

Review Article

Chromosomal Microarray Analysis in Autism Spectrum Disorder: Diagnostic Yield, Deletion/Duplication Syndromes, and Clinical Utility

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Background: Autism spectrum disorder (ASD) is clinically and etiologically heterogeneous. Chromosomal microarray analysis (CMA) detects copy-number variants (CNVs), but diagnostic yield varies markedly with phenotype. **Objective:** To assess CMA diagnostic yield in ASD, identify clinical features associated with higher yield, review recurrent clinically relevant CNVs, and distinguish diagnostic yield from downstream clinical utility. **Methods:** We conducted a PRISMA 2020-informed focused update. A contemporary four-database systematic review (January 2021–June 26, 2026; 434 records, 13 studies, 11,535 children) served as the evidence backbone, followed by a targeted update through October 4, 2026, and inclusion of landmark earlier studies for historical and technical context. **Results:** The contemporary review reported lower P/LP CNV yield in ASD (3.3%–15.2%) than in DD/ID phenotypes (17.1%–33.6%). Two 2026 ASD cohorts reinforced phenotype dependence: 17.1% in complex versus 4.7% in essential ASD, and 2.8% in a rigorously selected nonsyndromic cohort. In Tammimies et al., CMA yield was 24.5% in morphologically complex ASD versus 4.2% in essential ASD. Retrospective series support clinically actionable downstream evaluation, although prospective management-change evidence remains limited. **Conclusions:** CMA remains useful for detecting CNVs and genomic syndromes, especially when ASD co-occurs with developmental/intellectual impairment, dysmorphism, congenital anomalies, epilepsy, or growth abnormalities. A negative CMA does not exclude a genetic etiology; ES/GS and targeted testing are complementary. Phenotypic complexity appears more informative for pre-test yield than an ASD diagnosis considered in isolation.

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Key message. CMA primarily answers the question, "Is there a clinically relevant genomic loss or gain?" It does not by itself answer the question, "Is there a genetic cause?" Therefore, CMA yield, overall genetic diagnosis, and clinical utility should be analyzed as distinct outcomes.

1. Introduction

Autism spectrum disorder (ASD) is clinically defined by persistent impairments in social communication and interaction and restricted or repetitive patterns of behavior, interests, or activities. However, this phenotypic definition encompasses diverse trajectories and etiologies. In a proportion of children, autistic features occur within a broader neurodevelopmental disorder, a monogenic condition, a chromosomal abnormality, or a genomic syndrome. In others, ASD presents without dysmorphism, malformations, epilepsy, or evident intellectual disability. This heterogeneity directly affects the pretest probability of obtaining a molecular diagnosis. ^{[1][2][3][4]}

Copy-number variants (CNVs) are gains or losses of DNA segments. They may range from submicroscopic regions containing one or a few genes to large segments involving multiple dosage-sensitive genes. Chromosomal microarray analysis (CMA), using array-CGH and/or SNP-array platforms, can identify many of these deletions and duplications at a resolution far greater than conventional karyotyping. SNP-array platforms also provide information on regions of absence of heterozygosity, which in selected contexts may suggest consanguinity or uniparental disomy, although confirmation of the underlying mechanism may require additional testing. ^{[1][5]}

The 2010 consensus statement by Miller et al. established CMA as a first-tier cytogenetic test for developmental delay/intellectual disability (DD/ID), ASD, and multiple congenital anomalies. Among 21,698 individuals across these combined populations, the overall diagnostic yield was estimated at approximately 15%–20%, compared with about 3% for conventional karyotyping when clinically recognizable chromosomal syndromes were excluded. ^[1] However, this aggregate figure should not be interpreted as the expected yield in every child with ASD: it combines very different phenotypes and comes from an era preceding current standardization of CNV classification. ^[5]

Over the past decade, exome sequencing (ES) and genome sequencing (GS) have expanded the spectrum of detectable variants. ACMG guidelines recommend considering ES/GS as a first- or second-tier test in children with congenital anomalies and/or DD/ID; the AAP has also updated the genetic evaluation of

DD/ID toward phenotype-based selection and modern genomic technologies. ^{[6][7]} In ASD, comparative studies show that the relative yield of CMA, ES, and GS depends on cohort composition, the CNV detection pipeline, and the definition of a diagnostic result. ^{[4][8]}

Therefore, the current question is not simply whether CMA "works" in autism. A more precise question is: in which children with ASD does CMA provide clinically meaningful diagnostic yield, which CNVs does it identify, what information can it not provide, and how often does the result change medical follow-up? This review addresses these questions by separating three concepts that are often conflated: detection of any CNV, yield of pathogenic/likely pathogenic (P/LP) variants, and clinical utility after the result is obtained.

2. Objectives

Primary objective: to evaluate the diagnostic yield of CMA for detecting pathogenic or likely pathogenic CNVs in children and adolescents with ASD and to determine how yield varies according to phenotypic complexity.

- Compare the observed yield in essential/nonsyndromic ASD versus complex or syndromic ASD.
- Identify recurrent CNVs and deletion/duplication syndromes relevant to the neurodevelopmental phenotype.
- Assess whether CMA findings lead to additional testing, specific surveillance, or genetic counseling.
- Define the limitations of CMA and its current relationship to ES, GS, karyotyping, and targeted molecular tests.
- Propose a phenotype- and diagnostic-question-based clinical algorithm for test selection.

3. Methods

3.1. Design and reporting framework

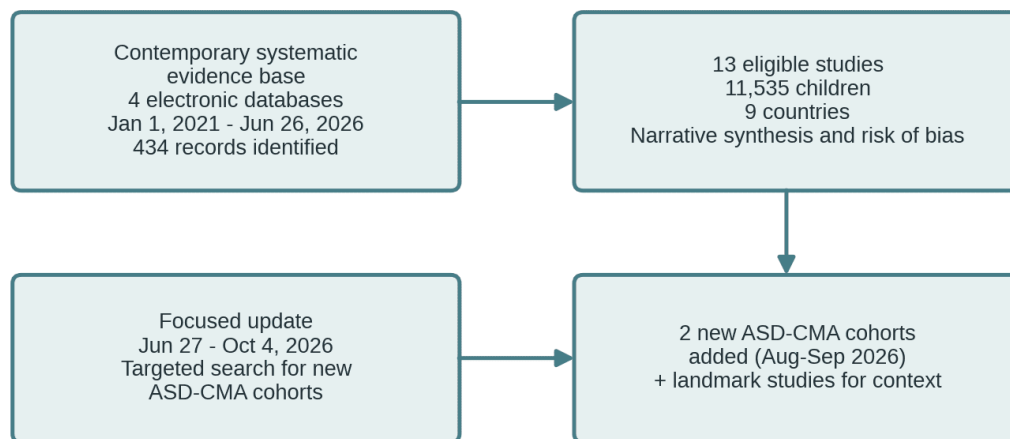
A focused systematic review and evidence update, informed by PRISMA 2020, was performed. ^[9] The objective was to specifically update the question of CMA diagnostic yield and utility in ASD without artificially duplicating a recent multibase search directly aligned with the topic. Accordingly, the methodology was structured as an update of a contemporary systematic review, supplemented by landmark studies and reference sources for genomic syndromes.

3.2. Contemporary systematic evidence base and update

The contemporary evidence base was the systematic review by Ahmed et al. (2026), which searched four electronic databases from January 1, 2021 through June 26, 2026, without language or country restrictions. It identified 434 records and included 13 primary studies comprising 11,535 children from nine countries. ^[10] That review assessed CMA yield in DD, ID, and/or ASD, used a critical appraisal tool for case series, and performed a narrative synthesis.

A targeted update was performed for the period after the close of that search (June 27 through October 4, 2026), prioritizing PubMed/MEDLINE, publisher websites, and cross-references. Search concepts included combinations of "autism spectrum disorder", "autism", "chromosomal microarray", "array CGH", "SNP array", "copy number variant", "microdeletion", "microduplication", "diagnostic yield", "complex autism", "essential autism", and "nonsyndromic autism". Two new ASD-CMA cohorts with explicit yield data published after the base review search closed were incorporated: Tüysüz et al. (August 30, 2026) and Santos et al. (September 11, 2026). ^{[11][12]}

Studies published before 2021 were added when they provided foundational information or information directly necessary to interpret contemporary yield: technical consensus, historical ASD cohorts, the morphologic gradient, retrospective impact on management, and CNV classification standards. ^{[1][2][3][5][13][14][15][16][17]} This historical component was used narratively and was not quantitatively pooled with the contemporary synthesis.



PRISMA 2020-informed update structure. The 434 records and 13 studies derive from Ahmed et al.; the later update was focused and did not repeat the four databases de novo.

Figure 1. Evidence flow used for the focused update. The structure is informed by PRISMA 2020; the 434 records and 13 studies correspond to the systematic review by Ahmed et al. ^[10]. The subsequent update incorporated two new ASD-CMA cohorts ^{[11][12]}.

3.3. Eligibility criteria

For yield analysis, priority was given to pediatric or predominantly pediatric cohorts with an ASD diagnosis that reported the denominator of patients studied by CMA and the number or proportion of P/LP results. Studies combining DD/ID and other indications were used to contextualize the effect of phenotype, but their aggregate yield was not attributed to isolated ASD. Case reports, series without an ASD denominator, and studies reporting only "any CNV" without separating clinical relevance were excluded from the comparative calculation.

Contemporary CNV classification was interpreted according to the five-category ACMG/ClinGen framework: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, and pathogenic. ^[5] Because older studies used different terminology and thresholds, their figures were not treated as directly interchangeable with modern P/LP classifications.

3.4. Outcomes of interest and synthesis

- Primary outcome: proportion of patients with a P/LP CNV detected by CMA.
- Yield modifiers: complex/syndromic phenotype, DD/ID, dysmorphism, malformations, epilepsy, and abnormalities of growth or head circumference.
- Clinical utility: tests, referrals, surveillance, or counseling generated by a molecular result.
- Secondary outcomes: VUS, technical limitations, and conceptual comparison with ES/GS.

No meta-analysis was performed because of clinical, technological, and temporal heterogeneity across cohorts: differing definitions of syndromic/nonsyndromic ASD, array platforms and resolutions, reporting policies, and classification criteria. Ranges, denominators, and within-cohort comparisons were prioritized. The base review rated seven studies as having low risk of bias, two as moderate risk, and four as high risk. ^[10]

4. Results

4.1. Contemporary overview

Ahmed et al. included 13 contemporary studies and 11,535 children. Across the combined DD/ID/ASD population, study-level P/LP yields ranged from 11.0% to 37.2%, with a median of 18.5%. However, when the ASD phenotype was considered separately, the range was clearly lower: 3.3%-15.2%. In DD/ID, the range was 17.1%-33.6% and reached 27.4% when DD/ID co-occurred with multiple congenital anomalies. VUS affected approximately 2.7%-12% of children in studies that reported them. ^[10] These data support the view that CMA yield is not a fixed property of the technology, but rather a function of the population in which it is applied.

Study	N	Population	P/LP / diagnostic yield	Comment
McGrew et al., 2012 ^[15]	85	Pediatric ASD practice	8/85 clinically significant = 9.4%	Total "abnormal CMA" 24%; only 8 were clinically significant.
Tammimies et al., 2015 ^[3]	258	ASD stratified by morphology	24/258 = 9.3%	Essential 4.2%; equivocal 10.8%; complex 24.5%.
Hnoonual et al., 2017 ^[16]	114	Thai ASD; subgroup with DD	7/114 = 6.1%	Additionally, 19.3% VUS; underrepresented population.
Sandoval- Talamantes et al., 2023 ^[18]	212	Primary/nonsyndromic ASD	28/212 = 13.2%	Custom array; demonstrates variability even within "nonsyndromic" ASD.
Cucinotta et al., 2023 ^[19]	329	Clinical ASD	50/329 = 15.2%	89/329 VUS (27.1%); retrospective series with clinical-impact data.
Lowther et al., 2023 ^[8]	1,612 families	ASD quartet; GS/CMA/ES comparison	CMA 4.3%	GS 7.8%; ES 2.7%, or 7.4% when CNV detection in ES was optimized.
Reka et al., 2026 ^[20]	234	Pediatric ASD	8.55%	Retrospective cohort; marked CNV heterogeneity.
Tüysüz et al., 2026 ^[11]	163	Essential vs complex ASD	7.4% overall	Complex 17.1%; essential 4.7%; higher positivity with IQ <50.
Santos et al., 2026 ^[12]	215	Rigorously nonsyndromic ASD	6/215 = 2.8% (95% CI 1.3–6.1)	Excluded dysmorphism, suspected syndromes, MCA, epilepsy, and micro/macrocephaly.

Table 1. Selected studies reporting CMA yield in ASD.

The figures should not be mechanically averaged. A 2.8% yield in rigorously nonsyndromic ASD and a 15.2% yield in a more heterogeneous clinical cohort can both be correct. The difference reflects phenotypic selection, platform, classification, and referral context.

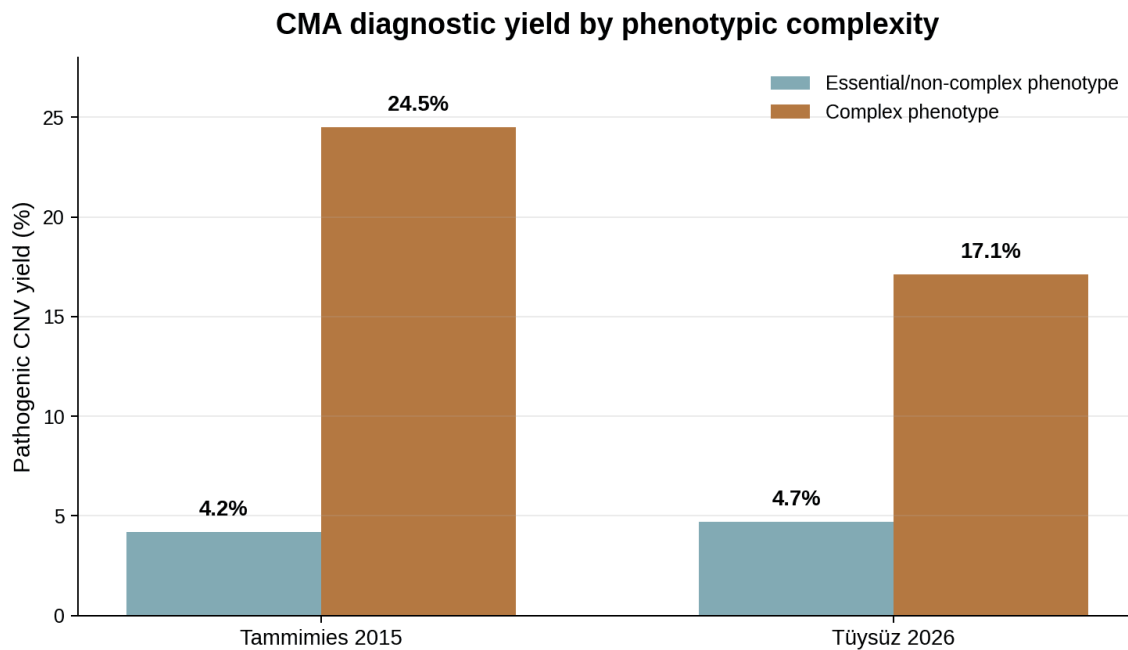
Interpretation of Table 1.

4.2. Phenotypic complexity and diagnostic yield

The most consistent finding is the gradient in yield according to phenotypic complexity. Tammimies et al. classified 258 children with ASD according to morphologic abnormalities. CMA yield was 4.2% (7/168) in the essential group, 10.8% (4/37) in the equivocal group, and 24.5% (13/53) in the complex group. Among 95 children who underwent both CMA and WES, the combined molecular yield was 6.3% in essential ASD and 37.5% in complex ASD. ^[3]

Eleven years later, Tüysüz et al. reproduced the same pattern in 163 Turkish children: pathogenic CNVs were found in 7.4% overall, but in 17.1% of the complex phenotype group and 4.7% of the essential group. Positivity was significantly higher in individuals with IQ <50, whereas verbal versus nonverbal status did not discriminate the result. ^[11]

Santos et al. provided the most recent contrast. They selected 215 individuals with clinically nonsyndromic ASD and excluded dysmorphism, known or suspected syndromes, major malformations, epilepsy, and macrocephaly/microcephaly. Only six had P/LP CNVs: 2.8% (95% CI 1.3%–6.1%). ^[12] This cohort reinforces that the absence of syndromic "red flags" substantially reduces CMA yield, although it does not reduce it to zero.



Descriptive comparison; phenotype definitions were not identical across studies and no meta-analysis was performed.

Figure 2. CMA diagnostic yield according to phenotypic complexity in two cohorts with essential/complex stratification. No statistical pooling was performed because of differences in definitions and study design. ^{[3][11]}

In a neurodevelopmental genetics clinic including 537 patients with ASD, global developmental delay and/or ID, Postma et al. found that the probability of a genetic diagnosis was approximately three times higher in syndromic than in nonsyndromic patients (OR 3.09; 95% CI 1.46–6.83). In that cohort, multigene sequencing (panel or exome) had an 8% yield, compared with 4% for CMA and fragile X testing combined. ^[4] Although the population was not exclusively ASD, the study supports the value of phenotyping before selecting the testing technology.

4.3. Deletion/duplication syndromes and relevant recurrent CNVs

A positive CMA result should not be interpreted simplistically as "genetic autism". It often identifies a genomic syndrome in which ASD is one dimension of a multisystem phenotype. Table 2 summarizes examples of high clinical value. Percentages vary by age, definition, and series; therefore, associations and clinical consequences are emphasized rather than a single prevalence estimate.

CNV / syndrome	Neurodevelopmental phenotype	Extra-neurodevelopmental implications	Interpretation point
16p11.2 recurrent deletion ^[21]	Speech/language, coordination, cognitive and psychiatric difficulties; ASD in a relevant proportion.	Childhood-onset obesity and seizures in a subgroup; growth and neurologic follow-up.	CMA detects the deletion; phenotype is variable and penetrance is not absolute.
16p11.2 duplication ^[21]	DD/ID, language difficulties, ADHD, anxiety, and ASD; variable expressivity.	May be associated with growth and neurologic features that differ from the reciprocal deletion.	Interpret size, gene content, and inheritance; the reciprocal CNV does not produce a perfect "mirror phenotype".
15q11.2-q13.1 maternal duplication / dup15q ^[22]	Hypotonia, DD, ID, ASD, and epilepsy; greater burden in idic(15).	High seizure risk; neurology referral and specific surveillance may be required.	Parental origin is critical because of imprinting; CMA may require complementary studies.
15q13.3 recurrent deletion ^[23]	DD/ID, epilepsy, ADHD, ASD, and psychiatric disorders.	Incomplete penetrance; a parent may be mildly affected or apparently unaffected.	Do not infer causality from presence alone; correlate phenotype and inheritance.
22q13.3 / SHANK3 deletion (Phelan-McDermid) ^[24]	Hypotonia, absent or severely delayed speech, ID, ASD/autistic features, possible regression.	Epilepsy and other systemic findings may require surveillance.	CMA detects deletions; intragenic SHANK3 variants require sequencing.
22q11.2 deletion ^[25]	Learning difficulties, ADHD, anxiety, ASD, and psychiatric vulnerability.	Cardiac disease, palate abnormalities, immune dysfunction, hypocalcemia, and renal anomalies may change follow-up.	Classic example of a CNV in which the diagnosis extends beyond the behavioral phenotype.

CNV / syndrome	Neurodevelopmental phenotype	Extra-neurodevelopmental implications	Interpretation point
3q29 deletion ^[26]	DD/ID, ASD, anxiety, ADHD, and increased neuropsychiatric risk.	Feeding/GI problems, cardiac disease, and neurologic findings in subgroups.	Important for longitudinal surveillance, including mental health.
7q11.23 duplication ^[27]	Speech/language delay, apraxia/dysarthria, social anxiety, selective mutism, ADHD, and ASD.	Social anxiety may overlap with social-communication difficulties.	Clinical assessment should avoid attributing all social avoidance to primary ASD.
1q21.1 deletion/duplication ^[28]	DD, learning difficulties, ADHD, and autistic features; microcephaly is more typical with deletion and macrocephaly in some duplications.	Highly variable expressivity and incomplete penetrance.	Parental testing may alter recurrence counseling and interpretation.
17p11.2 deletion - Smith-Magenis ^[29]	DD/ID, language difficulties, challenging behavior, stereotypies, and ASD/ADHD features.	Circadian sleep disorder and self-injurious behavior are important clinical clues.	CMA detects the deletion; RAI1 variants may require sequencing.
17p11.2 duplication - Potocki-Lupski ^[30]	DD/ID, language difficulties, ADHD/anxiety, and autistic features in a proportion of patients.	Hypotonia, feeding difficulties, and cardiac disease may occur.	CMA is a principal testing method for the recurrent duplication.
17q12 deletion ^[31]	DD/ID and neuropsychiatric phenotypes that may include ASD.	Renal/urinary anomalies and MODY5 diabetes may be clinically decisive.	Example of a CNV whose identification changes renal and endocrine surveillance.
2p16.3 / NRXN1 deletion ^[12]	Language difficulties, DD/ID, ASD, epilepsy, and other neuropsychiatric phenotypes.	Marked heterogeneity; risk is not uniform across deletions.	Interpret whether the deletion affects exons and its genomic

CNV / syndrome	Neurodevelopmental phenotype	Extra-neurodevelopmental implications	Interpretation point
			context; Santos et al. detected one P/LP case.

Table 2. Recurrent CNVs and examples of clinical utility.

4.4. Diagnostic yield is not the same as clinical utility

Diagnostic yield answers how many patients receive a P/LP molecular result. Clinical utility asks a different question: does the result change surveillance, testing, treatment, reproductive counseling, or family evaluation? Available evidence does not support assuming that every P/LP result generates the same benefit, nor that a low yield implies lack of value.

Coulter et al. reviewed 1,792 patients with DD/ID, ASD, and/or congenital anomalies. A total of 13.1% had results considered clinically relevant under the terminology of the time; abnormal variants generated recommendations for clinical action in 54%, compared with 34% for variants of possible significance. ^[14] Although this was a historical and heterogeneous series, it demonstrates the mechanism by which a CMA result can change care through referrals, imaging, or specific laboratory testing.

In a more recent ASD cohort, Cucinotta et al. identified P/LP CNVs in 50 of 329 patients (15.2%). In 13 of these 50 patients (26%), the finding led to 25 additional medical evaluations, including brain MRI, EEG, ECG, and echocardiography; 12 of 25 evaluations (48%) identified new findings. ^[19] This is clinically relevant, but the evidence comes from a retrospective design.

The contemporary systematic review by Ahmed et al. identified a key limitation: none of the included studies prospectively documented change in management as a predefined outcome. ^[10] It is therefore reasonable to state that examples of actionability and retrospective evidence of impact exist, but not that the prospective clinical utility of CMA in ASD has been quantified with the same strength of evidence as its diagnostic yield.

4.5. Variants of uncertain significance: a source of information and interpretive risk

VUS are common, and their frequency depends on platform, reporting policy, population databases, and laboratory criteria. The contemporary review found approximately 2.7%-12% in studies reporting VUS,

while some individual ASD cohorts reported higher rates. ^{[10][19]} A VUS is not equivalent to a confirmed etiology and should not be converted into a causal label simply because it includes a gene associated with neurodevelopment.

The ACMG/ClinGen framework recommends integrating size, gene content, evidence of haploinsufficiency/triplosensitivity, population frequency, case data, and segregation. ^[5] Parental testing can provide evidence, but inheritance from an apparently unaffected parent does not automatically make a CNV with incomplete penetrance benign; likewise, a de novo CNV is not automatically pathogenic. Periodic reanalysis may reclassify variants as the evidence base grows.

4.6. What CMA detects and what it may miss

The main strength of CMA is the detection of submicroscopic gains and losses of genetic material. SNP-array platforms can also reveal regions of absence of heterozygosity. However, a normal result does not exclude a genetic etiology. ^{[1][5]}

Test	Detects especially well	Major limitations	Conceptual use
CMA / array- CGH / SNP- array	CNVs (deletions/duplications), aneuploidies; SNP-array may reveal AOH	Most small SNVs/indels; balanced rearrangements; many repeat expansions; some low-level mosaicism; imprinting mechanisms without dosage change	Main question: change in genomic dosage/copy number.
Karyotype	Large aneuploidies and chromosomal rearrangements, including many balanced rearrangements	Submicroscopic CNVs	Useful when a balanced rearrangement, visible chromosomal syndrome, or specific reproductive context is suspected.
FMR1 / targeted expansion testing	CGG expansion associated with fragile X syndrome	Most CNVs and variants in other genes	Not replaced by a normal CMA.
Targeted methylation / imprinting testing	Methylation abnormalities and selected mechanisms of PWS/Angelman or other imprinting disorders	Most SNVs and CNVs outside the target region/assay	Choose when the phenotype or region requires demonstration of an imprinting mechanism.
Exome (ES)	SNVs/indels in coding regions; some pipelines detect CNVs	Variable coverage of noncoding regions, repeat expansions, and certain complex SVs	Yield depends strongly on CNV analysis and the pipeline.
Genome (GS)	SNVs/indels plus a broader spectrum of CNVs/SVs and noncoding regions	Does not eliminate interpretation challenges; some expansions/imprinting mechanisms require specific methods	May unify several variant classes, but access and clinical validation vary.

Table 3. Simplified comparison of relevant genetic technologies.

4.7. CMA versus exome and genome sequencing in the current era

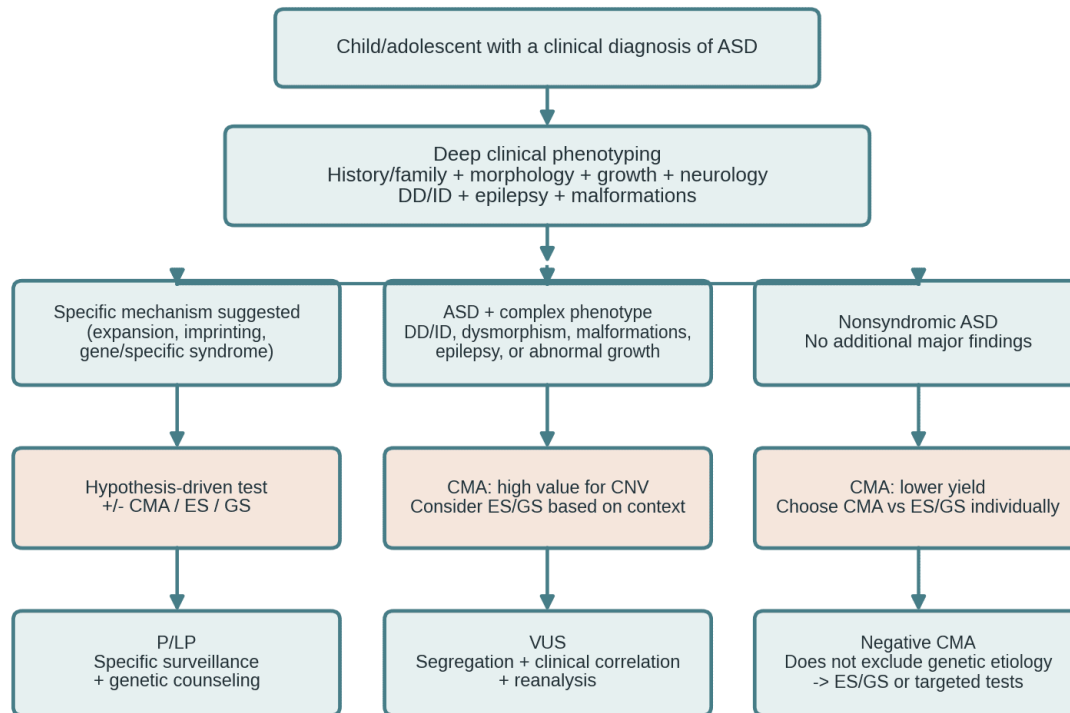
Technological advances require moving beyond a rigid hierarchy of "CMA first, everything else later" for all phenotypes. ACMG recommends considering ES/GS as a first- or second-tier test in children with congenital anomalies or DD/ID. ^[6] In its 2025 update for DD/ID, the AAP emphasizes phenotype-based selection and an agnostic approach when no specific hypothesis emerges. ^[7] These recommendations apply more clearly to DD/ID and congenital anomalies than to isolated ASD and therefore should not be extrapolated without nuance.

In 1,612 quartet ASD families, Lowther et al. compared matched GS, CMA, and ES data. Diagnostic yield was 7.8% for GS, 4.3% for CMA, and 2.7% for ES under standard analysis; when systematic CNV detection was implemented in exome data, ES yield increased to 7.4%. GS added only 0.4% beyond the combination of standard tests in that cohort, although it detected variant classes inaccessible or difficult to detect with other technologies. ^[8] This study shows that the comparison of "CMA vs ES" depends not only on the technology itself but also on the analytical pipeline.

In practice, CMA remains a robust, standardized tool directly focused on CNVs. ES/GS broaden the search to sequence variants and, increasingly, CNVs/SVs. The contemporary approach may therefore be sequential or concurrent depending on phenotype, resources, availability, turnaround time, and genetic interpretation capacity.

5. Evidence-based clinical algorithm proposal

The reviewed evidence supports an algorithm that begins before the test is ordered. The goal is to define which genetic mechanism is plausible and what the pretest probability of a CNV is. This avoids two opposite errors: ordering CMA indiscriminately without phenotyping, or concluding that CMA has no value because its yield is low in essential ASD.



Always interpret the result in clinical context. This algorithm does not replace clinical genetics consultation or local guidelines.

Figure 3. Conceptual algorithm integrating phenotype and test selection. DD/ID: developmental delay/intellectual disability; P/LP: pathogenic/likely pathogenic; VUS: variant of uncertain significance. Adapt to clinical genetics practice and local guidelines. ^{[5][6][7]}

5.1. Features that increase pretest probability

- Intellectual disability or global developmental delay, especially when moderate/severe or affecting multiple developmental domains.
- Dysmorphic features or multiple minor anomalies suggesting altered morphogenesis.
- Major congenital malformations or multisystem involvement.
- Epilepsy, focal neurologic findings, or an additional neurologic phenotype.
- Microcephaly, macrocephaly, or abnormal growth patterns.
- Hypotonia, significant feeding problems, regression, or a combination suggesting a specific syndrome.
- Family or reproductive history suggesting an inherited chromosomal abnormality.

These features are not absolute requirements for ordering CMA and do not imply that a child without them lacks genetic risk. They act as modifiers of pretest probability and help determine whether the main question concerns a CNV, a sequence variant, a repeat expansion, an imprinting mechanism, or a broader genomic strategy. ^{[3][4][7][10][11][12]}

6. Discussion

6.1. *Is chromosomal microarray useful in autism?*

Yes, but with an important condition: its utility is greater when the clinical question concerns a genomic dosage alteration and when the phenotype increases the pretest probability of a CNV. The evidence does not support a uniform yield for "autism" as a homogeneous category. In clinical ASD cohorts, P/LP yields are often in the high single digits or low double digits, but may fall to 2.8%-4.7% in strictly nonsyndromic/essential populations and exceed 17%-24% in complex subgroups. ^{[3][10][11][12]}

This variation explains why two apparently contradictory studies may both be correct. The clinical denominator matters as much as the platform. A genetics service receiving children with ASD, ID, dysmorphism, and congenital anomalies selects a high-risk population; a cohort that explicitly excludes these features addresses a different question. Therefore, reporting a single "microarray yield in autism" percentage without describing the phenotype is methodologically insufficient.

6.2. *An ASD diagnosis should not end etiologic reasoning*

Identification of a CNV can redefine the case: the child does not simply have "ASD plus a genetic alteration," but rather a genomic syndrome with its own neurodevelopmental, medical, and risk profile. This is particularly evident in 22q11.2 deletion, 17q12 deletion, dup15q, Phelan-McDermid syndrome, or 16p11.2, where the diagnosis may trigger specific cardiac, renal, endocrine, immune, neurologic, or metabolic surveillance. ^{[21][22][23][24][25][26][27][28][29][30][31]}

Clinical value, therefore, should not be measured only by the percentage of positive tests. A molecular diagnosis may also end a diagnostic odyssey, guide recurrence counseling and family testing, anticipate complications, and avoid nonspecific investigations. Even so, these benefits should be measured prospectively so that clinical plausibility is not converted into an unproven claim of effectiveness. ^{[10][14][19]}

6.3. A normal CMA is not a "normal genetic test"

This is one of the most important messages for clinical practice. CMA may be normal in a child with a monogenic condition caused by an SNV/indel, a repeat expansion, an imprinting disorder, a balanced rearrangement, or a structural variant outside the assay's sensitivity. Phelan-McDermid syndrome is illustrative: a 22q13.3 deletion involving SHANK3 may be detected by CMA, but a pathogenic intragenic SHANK3 variant requires sequencing. ^[24]

Similarly, a dosage finding in an imprinted region may not fully resolve the mechanism. In dup15q, Prader-Willi syndrome, or Angelman syndrome, parental origin and/or methylation may be essential for interpreting the result. A modern algorithm should be organized around mechanism and phenotype rather than a rigid list of universal tests.

6.4. CMA or ES/GS as the first test?

The evidence does not support a universal answer for all ASD. In children with DD/ID, congenital anomalies, and a complex phenotype, ES/GS has an increasingly strong first-line role, and CMA may be performed concurrently or as a complement depending on the pipeline's ability to detect CNVs. ^{[6][7][8]} In strictly nonsyndromic ASD, CMA yield is lower, making it especially important to discuss with the family the purpose of testing, the possibility of a VUS, and sequencing alternatives. ^[12]

Test selection also depends on the local health-system architecture: coverage, turnaround time, availability of trio testing, validation of CNVs detected by ES/GS, and access to clinical genetics. Therefore, the conclusion should be neither "abandon CMA" nor "perform CMA in everyone regardless of phenotype," but rather to integrate CMA into a stepwise or combined genomic strategy.

7. Limitations

- The update relied on a four-database systematic review published in 2026 and performed a focused search after June 26; it did not repeat the four databases de novo for the entire historical period. This is stated explicitly to avoid presenting as original a selection process that was not fully re-executed.
- ASD studies differ in diagnostic criteria, age, referral patterns, definition of a "syndromic/complex" phenotype, and proportion of DD/ID, limiting direct comparisons.
- CMA platforms differ in resolution and in their ability to detect AOH; reporting thresholds and criteria have also evolved over more than 15 years.

- Historical categories such as "abnormal," "clinically significant," or "possible significance" are not identical to the current ACMG/ClinGen P/LP/VUS classification.
- Clinical utility has been measured mainly in retrospective and heterogeneous studies. The contemporary review did not identify studies that prospectively documented change in management as the primary outcome.
- No meta-analysis was performed because of substantial heterogeneity and the intention to preserve phenotypic stratification rather than generate a potentially misleading average.
- This review was not prospectively registered; it should be considered a focused update addressing a clinical question rather than a formal clinical practice guideline.

8. Conclusions

Chromosomal microarray remains useful in the genetic evaluation of ASD because it identifies submicroscopic deletions and duplications that may establish a genomic syndrome, modify follow-up, and provide recurrence information. However, its yield is not uniform and appears to be strongly influenced by phenotypic complexity.

The most consistent evidence shows a gradient: yields around 3%–5% in rigorously nonsyndromic or essential cohorts versus approximately 17%–25% in complex-phenotype subgroups in studies that specifically stratified morphology and comorbidities. [\[3\]\[11\]\[12\]](#) Therefore, DD/ID, dysmorphism, malformations, epilepsy, and abnormalities of head size or growth should be considered central information when estimating pretest probability.

A negative CMA does not exclude a genetic etiology and should not end the evaluation when clinical suspicion persists. ES, GS, FMR1, methylation/imprinting studies, and other targeted tests answer questions that CMA cannot resolve. The most robust current approach is a phenotype- and mechanism-guided genetic evaluation with sequential or concurrent selection of technologies.

CMA remains useful in ASD, but its greatest value emerges when it is no longer ordered simply "because of the autism label" and instead becomes part of a deep genetic evaluation of the phenotype aimed at identifying a genomic syndrome and anticipating its clinical consequences.

Clinical conclusion in one sentence

Statements and Declarations

Funding

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Potential Competing Interests

No potential competing interests to declare.

Ethics

This manuscript is a review of published literature and does not use primary patient data, biological samples, or identifiable information; therefore, ethics committee approval is not required for its preparation.

Data Availability

All numerical data presented are derived from the cited publications. Individual clinical evaluation and the indication for genetic testing should follow clinical genetics standards, local regulations, informed consent, and pre- and post-test counseling.

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