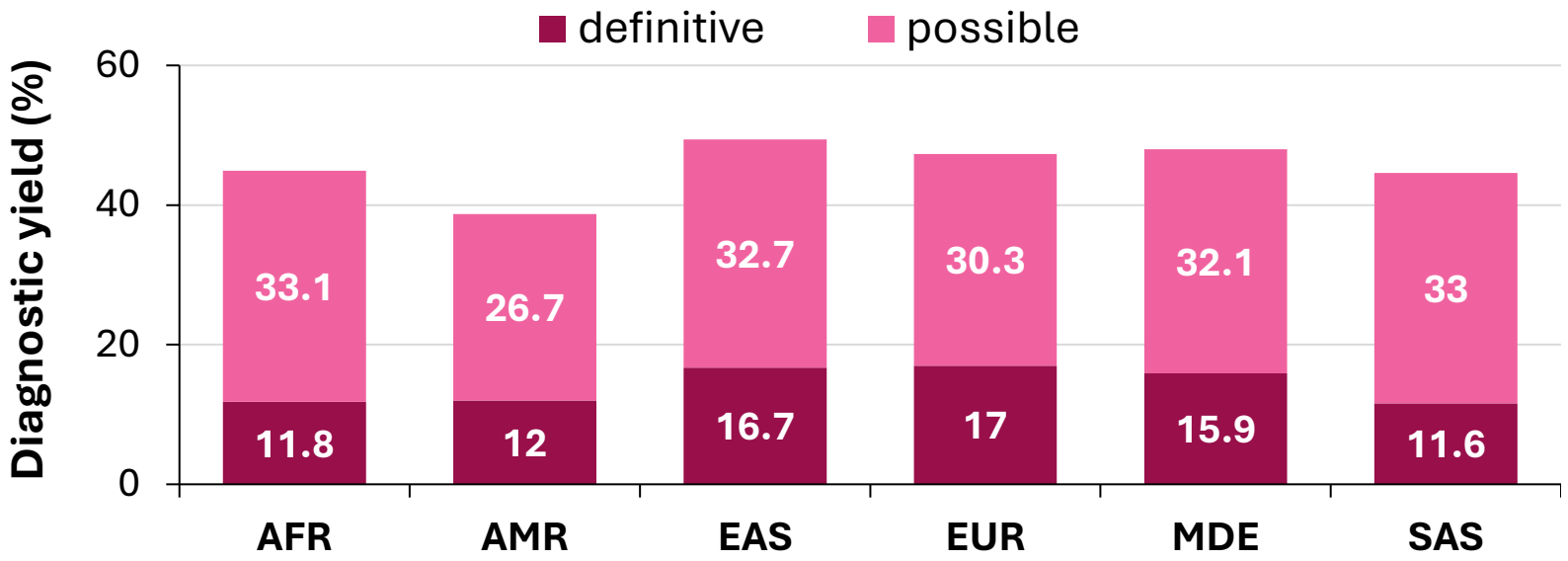
Yield (%) was higher for females



	Female	Male
N	29,818	72,120
%	29.3	70.7
Dx Yield	**47.2**	**43.1**

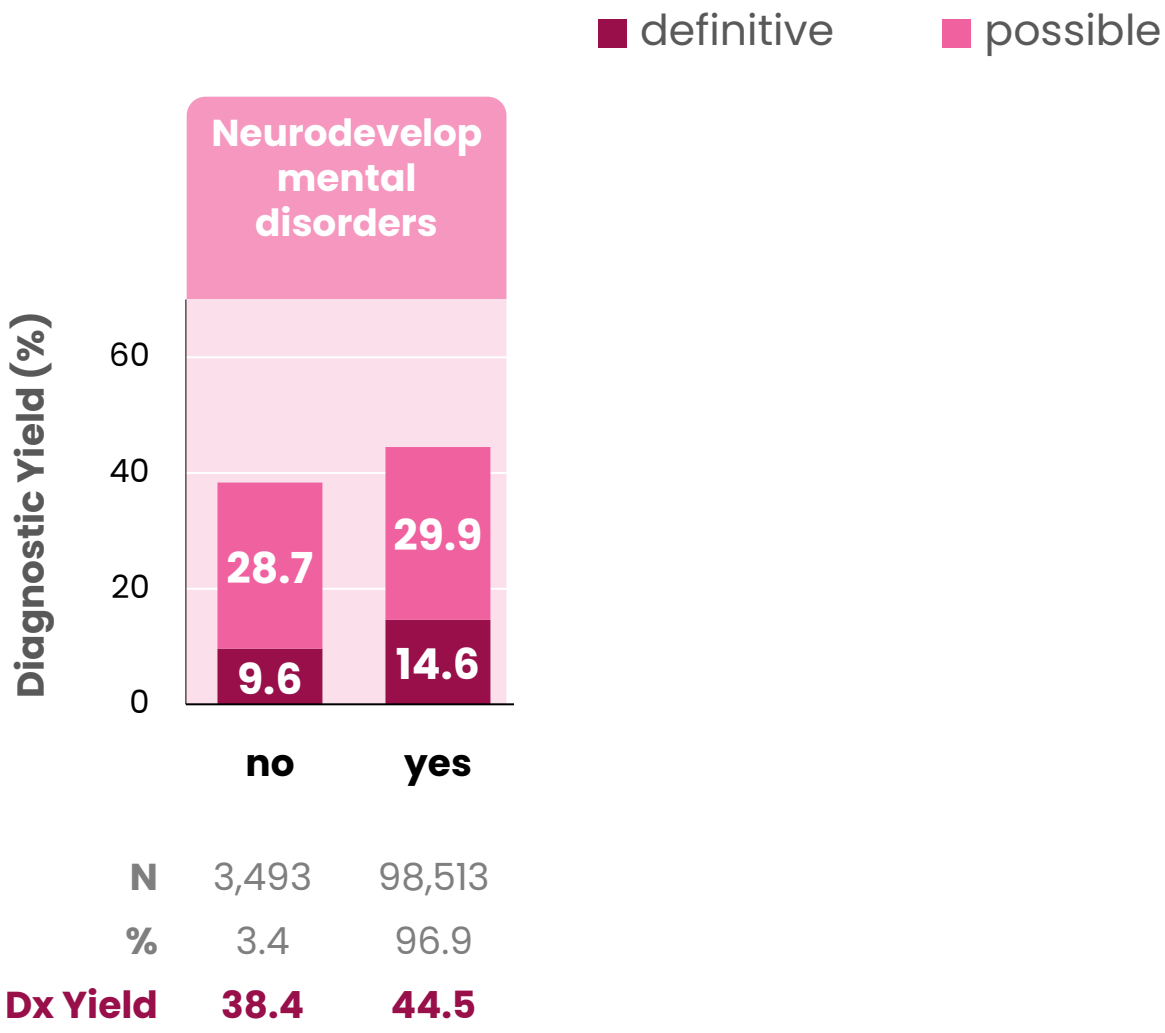
Diagnostic yield by genetic ancestry

Overall diagnostic yield exceeded 40% in all genetic ancestry groups except AMR



	AFR	AMR	EAS	EUR	MDE	SAS
N	15,900	29,812	2,249	44,447	4,919	3,393
%	15.8	29.6	2.2	44.1	4.9	3.4
Dx Yield	**44.9**	**38.7**	**49.4**	**47.3**	**48**	**44.6**

Diagnostic yield by phenotype complexity



	no	yes
N	3,493	98,513
%	3.4	96.9
Dx Yield	**38.4**	**44.5**

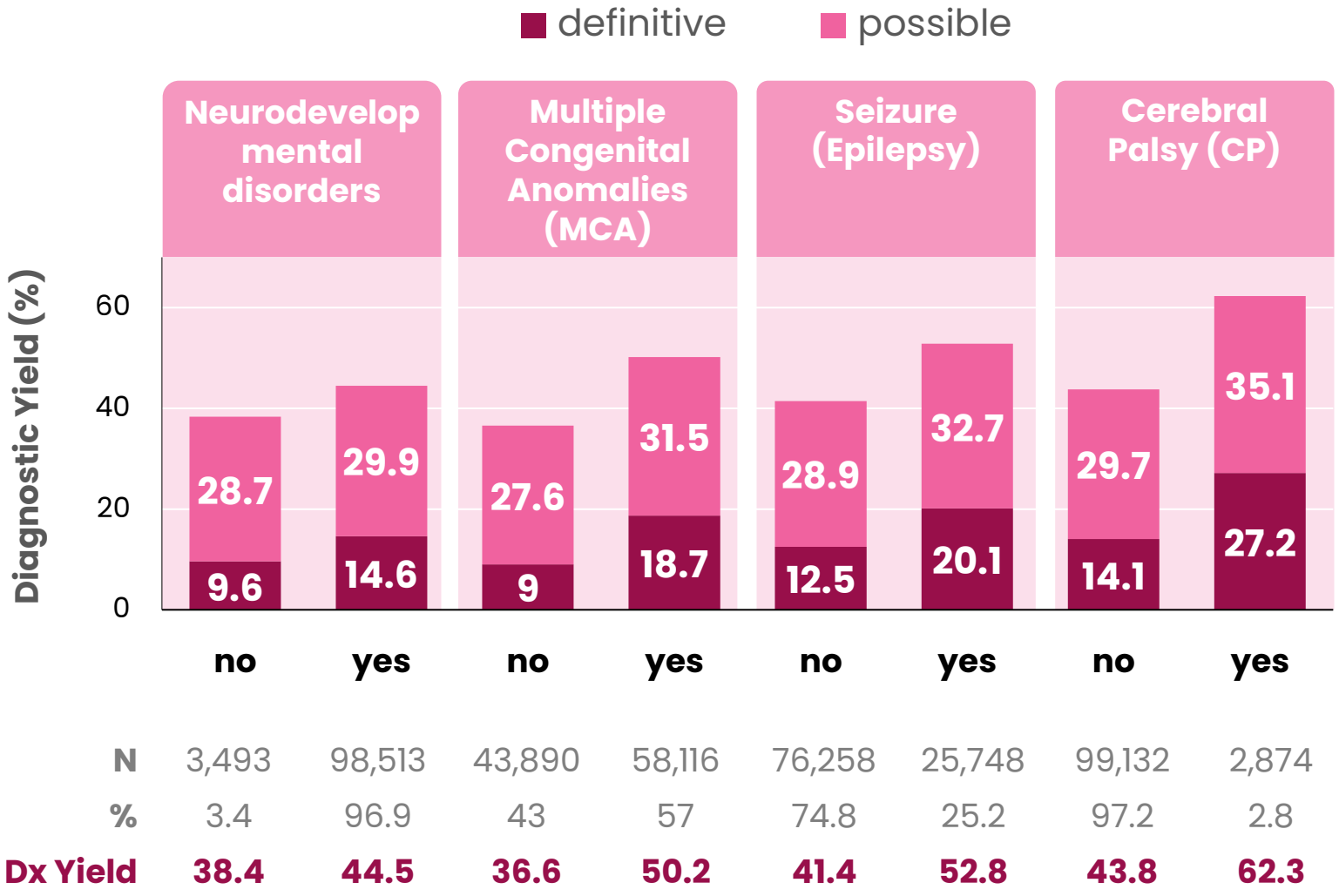
NOTE: Phenotype groups are not mutually exclusive

The impact of phenotype complexity on diagnostic yield was evaluated as the **absence (no) or presence (yes) of comorbidities**

Comorbidities with internally developed HPO-based definitions* were assessed

*Defined in consultation with internal subject matter experts

Diagnostic yield by phenotype complexity



N	3,493	98,513	43,890	58,116	76,258	25,748	99,132	2,874
%	3.4	96.9	43	57	74.8	25.2	97.2	2.8
Dx Yield	**38.4**	**44.5**	**36.6**	**50.2**	**41.4**	**52.8**	**43.8**	**62.3**

NOTE: Phenotype groups are not mutually exclusive

The impact of phenotype complexity on diagnostic yield was evaluated as the **absence (no) or presence (yes) of comorbidities**

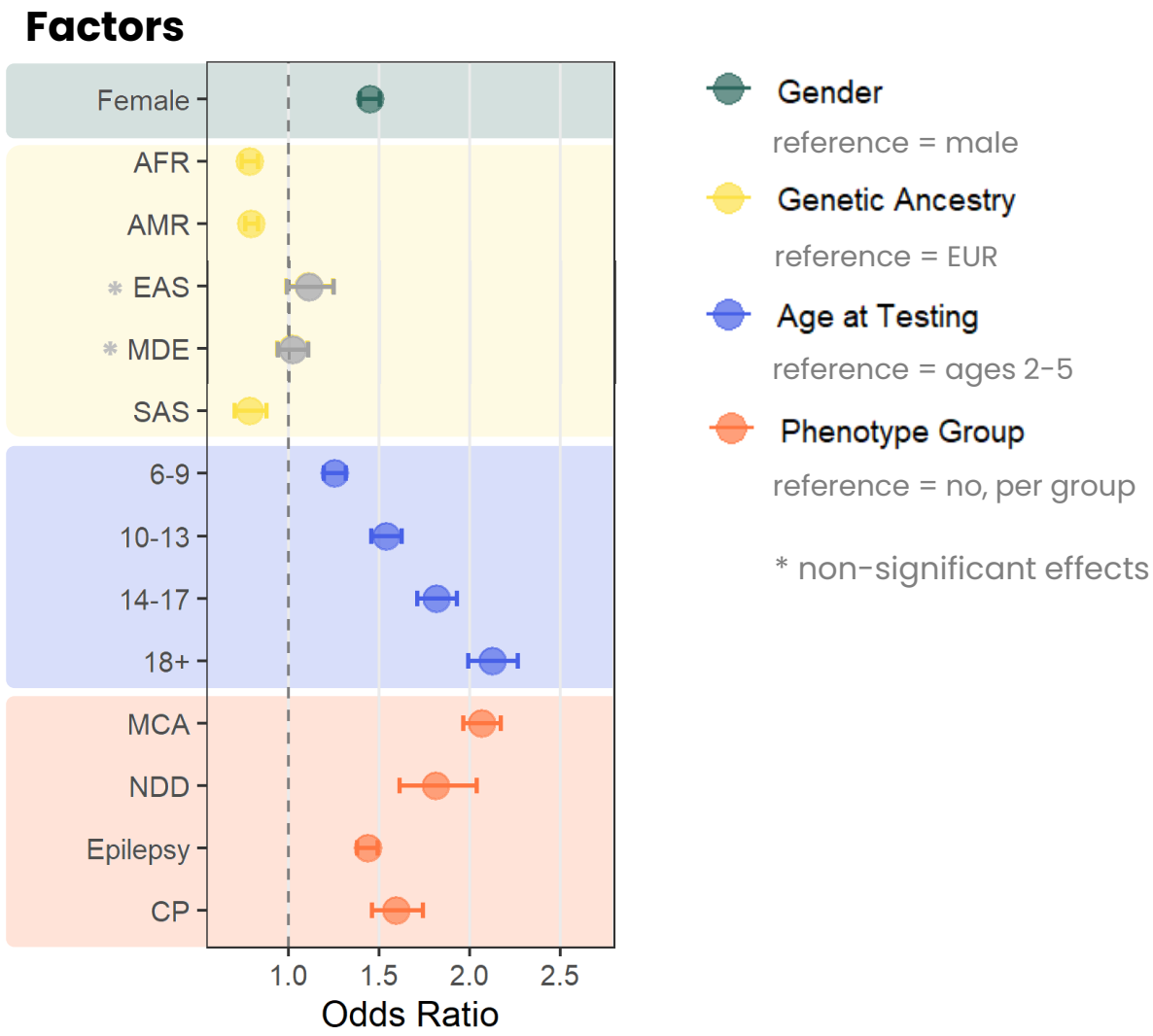
Comorbidities with internally developed HPO-based definitions* were assessed

*Defined in consultation with internal subject matter experts

Drivers of definitive diagnostic yield

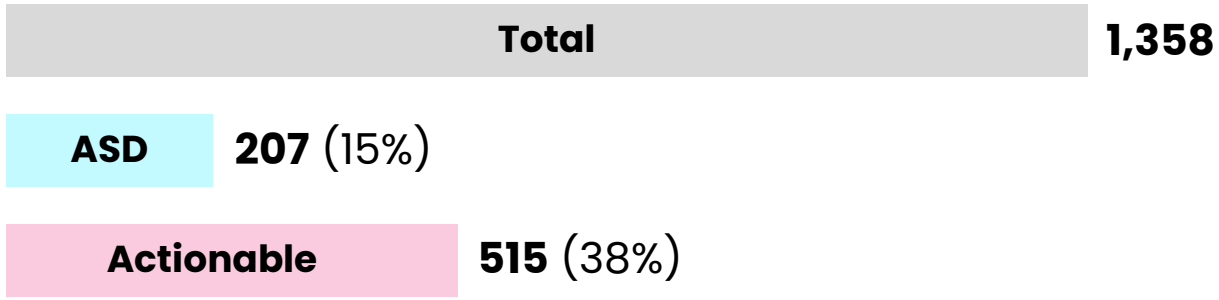
Multivariate Logistic Regression

Definitive diagnostic yield ~ genetic sex + genetic ancestry + age at testing + phenotype groups

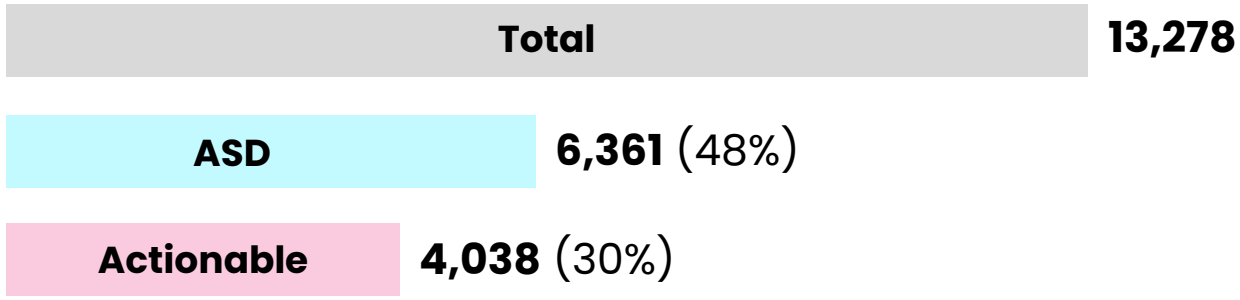


Landscape of diagnostic findings

Genes within definitive diagnostic findings



Patients with definitive diagnostic findings



ASD-Specific [1]

253 autosomal genes sourced from the Autism Sequencing Consortium

Medically Actionable [2-4]

1,505 genes with potential for a genetic or genomic finding to inform medical management or disease prevention

[1] Satterstrom et al. 2026, [2-4] Bick et al. 2021, Hunter et al. 2016, Minten et al. 2024

Top genes with definitive findings

Gene Symbol	Patients (n)	Variants (n)	ASD	Act.
MECP2	187	71		
PTEN	183	130		
SHANK3	157	94		
ANKRD11	153	123		
ARID1B	144	131		
SCN2A	138	128		
G6PD	126	19		
SYNGAP1	116	97		
DDX3X	109	94		
NF1	109	93		
CHD8	102	93		
NAA15	90	76		
CACNA1A	89	78		
GRIN2B	87	69		
SCN1A	87	83		
KMT2A	85	77		
FOXP1	76	65		
PTPN11	76	40		
TRIO	72	64		
CHD2	70	61		
GJB2	68	29		
POGZ	68	61		
WDFY3	68	62		
SETD5	65	58		
KMT2C	64	62		
SETD1B	63	47		
CUL3	62	53		
n patients =	**2,640**		**2,217**	**1,577**

19% (n = 2,640) of patients with a definitive diagnostic finding **had findings in top genes***

- **84% ASD Overlap (n = 2,217)**
  the majority of definitive findings in the top genes were in genes associated with autism

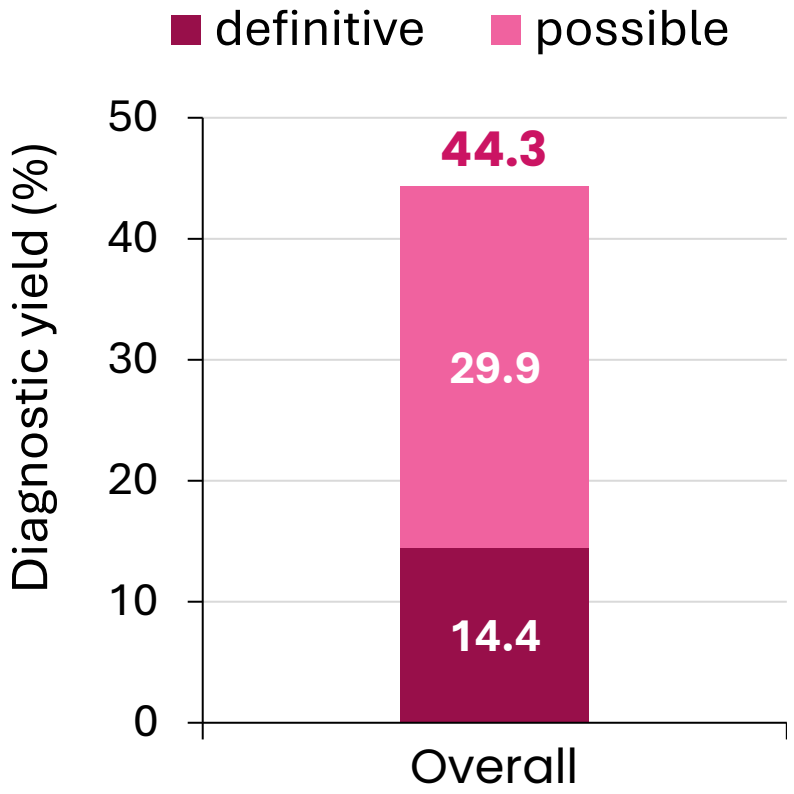
  does not include non-autosomal genes associated with ASD, including MECP2 and DDX3X

- **60% Medical Actionability Overlap (n = 1,577)**
  many definitive findings in the top genes were in medically actionable genes

*27 genes selected based on a threshold of ≥ 0.05% representation of DDx population

Diagnostic yield of ES in autism

- Diagnostic yield of ES in individuals with phenotypes including autism was shaped by both demographic and phenotypic factors, especially co-occurring phenotypes, in this large real-world cohort.
- A large proportion of the most common findings were in autism-associated genes, and many were medically actionable.
- These data support exome sequencing as a meaningful diagnostic tool for individuals with autism.



Thank You!

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