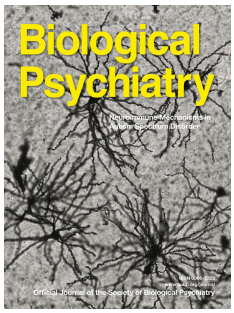


# Clinical Genetic Testing in Schizophrenia: A Systematic Review and Meta-Analysis

Harman Singh Brah, MD, Nimrat Sran, Sanjana Sanghani, BS, Luke Valmadrid, BS, Isabel Gandarilla, BS, Savannah Fakhouri, BS, Emma Longmire, BS, Karen M. Heskett, MSI, Kimberley Marie Kendall, MBBCh, PhD, Armin Raznahan, MD, PhD, Danielle Baribeau, MD, PhD, Chun Chieh Fan, MD, PhD, Aaron D. Besterman, MD

PII: S0006-3223(25)01485-4

DOI: https://doi.org/10.1016/j.biopsych.2025.09.010

Reference: BPS 15929

To appear in: *Biological Psychiatry*

Received Date: 18 November 2024

Revised Date: 17 September 2025

Accepted Date: 21 September 2025

Please cite this article as: Brah H.S., Sran N., Sanghani S., Valmadrid L., Gandarilla I., Fakhouri S., Longmire E., Heskett K.M., Kendall K.M., Raznahan A., Baribeau D., Fan C.C. & Besterman A.D., Clinical Genetic Testing in Schizophrenia: A Systematic Review and Meta-Analysis, *Biological Psychiatry* (2025), doi: https://doi.org/10.1016/j.biopsych.2025.09.010.

# Clinical Genetic Testing in Schizophrenia: A Systematic Review and Meta-Analysis

**Short Title:** Genetic Testing in Schizophrenia

Harman Singh Brah, MD[1,2]; Nimrat Sran[3]; Sanjana Sanghani, BS[1]; Luke Valmadrid, BS[1]; Isabel Gandarilla, BS[1]; Savannah Fakhouri, BS[1]; Emma Longmire, BS[1]; Karen M. Heskett, MSI[1,4]; Kimberley Marie Kendall, MBBCh, PhD[5]; Armin Raznahan, MD, PhD[6]; Danielle Baribeau, MD, PhD[7,8,9]; Chun Chieh Fan, MD, PhD[10]; Aaron D. Besterman, MD[11,12,13, *]

**Affiliations**

1. University of California, San Diego, School of Medicine, San Diego, CA
2. Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles, CA, USA.
3. Department of Chemistry and Biochemistry, Loyola Marymount University, Los Angeles, CA
4. University of California Library, San Diego, California, USA
5. Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff CF24 4HQ, United Kingdom

6. Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD
7. Department of Psychiatry, University of Toronto, Canada.
8. Department of Psychiatry, Hospital for Sick Children, Toronto, ON, Canada.
9. Autism Research Centre, Holland Bloorview Kids Rehabilitation Hospital, Toronto, ON, Canada.
10. Center for Population Neuroscience and Genetics, Laureate Institute for Brain Research, Tulsa, Oklahoma, USA
11. University of California San Diego, Department of Psychiatry, San Diego, CA, USA
12. Laura Rodriguez Research Institute of Family Health Centers of San Diego, San Diego, CA, USA
13. Rady Children's Institute for Genomic Medicine, San Diego, CA, USA

* Corresponding Author:

Aaron D. Besterman

abesterman@health.ucsd.edu

Address: 823 Gateway Center Way, San Diego, CA 92102

Phone: (619) 906-4587

Word Count: 4807

**Abstract**

**Background:**

Genetic testing may provide important diagnostic information for individuals with schizophrenia, but the frequency with which clinically significant variants are identified across different testing approaches has not been systematically evaluated.

**Methods:**

We conducted a systematic review and meta-analysis searching MEDLINE, EMBASE, and APA PsycINFO (January 2007–June 2023) for studies reporting results of clinical genetic testing in schizophrenia. Two independent reviewers performed abstract/title screening, full-text review, and data extraction following PRISMA guidelines. A random-effects model was used to estimate the pooled and platform-specific proportions of individuals with pathogenic or likely pathogenic variants, with heterogeneity assessed using the $I^2$ statistic.

**Results:**

Analysis of 31 studies (20,476 participants) showed that 6% (95% CI: 4% to 7%) of individuals with schizophrenia had a clinically significant genetic variant identified. Detection rates were 6% (95% CI: 4% to 8%) for chromosomal microarray, 5% (95% CI: –0.02% to 12%) for exome sequencing, and 7% (95% CI: 2% to 12%) for genome sequencing. Substantial heterogeneity was observed across studies ($I^2$ = 95.9%).

Geographic representation was limited, with no studies from Latin America, South Asia, or Africa.

**Conclusions:**

Genetic testing identifies clinically informative variants in approximately 6% of individuals with schizophrenia. However, substantial heterogeneity across studies and limited geographic representation underscore the need for more standardized testing approaches and broader population sampling in future genetic research on schizophrenia.

## Introduction

Schizophrenia is a severe psychiatric disorder with a global lifetime prevalence of approximately 1% (1). It is clinically characterized by hallucinations, delusions, motivational and cognitive dysfunction and is associated with significant functional impairment (2). Due to the enormous individual and societal burden of schizophrenia, there has been a concerted effort to understand its genetic basis in hopes of improving both diagnosis and treatment (3). Advances in genetic sequencing technologies have allowed for the investigation of the genetic architecture of schizophrenia (4). Both small effect-size common variants (e.g. single nucleotide polymorphisms {SNPs}) and large effect-size rare variants (e.g. copy number variants {CNVs} and single nucleotide variants {SNVs}) contribute to the genetic risk of schizophrenia (5–10).

Clinical genetic tests, such as chromosomal microarray (CMA), exome sequencing (ES), and genome sequencing (GS), are routinely used to detect large-effect size, rare SNVs and CNVs in several neurodevelopmental disorders (NDDs), including intellectual disability (ID) (11), developmental delay (DD) (12), autism spectrum disorders (ASD) (12), cerebral palsy (CP) (13), and epilepsy (14), but their use in schizophrenia is not yet widespread (15). A lag in identifying high-confidence rare genetic variants (5)a lack of genetics education in psychiatry (16), and less certain clinical benefit (15) all likely contribute to differences in genetic testing practices between individuals with other NDDs and schizophrenia.

## Table 1. Variants Detected at Elevated Rates in Schizophrenia Cohorts With Clinical Implications

| Genetic Variant[a] | Type | Clinical Implications | Reference(s) for Clinical Implications | Odds Ratio[b] | UKBB Prevalence Per 100,000[c] |
|---|---|---|---|---|---|
| 22q11.2 deletion | CNV | Routine neurocognitive surveillance to detect cognitive decline and support academic needs<br><br>Screen for early-onset Parkinsonism due to increased risk in adults<br><br>Monitor calcium, thyroid, and cardiac status as abnormalities may present with neuropsychiatric symptoms | (17,18) | 67.7 | 2.2 |
| 3q29 deletion | CNV | Increased anxiety and social disability; early behavioral support recommended<br><br>Feeding and growth issues may occur; monitor nutritional status<br><br>Consider cardiac and GI evaluation given associated anomalies | (19) | 57.7 | 2.0 |
| *NRXN1* deletion | CNV | Consider baseline EEG even without overt seizures, given elevated risk<br><br>Cardiology evaluation if any history or findings suggest possible congenital heart disease | (20) | 14.4 | 38.3 |
| 15q13.3 deletion | CNV | Elevated rates of aggressive and impulsive behavior in addition to schizophrenia<br><br>If co-managing psychiatric symptoms with epilepsy, consider avoiding oxcarbazepine because of reports of clinical worsening and consider prioritizing valproate because of reported effectiveness<br><br>Case reports of improved aggression and cognition with galantamine use, that may reflect correction of deficits in α7 nicotinic cholinergic receptor mediated neurotransmission, arising from haploinsufficiency of *CHRNA7* | (21–23) | 7.5 | 10.2 |
| 15q11.2-q13.1 duplication | CNV | Maintain vigilance for new-onset or recurrent epilepsy even in adulthood; As indicated, coordinate neurology follow-up, consider baseline/updated EEG, and avoid medications that substantially lower seizure threshold. | (24) | 13.2 | 4.1 |
| 15q11.2 BP1–BP2 Deletion | CNV | Low penetrance, but highly pleiotropic. Frequently inherited from unaffected parent, which could require additional counseling | (25) | 2.2 | 380.3 |
| 7q11.23 duplication | CNV | Close monitoring for anxiety disorders, which occur at very high rates<br><br>Consider non-stimulants for managing ADHD given high rates of stimulant-induced insomnia and anxiety<br><br>Consider referral to cardiology for assessment of aortic root dilation, which approximately half of patients have<br><br>Frequent feeding and gastrointestinal issues which may be mistaken for eating disorders | (26) | 16.1 | 3.5 |
| 16p11.2 duplication | CNV | Though ASD rates are similar to deletion carriers, duplication carriers with ASD are significantly more cognitively impaired and have higher rates of focal | (27) | 11.5 | 30.9 |

| | | | | | |
|---|---|---|---|---|---|
| | | epilepsy (~19%), requiring nuanced treatment approaches | | | |
| 16p13.11 duplication | CNV | Consider cardiology referral prior to starting psychotropics with cardiac effects given elevated risk of congenital heart defects and aortic aneurysms (>20% of cases)<br><br>Low penetrance, but highly pleiotropic. Frequently inherited from unaffected parent, which could require additional counseling | (28) | 2.3 | 193.3 |
| 1q21.1 duplication | CNV | Be aware that overgrowth (i.e., macrocephaly, tall stature, and obesity) is very common in this disorder, so additional etiological work-ups (e.g. endocrine dysfunction) are more likely to be negative.<br><br>Consider cardiology referral, given high rates of congenital heart disease | (29) | 3.5 | 42.0 |
| 1q21.1 deletion | CNV | Frequently have early-onset and persistent fine motor impairments and subtle neurologic signs (e.g., tremor, hyperreflexia) that could be mistaken for psychotropic side effects.<br><br>Monitor closely for internalizing disorders during adolescence | (30) | 8.4 | 25.9 |
| *GRIN2A* | SNV | In some GRIN2A loss-of-function or null variants, L-serine may improve behavior, development, EEG findings, and/or seizures.<br><br>In GRIN2A gain-of-function variants, avoid NMDAR agonists (e.g., L-serine); in loss-of-function or null variants, use NMDAR blockers (e.g., memantine, dextromethorphan, ketamine) with caution | (31–33) | 24.1 | 4.0 |
| *SETD1A* | SNV | Reported cases of treatment-resistance and clinical deterioration. Preclinical animal studies show rescue with *LSD1* antagonism, a potential future therapy. | (43–46) | 10.3 | 5.5 |

*CNV* Copy number variant, *SNV* Single Nucleotide Variant, *UKBB* United Kingdom Biobank. [a]Variants obtained from (5,7–9). [b]Odds ratios obtained from (4,5,8–10). [c]UKBB SNV Frequencies obtained from (52) and CNV frequencies obtained from (53)

The delay in genetic translation for schizophrenia has limited the potential opportunities for patients and families to reap the established benefits of genetic testing in NDDs and may further exacerbate healthcare disparities for those with mental illness. For example, genetic testing can inform reproductive decision-making, empower families to make more informed healthcare decisions, inform prognosis and medical surveillance, allow for gene-based clinical trial referral, and, in some instances, lead to changes in medical

and psychiatric management (Table 1) (16,54). Additional schizophrenia-associated rare variants *without* clinical implications are listed in the supplement (Table S1).

The significant uncertainty in the diagnostic yield of genetic testing for schizophrenia is an additional major barrier to appropriate implementation (12). Diagnostic yield refers to the rate at which pathogenic or likely pathogenic (P/LP) genetic variants are identified through clinical genetic testing. For virtually all psychiatric disorders, an identified genetic variant does not account for the full underlying disease risk, as many additional environmental, genetic, and epigenetic factors contribute beyond the P/LP variant (15). Moreover, in schizophrenia, these variants are neither necessary nor sufficient for diagnosis, and are often pleiotropic, associated with a broad range of neurodevelopmental and psychiatric outcomes. This means that the presence of a variant does not imply specificity to schizophrenia, nor does its absence rule out genetic contributions. Many individuals in the reviewed studies likely had co-occurring neurodevelopmental conditions such as intellectual disability, autism, or epilepsy, which may not have been consistently reported or fully characterized, especially in older studies. As a result, the reported detection rates may not generalize to the broader population of individuals with “typical” adult-onset schizophrenia without such comorbidities. Additionally, the landscape of variant detection is evolving, with earlier identification in childhood and improvements in variant classification over time—rendering “yield” a moving target. Current estimates of diagnostic yield range from as low as 1% (16) to as high as 51% (17). Without more reliable and contextually nuanced

estimates across genetic testing platforms—similar to those available in other neurodevelopmental disorders (Table 2)—full integration of genetic testing into the clinical management of schizophrenia will remain limited (12). Therefore, we conducted a systematic review and meta-analysis of studies that performed genetic testing with CMA, ES, or GS in individuals with schizophrenia to better characterize current variant detection rates and their potential relevance to clinical care.

**Table 2. Diagnostic yield of genetic testing across neurodevelopmental disorders**

| Neurodevelopmental disorder | Chromosomal microarray (%) | Exome sequencing (%) | Genome sequencing (%) |
|---|---|---|---|
| DD and/or ID | 15 – 20 (58) | 31(12) – 34 (11) | 35 - 43 (11,59,60) |
| ASD | 4.3 (61) - 9.3 (61) | 2.7 (61) - 8.4 (61) | 7.8 (61) – 10 (62) |
| Epilepsy | 8 (63) | 45 (63) | 47.5 (64) |
| Cerebral Palsy | 5 (13) | 31.1 (65) | 11.3 (66) |

*ASD* = Autism Spectrum Disorder, *DD* = Developmental Delay, *ID* = Intellectual Disability. Numbers in brackets are references for diagnostic yield values.



## Methods

We conducted a systematic review adhering to a registered PROSPERO protocol (CRD42023409096). Data extraction was performed in accordance with the protocol, with details available on PROSPERO. (67) We collected data on demographics, clinical characteristics, methodological specifics, and study outcomes. Articles were assessed for quality using the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions)

tool (68). The review followed guidelines from the Cochrane Handbook for Systematic Reviews of Interventions (69).

In brief, we conducted a systematic review of studies across the MEDLINE/PubMed (pubmed.gov), EMBASE (embase.com), and APA PsycINFO (proquest.com) databases that were published between January 1, 2007, and June 2, 2023. The search strategy employed disease-specific words such as “schizophrenia”, “schizoaffective disorder”, and “psychosis”; sequencing terms including “copy number variation”, “genome sequencing”, and “chromosomal microarray”; and related content terms including “diagnostic yield”.

For a study to be included, all patients had to have undergone genetic testing with CMA, ES, or GS. The included studies must have reported the number of patients who underwent diagnostic genetic testing, the number of patients with P/LP) results, and whether or not they used the American College of Medical Genetics (ACMG)/Association for Molecular Pathology (AMP) pathogenicity criteria (70). Studies were included even if they only reported a single variant type when the genetic platform could detect multiple variant types (e.g. GS study only reports SNV yield) (Table S2). Studies included all individuals with schizophrenia spectrum disorders who underwent genetic testing, with no exclusions based on the presence of known large-effect variants such as 22q11.2 deletion syndrome (22q11DS) or other pathogenic CNVs. There were no exclusions based on patient psychiatric or medical co-occurrences. Additional

exclusion criteria included studies that examined animals only, performed in a non-English language, were literature reviews or guidelines, or did not have the patient population or outcome of interest (Table S3).

After database searches were completed, all records were imported into Covidence (Veritas Health Innovation, Melbourne, Australia), which automatically removed 2,442 duplicate records. An additional 11 duplicates were removed manually by the review team, for a total of 2,453 duplicates excluded prior to screening. The remaining 6,918 records were screened by two independent reviewers using titles and abstracts. Full-text articles were retrieved and reviewed for all 109 studies meeting inclusion criteria or requiring further clarification (Tables S3 and S4). Discrepancies at both screening stages were resolved by consensus or third-party adjudication. Thirty-one studies were ultimately included in the final review and analysis (Figure 1).

One investigator assessed the risk of bias using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) across seven distinct domains (68). These domains include: bias due to confounding; bias in selecting participants for the study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in the selection of reported results. Each of the seven domains was characterized as having low, moderate, serious, or critical risk of bias. The composite of these domains was then characterized into an overall risk of bias.

Using a random-effects model from the 'metafor' package (71) in R version 4.3.0 (2023-04-21), we computed the pooled diagnostic yield—defined as the proportion of individuals with a P/LP variant on genetic testing. Individual diagnostic yields for each sequencing modality and the presence or absence of NDDs were also calculated. Publication bias was assessed via the rank correlation test for funnel plot asymmetry. Heterogeneity was assessed by calculating the amount of heterogeneity ($\boldsymbol{\tau}^2$) and how it affected between-study variability ($I^2$) with the Wald and likelihood ratio tests.

To investigate the source of the heterogeneity, we then applied a mixed effects meta-regression, including the following study characteristics as the fixed effects: 1) genotyping platform, 2) ancestry compositions of the participants, 3) the version of ACMG criteria, 4) reported neurodevelopmental co-occurrences, 5) use of pre-selected variants, 6) proportions of biological sex, 7) year of publication, and 8) CNV reporting practices (Table S3). The co-occurrences included epilepsy, ID, ASD, attention deficit hyperactivity disorder, learning disabilities, obsessive-compulsive disorder, and DD (Table S3). Developmental delay was defined broadly as including any individual with delays in one or more milestones. Most studies were not specific enough in the use of this terminology to determine if they patients met formal diagnostic criteria for global developmental delay, having delays in ≥2 domains. We also conducted a separate meta-regression to compare the diagnostic yield of studies using ES or GS that reported both CNVs and SNVs, versus studies using CMA that reported only CNVs. This

analysis was performed to control for differences in reporting scope across sequencing platforms.

**Results**

6,918 studies were initially identified, 109 studies underwent full-text review, and 31 studies were ultimately included for data extraction (Figure 1). Of note, Farrell et al. (2023) performed both CMA and ES on their cohort and reported the CNV diagnostic yield of each platform separately, so results from that study are included in both CMA and ES analyses. Therefore, their diagnostic yield results were included in both our CMA and ES analyses. The extracted studies were published between 2008 and 2023 and analyzed 20,476 participants. Among these, twenty-seven studies focused on patients with adult-onset schizophrenia, while four studies considered patients with childhood-onset schizophrenia or early-onset psychosis and one with both age groups. Included studies reported diagnostic findings for well-established large-effect schizophrenia-associated variants (Table S3).

Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) was used to determine a composite risk of bias. Eleven of the included studies had a serious risk of bias, sixteen had a moderate risk of bias, and four had a low risk of bias (Figure S1). We stratified the included studies into cohorts based on the sequencing technology used with Farrell et al (2023) being counted in both CMA and ES groups: CMA (n = 26), ES (n = 3), and GS (n = 3). A random effects meta-analysis revealed the pooled

diagnostic yield to be 6% (95% CI 4% to 7%) (Figure 2). The diagnostic yield by sequencing subgroup was 6% for CMA (95% CI 4% to 7%), 5% for ES (95% CI -0.02% to 12%), and 7% for GS (95% CI 2% to 13%). Note that confidence intervals for subgroup estimates may extend slightly below 0 due to model-based transformation and small sample size, not reflecting true negative proportions. $I^2$ for the included studies was 95.9%, indicating substantial heterogeneity in the included cohorts. To check for publication bias, funnel plot asymmetry tests were performed (Figures S2-S5). Rank correlation tests for funnel plot asymmetry indicate publication bias in the studies that employed CMA (Kendall's tau = 0.35, p = 0.01) and in the pooled analysis (Kendall's tau = 0.43, p = 0.0004) (Figures S2 and S3). The tests for the ES and GS studies did not show significant publication bias (Kendall's tau = 1, p = 0.33 for both), but these subsets consisted only of three studies each, suggesting that they may be underpowered (Figures S4 and S5).

To better understand the high heterogeneity, we evaluated several key characteristics that varied across the studies using meta-regression: the technology used to analyze genes, the ethnic/ancestral background of the participants, which version of genetic testing guidelines was used, NDD co-occurrences, year of publication, CNV reporting practices (including size thresholds and gene annotation), whether the studies looked at specific pre-selected genetic variants, and proportion of each sex. When we accounted for all these factors, we were able to explain a significant portion of the differences between studies, reducing the unexplained variation from 97.5% to 76.9%. The

strongest driver of diagnostic yield was the presence of NDD co-occurrences, which alone explained 13.6% of between-study variance (LRT = 67.5, p < 1e-12). Specifically, intellectual disability was significantly associated with increased diagnostic yield (estimate = 0.0457, p = 0.0011), as was early age of onset (estimate = 0.0348, p = 0.0893). Studies that reported overlap of CNVs with known NDD or schizophrenia-associated genes also had significantly higher yield (Q = 9.62, p = 0.0019). Finally, more permissive CNV size thresholds (e.g., >10 kb or >20 kb) were associated with significantly higher yield (Q > 7.4, p < 0.01), suggesting that inclusive reporting practices may improve the likelihood of identifying pathogenic variants in schizophrenia. We also tested for potential time-lag bias by including publication year as a moderator in the meta-regression; however, year of publication was not significantly associated with diagnostic yield (Q = 1.98, p = 0.159), suggesting that shifts in interpretation standards over time did not substantially influence the pooled results. In a separate analysis comparing only studies that used ES or GS and reported both CNVs and SNVs (n = 3) to CMA studies reporting only CNVs (n = 24), the diagnostic yield for ES+GS studies was 7.5%, slightly higher than that of CMA studies; however, this difference was not statistically significant (estimate = –0.0160, 95% CI: –0.0688 to 0.0368, p = 0.55).

## Discussion

This systematic review and meta-analysis provides a comprehensive assessment of the diagnostic yield of genetic testing in individuals with schizophrenia, revealing a pooled diagnostic yield of 6% across all genetic testing modalities and yields of 6%, 5%, and

7% for CMA, ES, and GS, respectively. The Royal College of Psychiatrists recently recommended considering CMA testing for individuals with schizophrenia, based on a reported 2.5% yield of CNVs (72). Therefore, our observed yield estimate of 6% (an almost 2.5-fold increase) further strengthens the argument in favor of genetic testing for individuals with schizophrenia. These results suggest that genetic testing has the potential to inform (although not necessarily change) clinical management for approximately one in 17 patients with schizophrenia —a useful average estimate based on our pooled diagnostic yield of 6%. However, this figure should be interpreted in the context of substantial between-study heterogeneity, and importantly, the term "diagnostic yield" should be interpreted with caution in this context, as the identified variants are neither necessary nor sufficient for a diagnosis of schizophrenia and often show pleiotropy across multiple neurodevelopmental and psychiatric conditions. Meta-regression revealed that diagnostic yield was significantly higher in individuals with co-occurring neurodevelopmental disorders—particularly those with intellectual disability—and in those with earlier age of onset, indicating that these populations may especially benefit from clinical genetic testing, in line with Royal College of Psychiatrists guidelines (72). Previously reported enrichment of CNVs in childhood-onset schizophrenia vs adult-onset schizophrenia cohorts (73) and elevated yields (19%) in ES studies of childhood-onset schizophrenia (74) suggest that the diagnostic yield of P/LP variants in these groups may be higher than in adult-onset schizophrenia, but larger sequencing studies in young patients with NDDs and schizophrenia are required to confirm this. Our meta-regression confirms that the presence of neurodevelopmental co-occurrences is

the strongest predictor of diagnostic yield, with intellectual disability and earlier age of onset each independently associated with significantly higher yield. These findings provide further evidence to prioritize genetic testing in individuals with schizophrenia and NDD features.

We found no significant difference in diagnostic yield between CMA, ES, and GS, contrasting with some NDDs where next-generation sequencing techniques show higher yields than CMA (Table 2). This may suggest that CNVs are a relatively more frequent rare variant than SNVs in schizophrenia (5), which is different from other NDDs (75). However, if that were the case, we would expect GS, which can detect both CNVs and SNVs most reliably, to have a significantly higher diagnostic yield than either CMA or ES alone, which is not observed. One factor that could help account for this observed discrepancy is the inconsistent reporting of both SNVs and CNVs across studies. Some of the GS and ES studies only reported one variant type (Table S2) (42,76,77), which may have led to artificially depressed diagnostic yields. In a subset analysis limited to ES and GS studies that reported both CNVs and SNVs, we observed a higher diagnostic yield (7.5%) compared to CMA-only studies (6.0%), though the difference did not reach statistical significance, likely due to limited sample size. These results suggest that when both variant types are systematically reported, ES and GS may ultimately outperform CMA in diagnostic sensitivity (74,78,79). In addition, we found that more permissive CNV size thresholds and reporting of CNV overlap with neurodevelopmental or schizophrenia-associated genes were both significantly associated with higher

diagnostic yield, suggesting that inclusive and gene-informed reporting practices can improve clinical return. Taken together, this suggests that more complete reporting of variants of all types and sizes may significantly increase the diagnostic yield seen with ES and GS.

An additional factor that may have depressed diagnostic yields across all platforms is challenges in applying ACMG/AMP P/LP classification criteria to variants found in schizophrenia, which are underrepresented in clinical testing databases. Multiple individuals with the same variant and phenotype must have been previously reported and recorded in public databases such as ClinVar (80) to meet the threshold for ACMG/AMP P/LP status (70). While this is practical for disorders with high rates of clinical genetic testing and reporting, such as ID or epilepsy, it may result in many variants associated with schizophrenia being classified as variants of uncertain significance, as we have encountered in our experience with GS in early-onset psychosis (unpublished). This is further supported by the increase in diagnostic yield of GS from 1.8% to 8.9% for extremely treatment-resistant schizophrenia when pathogenicity criteria were relaxed from ACMG/AMP criteria to include any missense or loss-of-function variant in an intolerant, schizophrenia-associated genes (77). We also expect the yield of GS will likely increase over time as the role of additional variant classes detectable on GS, such as short-tandem repeats, are further characterized for schizophrenia (81). Long-term follow-up and psychiatric phenotyping of patients who receive genetic testing as part of newborn screening (82) or very early in childhood for

developmental delays (83), will help further establish associations between genetic variants and schizophrenia onset. However, clinicians will need to be increasingly conscious about appropriately counseling parents on their child's future risk of developing schizophrenia (15,84).

There are some limitations to our study. First, the lack of geographic diversity in the included studies, with notable absences from Latin America, South Asia, and Africa, limits the generalizability of our results to populations of non-European ancestry and highlights significant disparities in global genetic research. Next, we observed high heterogeneity between studies. Through meta-regression analysis, we were able to explain approximately 21% of this heterogeneity through measured variables, with NDD co-occurrences being the strongest predictor (13.6% of variation). This also is a likely underestimate of the true value, as NDDs may not have been equally captured in all study populations, as it is known that diagnostic rates vary between populations of different socioeconomic and ancestral backgrounds. Furthermore, diagnostic criteria for ASD changed in 2013, and may have resulted in a decrease in ASD prevalence by as much as 9% (85), although overall diagnostic rates of ASD have risen globally (86). How these changes impacted reported NDD co-occurrence rates is unclear and requires further follow-up. However, substantial unexplained heterogeneity remains, likely due to differences in study populations, methodologies, and unmeasured factors such as detailed clinical phenotyping methods and variant interpretation practices. Additionally, our risk of bias assessment (Figure S1) revealed that nearly half of the

included studies had a serious risk of bias, with the remainder split between moderate and low risk. In combination with the limited phenotyping data available for many cohorts, these factors make it difficult to determine the extent to which our findings generalize to individuals with “typical” adult-onset schizophrenia without cooccurring neurodevelopmental disorders. These limitations collectively highlight the need for more standardized approaches to genetic testing and variant interpretation in schizophrenia research.

Another limitation was the variability in methods for evaluating P/LP variants across studies. ACMG/AMP criteria for interpreting variant data were published in 2015 (70), while some of the included studies were published before then. Future studies should aim to use consistent methodologies and reporting standards to facilitate more robust meta-analyses and to provide clearer guidance for clinical practice. Specifically, we would recommend the following approaches (1) using consistent variant interpretation guidelines such as the ACMG/AMP criteria (70); (2) ensuring uniform diagnostic yield reporting by including all detected pathogenic or likely pathogenic variants; (3) increasing diversity by enrolling participants from underrepresented populations to ensure broader genetic representation; (4) ensuring that the presence of NDD co-occurrences are captured and reported.

Based on the findings of this systematic review and meta-analysis, genetic testing shows promise in identifying underlying genetic factors in a subset of individuals with schizophrenia. The pooled diagnostic yield of 6% suggests that genetic testing could potentially provide valuable insights for some patients. While this yield is lower than in some other NDDs, it highlights the complex genetic architecture of schizophrenia and opens avenues for further research. The results encourage continued exploration of genetic testing in schizophrenia, with the potential to inform clinical practice. However, the high heterogeneity between studies and the lack of ancestral diversity in the included studies underscores the need for more standardized approaches and broader representation in future genetic testing studies in schizophrenia. As our understanding of the genetic basis of schizophrenia continues to grow, refinement of variant interpretation methods may lead to improved diagnostic yields and, ultimately, more precision approaches to schizophrenia management. At the same time, caution is warranted when applying terms like “diagnostic yield” to schizophrenia, given the nonspecific and incompletely penetrant nature of these variants. The concept remains useful as a general indicator of returnable results, but should not be equated with diagnostic certainty. These findings lay a foundation for future research that could bridge the gap between genetic insights and clinical applications in schizophrenia care.

## Contributors

HSB and ADB conceptualized the study and its design. NS, SS, LV, IG, SF, and EL conducted the literature search, screened the articles, and did the quality assessments, supervised by HSB and ADB. NS, SS, LV, IG, SF, and EL reviewed all full texts for inclusion and collected the data independently, supervised by ADB. KMH provided expert guidance on the literature search strategy. HSB and CCF analyzed the data. KMK, AR, DB, and CCF gave expert input to data analysis and interpretation. HSB drafted the paper, supervised by ADB; all authors revised the paper and approved the final version. All authors had full access to all the data in the study. HSB and ADB verified all data and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Declaration of Interests

The authors report no biomedical financial interests or potential conflicts of interest.

## Data Sharing

The extracted study data and all code necessary for analyses from this study will be made available. The study protocol and statistical analysis plan will also be shared. These materials will be available beginning 3 months following article publication, with no end date. The data will be accessible on Dr. Besterman's website at

https://abesterman.github.io/bestermanlab.github.io/. Access will be fully available to all researchers without the need for inquiry or request.

**Acknowledgements**

ADB received funding for this study from the Transforming Mental Health Initiative, Rady Children's Hospital San Diego. Outside of this study, he was the recipient of a Young Investigator Award from the Brain and Behavior Research Foundation, a Yankelovich Center Research Grant, and a UCSD Institute of Engineering Galvanizing Engineering in Medicine Student Teams on Needed E-Health Solutions (GEMSTONES) Grant. He is an unpaid Member of the Medical and Scientific Advisory Board of the Smith-Kingsmore Syndrome Foundation. Outside of this study, DB has received research funding from MapLight therapeutics and has received grant funding from the Arthur Family Foundation and the Kimmel Foundation for supporting her research.

**Supplement Description:**
Supplement Methods, Figures S1-S5, Tables S1-S4

## References

1. Saha S, Chant D, Welham J, McGrath J (2005): A Systematic Review of the Prevalence of Schizophrenia. *PLOS Med* 2: e141.

2. Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, *et al.* (2015): Schizophrenia. *Nat Rev Dis Primer* 1: 1–23.

3. Owen MJ, Legge SE, Rees E, Walters JTR, O'Donovan MC (2023): Genomic findings in schizophrenia and their implications. *Mol Psychiatry* 28: 3638–3647.

4. Kato H, Kimura H, Kushima I, Takahashi N, Aleksic B, Ozaki N (2023): The genetic architecture of schizophrenia: review of large-scale genetic studies [no. 3]. *J Hum Genet* 68: 175–182.

5. Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD, *et al.* (2022): Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nat 2022 6047906* 604: 509–516.

6. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, *et al.* (2022): Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 604: 502–508.

7. Rees E, Kirov G (2021): Copy number variation and neuropsychiatric illness. *Curr Opin Genet Dev* 68: 57–63.

8. Chick SL, Holmans P, Cameron D, Grozeva D, Sims R, Williams J, *et al.* (2025): Whole-exome sequencing analysis identifies risk genes for schizophrenia. *Nat Commun* 16: 7102.

9. Liu D, Meyer D, Fennessy B, Feng C, Cheng E, Johnson JS, *et al.* (2023): Schizophrenia risk conferred by rare protein-truncating variants is conserved across diverse human populations. *Nat Genet* 55: 369–376.

10. Marshall CR, Howrigan DP, Merico D, Thiruvahindrapuram B, Wu W, Greer DS, *et al.* (2016): Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat Genet 2016 491* 49: 27–35.

11. Manickam K, McClain MR, Demmer LA, Biswas S, Kearney HM, Malinowski J, *et al.* (2021): 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). *Genet Med* 1–9.

12. Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, Chung WK, *et al.* (2019): Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genet Med* 21: 2413–2421.

13. Srivastava S, Lewis SA, Cohen JS, Zhang B, Aravamuthan BR, Chopra M, *et al.* (2022): Molecular Diagnostic Yield of Exome Sequencing and Chromosomal Microarray in Cerebral Palsy: A Systematic Review and Meta-analysis. *JAMA Neurol* 79: 1287–1295.

14. McKnight D, Morales A, Hatchell KE, Bristow SL, Bonkowsky JL, Perry MS, *et al.* (2022): Genetic Testing to Inform Epilepsy Treatment Management From an International Study of Clinical Practice. *JAMA Neurol* 79: 1267–1276.

15. Besterman AD (2023): A genetics-guided approach to the clinical management of schizophrenia. *Schizophr Res*. https://doi.org/10.1016/j.schres.2023.09.042

16. Besterman AD, Moreno-De-Luca D, Nurnberger JI (2019): 21st-Century Genetics in Psychiatric Residency Training: How Do We Get There? *JAMA Psychiatry* 76: 231–232.

17. Boot E, Óskarsdóttir S, Loo JCY, Crowley TB, Orchanian-Cheff A, Andrade DM, *et al.* (2023): Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med* 25: 100344.

18. McDonald-McGinn DM, Hain HS, Emanuel BS, Zackai EH (1993): 22q11.2 Deletion Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle. Retrieved July 17, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK1523/

19. Mulle JG, Gambello MJ, Sanchez Russo R, Murphy MM, Burrell TL, Klaiman C, *et al.* (1993): 3q29 Recurrent Deletion. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle. Retrieved July 17, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK385289/

20. Castronovo P, Baccarin M, Ricciardello A, Picinelli C, Tomaiuolo P, Cucinotta F, *et al.* (2020): Phenotypic spectrum of NRXN1 mono- and bi-allelic deficiency: A systematic review. *Clin Genet* 97: 125–137.

21. van Bon BW, Mefford HC, de Vries BB, Schaaf CP (1993): 15q13.3 Recurrent Deletion. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle. Retrieved July 31, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK50780/

22. Casas-Alba D, Nolasco GA, Díez-Juan M, Mezzatesta M, Balañá G, Fons C (2021): Targeted therapy with galantamine in a pediatric patient with 15q13.3 deletion syndrome. *Am J Med Genet A* 185: 3897–3899.

23. Cubells JF, Deoreo EH, Harvey PD, Garlow SJ, Garber K, Adam MP, Martin CL (2011): Pharmaco-genetically guided treatment of recurrent rage outbursts in an adult male with 15q13.3 deletion syndrome. *Am J Med Genet A* 155: 805–810.

24. Lusk L, Vogel-Farley V, DiStefano C, Jeste S (1993): Maternal 15q Duplication Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle. Retrieved July 31, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK367946/

25. Cox D, Butler M (2015): The 15q11.2 BP1–BP2 Microdeletion Syndrome: A Review. *Int J Mol Sci* 16: 4068–4082.

26. Mervis CB, Morris CA, Klein-Tasman BP, Velleman SL, Osborne LR (1993): 7q11.23 Duplication Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University

of Washington, Seattle. Retrieved July 31, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK327268/

27. D'Angelo D, Lebon S, Chen Q, Martin-Brevet S, Snyder LG, Hippolyte L, *et al.* (2016): Defining the Effect of the 16p11.2 Duplication on Cognition, Behavior, and Medical Comorbidities. *JAMA Psychiatry* 73: 20–30.

28. 16p13.11 microduplication in 45 new patients: refined clinical significance and genotype–phenotype correlations | Journal of Medical Genetics (n.d.): Retrieved July 31, 2025, from https://jmg.bmj.com/content/57/5/301?papetoc=&int_source=trendmd&int_medium=cpc&int_campaign=usage-042019

29. Dolcetti A, Silversides CK, Marshall CR, Lionel AC, Stavropoulos DJ, Scherer SW, Bassett AS (2013): 1q21.1 Microduplication expression in adults. *Genet Med* 15: 282–289.

30. Bernier R, Steinman KJ, Reilly B, Wallace AS, Sherr EH, Pojman N, *et al.* (2016): Clinical phenotype of the recurrent 1q21.1 copy-number variant. *Genet Med* 18: 341–349.

31. Mir A, Qahtani M, Bashir S (2020): GRIN2A-Related Severe Epileptic Encephalopathy Treated with Memantine: An Example of Precision Medicine. *J Pediatr Genet* 09: 252–257.

32. Strehlow V, Myers KA, Morgan AT, Hons A, Scheffer IE, Lemke JR (n.d.): GRIN2A-Related Disorders.

33. Juliá-Palacios N, Olivella M, Sigatullina Bondarenko M, Ibáñez-Micó S, Muñoz-Cabello B, Alonso-Luengo O, *et al.* (2024): L-serine treatment in patients with GRIN-related encephalopathy: a phase 2A, non-randomized study. *Brain J Neurol* 147: 1653–1666.

34. Rinaldi B, Bayat A, Zachariassen LG, Sun J-H, Ge Y-H, Zhao D, *et al.* (2024): Gain-of-function and loss-of-function variants in *GRIA3* lead to distinct neurodevelopmental phenotypes. *Brain* 147: 1837–1855.

35. XiangWei W, Perszyk RE, Liu N, Xu Y, Bhattacharya S, Shaulsky GH, *et al.* (2023): Clinical and functional consequences of GRIA variants in patients with neurological diseases. *Cell Mol Life Sci* 80: 345.

36. Lehalle D, Mosca-Boidron A-L, Begtrup A, Boute-Benejean O, Charles P, Cho MT, *et al.* (2017): STAG1 mutations cause a novel cohesinopathy characterised by unspecific syndromic intellectual disability. *J Med Genet* 54: 479–488.

37. Berecki G, Helbig KL, Ware TL, Grinton B, Skraban CM, Marsh ED, *et al.* (2020): Novel Missense CACNA1G Mutations Associated with Infantile-Onset Developmental and Epileptic Encephalopathy. *Int J Mol Sci* 21: 6333.

38. Chemin J, Siquier-Pernet K, Nicouleau M, Barcia G, Ahmad A, Medina-Cano D, *et al.* (2018): De novo mutation screening in childhood-onset cerebellar atrophy identifies gain-of-function mutations in the CACNA1G calcium channel gene. *Brain* 141: 1998–2013.

39. Ito D, Suzuki N (2009): Seipinopathy: a novel endoplasmic reticulum stress-associated disease. *Brain* 132: 8–15.

40. Ahmed MY, Chioza BA, Rajab A, Schmitz-Abe K, Al-Khayat A, Al-Turki S, *et al.* (2015): Loss of PCLO function underlies pontocerebellar hypoplasia type III. *Neurology* 84: 1745–1750.

41. Oates S, Absoud M, Goyal S, Bayley S, Baulcomb J, Sims A, *et al.* (2021): ZMYND11 variants are a novel cause of centrotemporal and generalised epilepsies with neurodevelopmental disorder. *Clin Genet* 100: 412–429.

42. Balakrishna T, Curtis D (2020): Assessment of Potential Clinical Role for Exome Sequencing in Schizophrenia. *Schizophr Bull* 46: 328–335.

43. Kummeling J, Stremmelaar DE, Raun N, Reijnders MRF, Willemsen MH, Ruiterkamp-Versteeg M, *et al.* (2021): Characterization of SETD1A haploinsufficiency in humans and Drosophila defines a novel neurodevelopmental syndrome. *Mol Psychiatry* 26: 2013–2024.

44. Colijn MA, Carrion P, Poirier-Morency G, Rogic S, Torres I, Menon M, *et al.* (2024): *SETD1A* variant-associated psychosis: A systematic review of the clinical literature and description of two new cases. *Prog Neuropsychopharmacol Biol Psychiatry* 129: 110888.

45. Singh T, Kurki MI, Curtis D, Purcell SM, Crooks L, Mcrae J, *et al.* (2016): Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. *Christina M Hultman* 19: 41.

46. Mukai J, Cannavò E, Crabtree GW, Sun Z, Diamantopoulou A, Thakur P, *et al.* (2019): Recapitulation and Reversal of Schizophrenia-Related Phenotypes in Setd1a-Deficient Mice. *Neuron* 104: 471-487.e12.

47. Varvagiannis K, Vissers LE, Baralle D, de Vries BB, Gazdagh G (1993): TRIO-Related Neurodevelopmental Disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle. Retrieved August 22, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK447257/

48. Goodspeed K, Pérez-Palma E, Iqbal S, Cooper D, Scimemi A, Johannesen KM, *et al.* (2020): Current knowledge of SLC6A1-related neurodevelopmental disorders. *Brain Commun* 2: fcaa170.

49. Goodspeed K, Demarest S, Johannesen K, Kang J, Lal D, Angione K (1993): SLC6A1-Related Neurodevelopmental Disorder. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews*®. Seattle (WA): University of Washington, Seattle. Retrieved August 22, 2025, from http://www.ncbi.nlm.nih.gov/books/NBK589173/

50. Cuinat S, Nizon M, Isidor B, Stegmann A, van Jaarsveld RH, van Gassen KL, *et al.* (2022): Loss-of-function variants in *SRRM2* cause a neurodevelopmental disorder. *Genet Med* 24: 1774–1780.

51. Palmer DS, Howrigan DP, Chapman SB, Adolfsson R, Bass N, Blackwood D, *et al.* (2022): Exome sequencing in bipolar disorder identifies AKAP11 as a risk gene shared with schizophrenia. *Nat Genet* 54: 541–547.

52. Curtis D (2022): Clinical features of UK Biobank subjects carrying protein-truncating variants in genes implicated in schizophrenia pathogenesis. *Psychiatr Genet* 32: 156.

53. Katzourou IK, Timpson N, Tsang R, Underwood J, Wood M, Kirov G, *et al.* (n.d.): Neurodevelopmental copy number variants increase risk of internalising and cardiometabolic multimorbidity: findings from UK Biobank.

54. Riggs ER, Wain KE, Riethmaier D, Smith-Packard B, Faucett WA, Hoppman N, *et al.* (2014): Chromosomal microarray impacts clinical management. *Clin Genet* 85: 147–153.

55. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger Jr JI, Hallmayer JF (2017): Autism genetics: opportunities and challenges for clinical translation. *Nat Rev Genet* 18: 362–376.

56. Levinson DF, Shi J, Wang K, Oh S, Riley B, Pulver AE, *et al.* (2012): Genome-Wide Association Study of Multiplex Schizophrenia Pedigrees. *Am J Psychiatry* 169: 963–973.

57. Xu B, Roos JL, Dexheimer P, Boone B, Plummer B, Levy S, *et al.* (2011): Exome sequencing supports a de novo mutational paradigm for schizophrenia. *Nat Genet* 43: 864–868.

58. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, *et al.* (2010): Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies. *Am J Hum Genet* 86: 749–764.

59. Lindstrand A, Ek M, Kvarnung M, Anderlid B-M, Björck E, Carlsten J, *et al.* (2022): Genome sequencing is a sensitive first-line test to diagnose individuals with intellectual disability. *Genet Med* 24: 2296–2307.

60. Lionel AC, Costain G, Monfared N, Walker S, Reuter MS, Hosseini SM, *et al.* (2018): Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test [no. 4]. *Genet Med* 20: 435–443.

61. Tammimies K, Marshall CR, Walker S, Kaur G, Thiruvahindrapuram B, Lionel AC, *et al.* (2015): Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder. *JAMA* 314: 895.

62. Callaghan DB, Rogic S, Tan PPC, Calli K, Qiao Y, Baldwin R, *et al.* (2019): Whole genome sequencing and variant discovery in the ASPIRE autism spectrum disorder cohort. *Clin Genet* 96: 199–206.

63. Sánchez Fernández I, Loddenkemper T, Gaínza-Lein M, Sheidley BR, Poduri A (2019): Diagnostic yield of genetic tests in epilepsy. *Neurology* 92: e418–e428.

64. Lee H-F, Chi C-S, Tsai C-R (2021): Diagnostic yield and treatment impact of whole-genome sequencing in paediatric neurological disorders. *Dev Med Child Neurol* 63: 934–938.

65. Gonzalez-Mantilla PJ, Hu Y, Myers SM, Finucane BM, Ledbetter DH, Martin CL, Moreno-De-Luca A (2023): Diagnostic Yield of Exome Sequencing in Cerebral Palsy and Implications for Genetic Testing Guidelines: A Systematic Review and Meta-analysis. *JAMA Pediatr* 177: 472–478.

66. Fehlings DL, Zarrei M, Engchuan W, Sondheimer N, Thiruvahindrapuram B, MacDonald JR, *et al.* (2024): Comprehensive whole-genome sequence analyses

provide insights into the genomic architecture of cerebral palsy. *Nat Genet* 56: 585–594.

67. Schiavo JH (2019): PROSPERO: An International Register of Systematic Review Protocols. *Med Ref Serv Q* 38: 171–180.

68. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al.* (2016): ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355. https://doi.org/10.1136/bmj.i4919

69. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (Eds.) (2019): *Cochrane Handbook for Systematic Reviews of Interventions*, 1st ed. Wiley. https://doi.org/10.1002/9781119536604

70. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al.* (2015): Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 17: 405–424.

71. Viechtbauer W (2010): Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw* 36: 1–48.

72. The Royal College of Psychiatrists (2023, October): The role of genetic testing in mental health settings. Retrieved February 21, 2024, from https://www.rcpsych.ac.uk/improving-care/campaigning-for-better-mental-health-policy/college-reports/2023-college-reports/the-role-of-genetic-testing-in-mental-health-settings-(cr237)

73. Ahn K, Gotay N, Andersen TM, Anvari AA, Gochman P, Lee Y, *et al.* (2014): High rate of disease-related copy number variations in childhood onset schizophrenia. *Mol Psychiatry* 19: 568–572.

74. Alkelai A, Greenbaum L, Shohat S, Povysil G, Malakar A, Ren Z, *et al.* (2023): Genetic insights into childhood-onset schizophrenia: The yield of clinical exome sequencing. *Schizophr Res* 252: 138–145.

75. Trost B, Thiruvahindrapuram B, Chan AJS, Engchuan W, Higginbotham EJ, Howe JL, *et al.* (2022): Genomic architecture of autism from comprehensive whole-genome sequence annotation. *Cell* 185: 4409-4427.e18.

76. Farrell M, Dietterich TE, Harner MK, Bruno LM, Filmyer DM, Shaughnessy RA, *et al.* (2023): Increased Prevalence of Rare Copy Number Variants in Treatment-Resistant Psychosis. *Schizophr Bull* 49: 881–892.

77. Zoghbi AW, Dhindsa RS, Goldberg TE, Mehralizade A, Motelow JE, Wang X, *et al.* (2021): High-impact rare genetic variants in severe schizophrenia. *Proc Natl Acad Sci U S A* 118: e2112560118.

78. Alkelai A, Greenbaum L, Docherty AR, Shabalin AA, Povysil G, Malakar A, *et al.* (2022): The benefit of diagnostic whole genome sequencing in schizophrenia and other psychotic disorders. *Mol Psychiatry* 27: 1435–1447.

79. Mojarad BA, Yin Y, Manshaei R, Backstrom I, Costain G, Heung T, *et al.* (2021): Genome sequencing broadens the range of contributing variants with clinical implications in schizophrenia. *Transl Psychiatry* 11: 84.

80. Landrum MJ, Lee JM, Riley GR, Jang W, Rubinstein WS, Church DM, Maglott DR (2014): ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res* 42: D980-985.

81. Wen J, Trost B, Engchuan W, Halvorsen M, Pallotto LM, Mitina A, *et al.* (2023): Rare tandem repeat expansions associate with genes involved in synaptic and neuronal signaling functions in schizophrenia [no. 1]. *Mol Psychiatry* 28: 475–482.

82. Kingsmore SF, Smith LD, Kunard CM, Bainbridge M, Batalov S, Benson W, *et al.* (2022): A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases. *Am J Hum Genet* 109: 1605–1619.

83. Zhang J, Xu Y, Liu Y, Yue L, Jin H, Chen Y, *et al.* (2024): Genetic Testing for Global Developmental Delay in Early Childhood. *JAMA Netw Open* 7: e2415084.

84. Besterman AD, Alnor MA, Castaño M, DeLisi LE, Grice DE, Lohoff FW, *et al.* (2025): Psychiatric Genetics in Clinical Practice: Essential Knowledge for Mental Health Professionals. *Am J Psychiatry* appi.ajp.20240295.

85. Maenner MJ, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, *et al.* (2014): Potential Impact of DSM-5 Criteria on Autism Spectrum Disorder Prevalence Estimates. *JAMA Psychiatry* 71: 292–300.

86. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, *et al.* (2022): Global prevalence of autism: A systematic review update. *Autism Res* 15: 778–790.

**Figure Titles and Legends**

**Figure 1:** PRISMA flow diagram

**Figure 1 Legend**: Abbreviations: CMA = chromosomal microarray, ES = exome sequencing, GS = genome sequencing, SCZ = schizophrenia.

**Figure 2:** Forest plot of diagnostic yield for genetic testing in schizophrenia by sequencing modality

**Figure 2 Legend:** Abbreviations: df = Degrees of Freedom, $I^2$ = Percentage of variation across studies due to heterogeneity, n = number of individuals with a positive genetic test, N = sample size, Q = Cochran's Q statistic for heterogeneity, QM = Q statistic for subgroup differences, RE = Random effects, $\tau^2$ = estimate of between-study variance. Note: Squares represent the effect size for individual studies, with larger squares indicating greater weight. Horizontal lines represent 95% confidence intervals. Diamonds represent pooled estimates for each subgroup and overall.