What are the sources of Heterogeneity in Neurodevelopmental and Psychiatric Disorders and how is it driving the need for Precision Medicine?

Sources of Heterogeneity and the Drive Toward Precision Medicine

Heterogeneity in neurodevelopmental and psychiatric disorders arises from genetic, phenotypic, environmental, and biological sources, and this multi-layered variability is a primary catalyst for precision medicine approaches (Uddin et al., 2019; Chen & Geschwind, 2022; Zhang et al., 2023).

Genetic and Genomic Heterogeneity

Hundreds of risk genes have been implicated across neurodevelopmental disorders, with over 250 genes showing strong association and more than 1,000 confirmed pathogenic mutations for intellectual disability alone (Uddin et al., 2019; Verdura et al., 2021). Many rare genomic variants of large effect can produce the same clinical diagnosis, while a single variant can lead to multiple distinct diagnoses, a pattern described as pervasive pleiotropy and variable expressivity (Moreno-De-Luca & Martin, 2021). Most NDD cases arise not from rare highly penetrant mutations but from complex polygenic architectures involving common variants of small effect, de novo mutations, and copy number variations interacting with epigenetic and environmental factors (Uddin et al., 2019; Chen & Geschwind, 2022). Individuals carrying pathogenic variants in the same gene frequently exhibit diverse clinical presentations, with phenotypic outcomes modulated by variant-level features, modifying background variation, and developmental noise (Dvir et al., 2026). Commercial gene panels for ASD detection show diagnostic yields between 0.22% and 10%, underscoring the gap between genetic discovery and clinical utility (Chen & Geschwind, 2022).

Heterogeneity Source	Key Finding	Citation
Rare variants of large effect	Many variants → one diagnosis; one variant → many diagnoses	(Moreno-De-Luca & Martin, 2021)
Polygenic architecture	Common + rare variants interact with environment	(Chen & Geschwind, 2022)
Variable expressivity	Same gene → diverse clinical presentations	(Dvir et al., 2026)
Diagnostic yield	Gene panels detect only 0.22–10% of ASD cases	(Chen & Geschwind, 2022)

Phenotypic and Clinical Heterogeneity

Clinical diagnoses of NDDs are defined by symptom inventories that provide little information about affected genes or molecular mechanisms, and diagnostic criteria have evolved significantly due to the lack of objective biomarkers (Chen & Geschwind, 2022; Uddin et al., 2019). Phenotypic variability between individuals sharing the same diagnosis is substantial, with overlap across different disorders and high rates of comorbidity that complicate diagnosis (Uddin et al., 2019; Verdura et al., 2021). In depression, approximately 75% of patients have at least one comorbid neuropsychiatric illness, and longitudinal tracking identified 692 unique disorder trajectories among 1,037 participants (Buch & Liston, 2020). Symptom expression also varies over time in severity, developmental course, and treatment response, with age of onset linked to different biological processes (Chen & Geschwind, 2022; Buch & Liston, 2020). Sex differences represent an important but poorly defined contributor to diagnostic heterogeneity across psychiatric conditions (Buch & Liston, 2020; Shwab et al., 2025).

Environmental and Biological Heterogeneity

Environmental risk factors — including inflammatory, metabolic, and psychosocial exposures — are understudied relative to genetic factors, yet their cumulative influence along causal pathways is likely critical for most children with NDDs (Woolfenden et al., 2022). Prenatal and early-life environmental exposures modulate phenotypic outcomes of pathogenic variants, requiring integrative approaches combining genetics with environmental monitoring (Dvir et al., 2026). Neuroimaging studies reveal that person-specific deviations from population norms are highly heterogeneous, affecting the same brain area in fewer than 7% of people with the same diagnosis, though these deviations cluster within common functional circuits in up to 56% of cases (Segal et al., 2022). EEG-based normative modeling shows that spectral and connectivity deviation overlap across patients does not exceed 40% and 24%, respectively, confirming intrinsic heterogeneity rather than comorbidity-driven artifact (Ebadi et al., 2024). Biochemical heterogeneity is also substantial, with circulating glucose and glycated hemoglobin ranking among the most variable traits across 65% of diagnoses (Di Biase et al., 2026).

How Heterogeneity Drives Precision Medicine

Behavior-based diagnostic criteria overlook clinical and genomic heterogeneity, repeatedly resulting in failed clinical trials and underscoring the need for precision medicine frameworks (Perez-Cano et al., 2023).

- **Patient stratification** into biologically homogeneous subgroups is necessary to identify clinically relevant populations for targeted treatment (Chen & Geschwind, 2022; Ellegood et al., 2025).
- **Unsupervised clustering** of multidimensional biological data may reveal hidden structures more closely aligned with endophenotypes, treatment response, and prognosis than existing diagnostic categories (Uddin et al., 2019).
- **Drug responder profiles** based on specific biomarkers can associate patients with different genetic backgrounds to the same candidate drug, enabling repositioning across NDDs (Verdura et al., 2021).
- **Mechanism-based therapeutics** will only succeed when heterogeneity is explicitly incorporated into treatment design through multidisciplinary integration (Sahin & Sur, 2015; Wang et al., 2023).

Precision medicine in neurodevelopmental and psychiatric disorders requires moving beyond one-size-fits-all approaches toward multimodal biomarker integration, biologically informed subtyping, and individually tailored interventions that address the full spectrum of heterogeneity (Ebadi et al., 2024; Hampel et al., 2023; Arango et al., 2026).

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