Florida State University's Autism Institute

2023 Summer Training Institute on Autism:

Advances in Evidence-Based Practice for Autism Spectrum Disorder

June 13 – June 15, 2023

Presenter: John N. Constantino, MD

Title and Format: Causation, Disparity, and Comorbidity in Autism: Clinical and translational advances from longitudinal research (PDF of PowerPoint slides)

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Causation, Disparity, and Comorbidity in Autism: Clinical and translational advances from longitudinal research

John N. Constantino, MD
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Chief, Behavioral and Mental Health, Children's Healthcare of Atlanta

EMORY UNIVERSITY

1

Disclosures

- Industry Consulting: None
- Stock Equity: None
- Royalties: Western Psychological Services
  The Social Responsiveness Scale (SRS-2)
- Research Support:
  - *NICHD*
  - *U.S. CDC*
  - *NIMH*

2

COMMENTARY

Insufficient Evidence for "Autism-Specific" Genes

Scott M. Myers,[1,*] Thomas D. Challman,[1] Raphael Bernier,[2] Thomas Bourgeron,[3] Wendy K. Chung,[4,5] John N. Constantino,[6,7] Evan E. Eichler,[8] Sebastien Jacquemont,[9] David T. Miller,[10] Kevin J. Mitchell,[11,12] Huda Y. Zoghbi,[13,14,15,16,17] Christa Lese Martin,[1] and David H. Ledbetter[1,*]

Despite evidence that deleterious variants in the same genes are implicated across multiple neurodevelopmental and neuropsychiatric disorders, there has been considerable interest in identifying genes that, when mutated, confer risk that is largely specific for autism spectrum disorder (ASD). Here, we review the findings and limitations of recent efforts to identify relatively "autism-specific" genes, efforts which focus on rare variants of large effect size that are thought to account for the observed phenotypes. We present a divergent interpretation of published evidence; discuss practical and theoretical issues related to studying the relationships between rare, large-effect deleterious variants and neurodevelopmental phenotypes; and describe potential future directions of this research. We argue that there is currently insufficient evidence to establish meaningful ASD specificity of any genes based on large-effect rare-variant data.

SPORADIC AUTISTIC SYNDROMES ASSOCIATED WITH HIGHLY-PENETRANT DE NOVO MUTATIONS HAVE COLLECTIVE FEATURES THAT ARE NOT SHARED BY FAMILIAL AUTISTIC SYNDROMES:

--near-universal association with intellectual disability
--absence of sex differences

The American Journal of Human Genetics *106*, 587–595, May 7, 2020 587

3

Recurrence Rates and Inherited Transmission in Autism

MZ concordance:	**90%**
DZ concordance:	**20%**
Non-twin sib recurrence:	**18%**
Half-sib recurrence	**6%**
General population risk	**1%**

Table. Autism Spectrum Disorder Heritability Model Comparisons and Parameter Estimates

	Model Comparison Measures				Estimated Variance (95% CI)[a]				
Models[b]	No. of Model Parameters	−2LL	Diff − 2LL	*P* Value[c]	Additive Genetic (Narrow-Sense Heritability)	Nonadditive Genetic	Environment		Total Genetic (Broad-Sense Heritability)
							Shared	Nonshared	
ACDE	14	146 836	NA	NA	0.69 (0.40-0.86)	0.10 (0.00-0.38)	0.04 (0.00-0.14)	0.16 (0.05-0.30)	0.80 (0.59-0.95)
ACE	13	146 836	0.4	.52	0.77 (0.58-0.87)	NA	0.03 (0.00-0.13)	0.20 (0.13-0.30)	0.77 (0.58-0.87)
ADE	13	146 836	0.8	.38	0.80 (0.68-0.87)	0.05 (0.00-0.26)	NA	0.15 (0.05-0.21)	0.85 (0.79-0.95)
CDE	13	146 856	20.9	<.001	NA	0.64 (0.48-0.75)	0.25 (0.21-0.29)	0.11 (0.03-0.24)	0.64 (0.48-0.75)
AE	12	146 836	0.9	.64	0.83 (0.79-0.87)	NA	NA	0.17 (0.13-0.21)	0.83 (0.79-0.87)
DE	12	147 100	264	<.001	NA	0.99 (0.97-1.00)	NA	0.01 (0.00-0.03)	0.99 (0.97-1.00)
CE	12	146 897	61	<.001	NA	NA	0.39 (0.37-0.41)	0.61 (0.59-0.63)	NA
E	11	147 996	1160	<.001	NA	NA	NA	1.00 (1.00-1.00)	NA

Abbreviations: 2LL, 2 × logarithm of the likelihood; Diff − 2LL, 2 × difference in log-likelihood between the model and the full model; NA, not applicable.

[a] The 95% CIs are 2-sided CIs. Variances are based on the tetrachoric correlations. The unadjusted tetrachoric correlation (SD) was estimated to 0.87 (0.08) and 0.40 (0.10) for monozygotic and dizygotic twins; 0.41 (0.01) for full siblings; 0.22 (0.03) and 0.17 (0.04) for maternal and paternal half siblings.

[b] All models adjusted for sex and birth cohort. The genetic terms for each model are shown in each row, which include additive genetic effect (A; inherited additive effects of different alleles), shared environmental factors (C; nongenetic influences contributing to similarity within sibling pairs), nonadditive (dominant) genetic factors (D; interaction effects between alleles at the same locus), and nonshared environmental factors (E; making siblings dissimilar).

[c] *P* value for testing the hypothesis: the parameters not in the model but in the full model are all equal to 0.

JAMA September 26, 2017 Volume 318, Number 12 1183

4

Core, characterizing features of autism:
Quantitative in nature, continuously distributed in the population

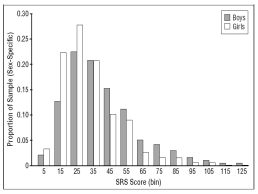
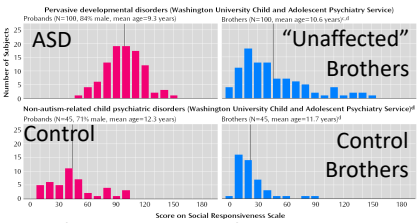


Figure 2. Distribution of Social Responsiveness Scale (SRS) scores as a function of sex (n=1576).

General Population Twins
h^2 = 0.85



Male First Degree Relatives:
Shifted Unimodal Distribution

1. Under contemporary diagnostic criteria for ASD, the srs-2 exhibits a THREE STANDARD DEVIATION DIFFERENCE between children with autism and their unaffected siblings (*J Child Psychol Psychiatry*. 2013; 54:695-7).
2. Common additive (polygenic) genetic risk is the principal cause of a vast share of the population-attributable risk for autism (*JAMA*. 2017; 318:1182-1184)
3. This inherited liability overlaps >90% with additive genetic influence on population-wide variation in sub clinical autistic traits (Robinson et al.) and overlaps 50% with the genetic cause of ADHD (Lichtenstein et al., Jokiranta-Olkoniemi et al.).

5

Original Investigation

JAMA *Psychiatry* 2014

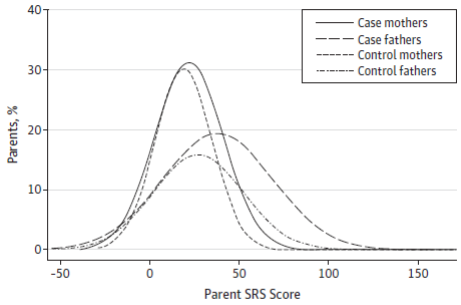
Parental Social Responsiveness and Risk of Autism Spectrum Disorder in Offspring

Kristen Lyall, ScD; John N. Constantino, MD; Marc G. Weisskopf, PhD, ScD; Andrea L. Roberts, PhD; Alberto Ascherio, MD, DrPH; Susan L. Santangelo, ScD

Parent-child correlation
= 0.30

Upper quintile mating
doubles RR for clinical
ASD in offspring

Figure 1. Density Plot of Raw Social Responsiveness Scale (SRS-A) Scores



Values below 0 are due to the plotting of the smoothed density distribution of the SRS-A score.

Nurses Health II Study N=756 cases, 3,000 controls

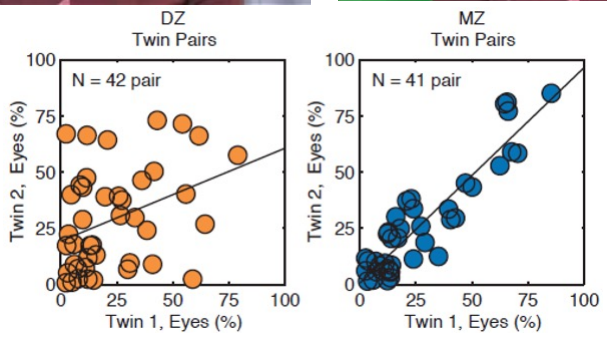
6

CHILD DEVELOPMENT

Developmental Theories for the 1990s: Development and Individual Differences

Sandra Scarr

Given a wide range of environmental opportunities and emotional supports, most children grow up to be individually different based on their individual genotypes. S. Scarr



nature

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nature > letters > article

Published: 12 July 2017

Infant viewing of social scenes is under genetic control and is atypical in autism

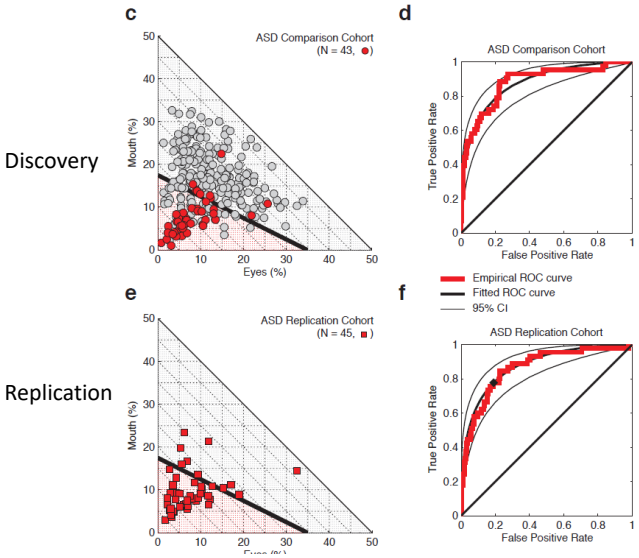
John N. Constantino, Stefanie Kennon-McGill, Claire Weichselbaum, Natasha Marrus, Alyzeh Haider, Anne L. Glowinski, Scott Gillespie, Cheryl Klaiman, Ami Klin & Warren Jones

Nature **547**, 340–344 (2017) | Cite this article

30k Accesses | 162 Citations | 468 Altmetric | Metrics

7

Constantino et al., *Nature* 2017



Discovery

Replication

1. Most children with ASD are in the lower range of eye and mouth looking
2. Some children in the lower range of eye and mouth looking are typically-developing

Early eye gaze abnormalities as "necessary but not sufficient" to cause ASD

8

Forthcoming…

Early Diagnosis and Assessment of Autism Spectrum Disorder via an Objective, Performance-Based Eye-Tracking Tool

Warren Jones[1,2,3], Cheryl Klaiman[1,2], Shana Richardson[1,2], Meena Lambha[1,2], Morganne Reid[1], Taralee Hamner[1], Chloe Beacham[1], Peter Lewis[1,2], Jose Paredes[1,2], Natasha Marrus[4,5], John N. Constantino[4,5,6], and Ami Klin[1,2,3]

9

Mous *et al. Journal of Neurodevelopmental Disorders* (2017) 9:32
DOI 10.1186/s11689-017-9212-y

Candidate #4 ADHD

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Attention and motor deficits index non-specific background liabilities that predict autism recurrence in siblings

Sabine E. Mous[1,2], Allan Jiang[2], Arpana Agrawal[2] and John N. Constantino[2*]

S. Mous
Erasmus University
The Netherlands

Table 4. Linear regression analyses predicting parent-reported autistic trait severity in siblings

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	p	β	p	β	p	β	p	β	p
Proband SRS-2 score (teacher-report)	0.30	0.086	0.26	0.098	0.19	0.109	0.19	0.111		
Sibling TRF ADHP score (teacher-report)			0.45	0.005	0.24	0.066	0.25	0.074	0.24	0.063
Sibling DCDQ score (parent-report)					-0.60	<0.001	-0.60	<0.001	-0.62	<0.001
TRF ADHP x DCDQ interaction							0.03	0.793		
Adjusted R^2	0.059		0.247		0.554		0.540		0.530	

10

IN CONTEXT

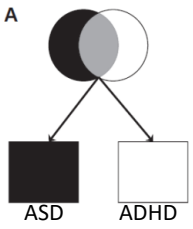
Check for updates

Neuropsychiatric "Comorbidity" as Causal Influence in Autism

Zoë W. Hawks, MA, and John N. Constantino, MD

J Am Acad Child Adolesc Psychiatry 2020;59(2):229–235.

FIGURE 1 Potential Pathways to Autism Comorbidity



Candidate trait characteristics	A	B	C (i)	C (ii)	C (iii)
1. More common in ASD than general population	+	+	-	+	+
2. Highly heritable	+	+/-	+/-	+/-	+/-
3. Predicts recurrence in multiplex families	+	-	-	+	+/-
4. Aggregates in unaffected first-degree relatives	+/-	-	+/-	+/-	+/-
5. Correlates with severity in individuals with ASD	+/-	+/-	-	+	+/-
6. Correlates with ASD traits in infancy	+	-	-	-	-
7. Correlates with ASD traits in school-age children	+	+/-	-	+	+/-

11

Psychological Medicine

cambridge.org/psm

Attention-deficit/hyperactivity disorder and risk for psychiatric and neurodevelopmental disorders in siblings

Original Article

Elina Jokiranta-Olkoniemi[1], Keely Cheslack-Postava[2], Petteri Joelsson[1], Auli Suominen[1], Alan S. Brown[2,3] and Andre Sourander[1,2]

Methods. Every child born in Finland in 1991–2005 and diagnosed with ADHD in 1995–2011 were identified from national registers. Each case was matched with four controls on sex, place, and date of birth. The full siblings of the cases and controls were born in 1981–2007 and diagnosed in 1981–2013. In total, 7369 cases with 12 565 siblings and 23 181 controls with 42 753 siblings were included in the analyses conducted using generalized estimating equations.

Table 2. Associations between ADHD and psychiatric and neurodevelopmental disorders among the siblings of cases and matched controls

	ADHD[a]		Adjusted[b] (model I)		Adjusted[c] (model II)		Adjusted[d] (model III)	
	Case *n* = 7369 (%)	Control *n* = 23 181 (%)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
ADHD	1134 (15.4)	598 (2.6)	7.1	(6.4–7.8)***	6.5	(5.9–7.2)***	5.7	(5.1–6.3)***
Conduct and oppositional disorders	705 (9.6)	461 (2.0)	5.6	(5.0–6.3)***	5.0	(4.5–5.7)***	4.0	(3.5–4.5)***
ASD	322 (4.4)	264 (1.1)	4.6	(3.9–5.4)***	4.4	(3.7–5.2)***	3.9	(3.3–4.6)***

12

Pohl et al. *Translational Psychiatry* (2019)9:202
https://doi.org/10.1038/s41398-019-0545-z

Translational Psychiatry

ARTICLE Open Access

Behavioral predictors of autism recurrence are genetically independent and influence social reciprocity: evidence that polygenic ASD risk is mediated by separable elements of developmental liability

Alexa Pohl[1], Warren R. Jones[2], Natasha Marrus[3], Yi Zhang[3], Ami Klin[2] and John N. Constantino[4]

Table 3 Results of linear regression analysis examining the joint contribution of three behavioral predictors of autism recurrence (measured at 36-48 months) to variation in autism-related variation in early childhood reciprocal social behavior

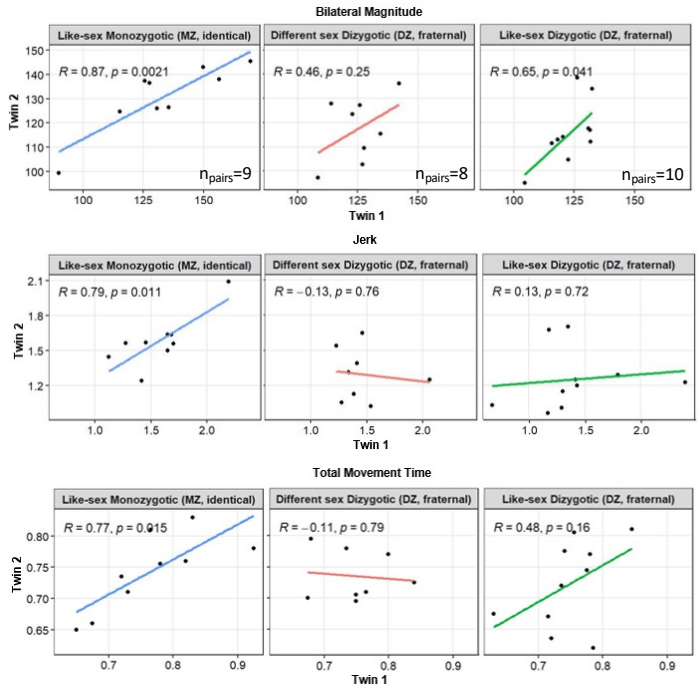
Outcome modeled	Adj R^2	BPAR	*B*	*t*	Sig	Δ Adj R^2
SRS at 36 months	0.35	Biparental QAT	0.255	5.568	<0.001	0.06
		Variation in attentional impairment	0.355	3.996	<0.001	0.12
		Variation in motor coordination	−0.242	−3.830	<0.001	0.05
		Site	.079	1.252	0.212	0.00

Adjusted R square is reported for the full regression model, along with changes in adjusted R square that occur when a given individual behavioral trait is excluded from the model, and the result compared with that for the full model. A companion table for SRS outcome at 48 months (for which there were fewer twin pairs with complete data) yielded highly comparable results and is provided in Supplementary Table 2
SRS social responsiveness scale

13

WATCH Study

Lang, Lohse, Iverson, Limperopoulos, White, Klin, Jones, Constantino & Marrus



Magnitude
Intensity of overall upper-limb activity

Jerk
Smoothness of the limb movements (lower →smoother)

Movement Time
Percent of waking hours with movement

14

INTERNATIONAL REVIEW OF PSYCHIATRY, 2018
https://doi.org/10.1080/09540261.2018.1433133

Taylor & Francis
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ARTICLE

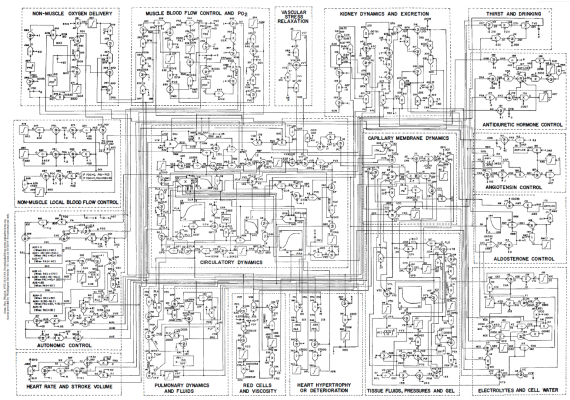
OPEN ACCESS Check for updates

Deconstructing autism: from unitary syndrome to contributory developmental endophenotypes

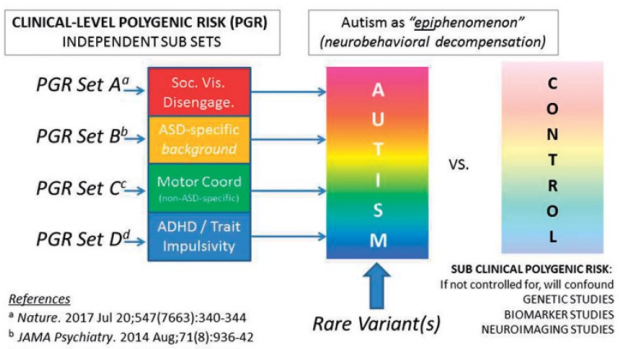
John N. Constantino

Departments of Psychiatry and Pediatrics, Washington University School of Medicine, St Louis, MO, USA

Deconstructing blood pressure (Guyton, 1972)



Deconstructing familial autism
(by early developmental endophenotypes)



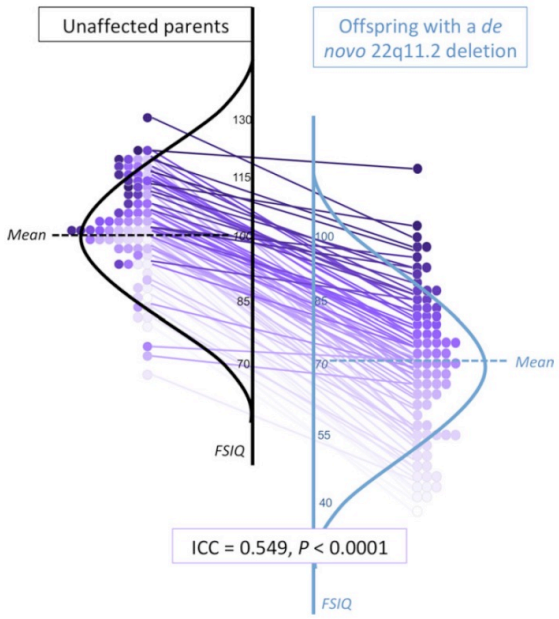
References
[a] *Nature*. 2017 Jul 20;547(7663):340-344
[b] *JAMA Psychiatry*. 2014 Aug;71(8):936-42
[c] *J Neurodev Disord*. 2017 Sep 5;9(1):32
[d] *Twin Res Hum Genet*. 2017 Aug;20(4):319-329

15

Autism Heterogeneity

CATEGORICAL MODIFIERS

16



Within-family influences on dimensional neurobehavioral traits in a high-risk genetic model

Fig. 2. Within-family proband-parent correlation of FSIQ for adults with a *de novo* 22q11.2 deletion. Details of within-family FSIQ data for adult probands with a *de novo* 22q11.2 deletion, each purple-colored circle representing one family (total $n = 77$), ordered by proband FSIQ level (deepest intensity, highest FSIQ), with the same colored circle used for the corresponding biparental FSIQ result and within-family connections indicated by straight lines between each 22q11DS proband-unaffected parent pair. These data are superimposed on schematic depictions of their normalized distributions, for adult probands (blue, right) and their unaffected parents (black, left). While the results for those with a 22q11.2 deletion are on average lower, the individual datapoints and connector lines indicate the overall preserved relationship of FSIQ within families, regardless of proband FSIQ level. Online Supplementary Figs. 2A–2C show the scales shifted so that idealized curves mirror each other, and present schematic representations of FSIQ distributions for the overall sample and for the no psychotic illness and schizophrenia subgroups.

Fiksinski et al., 2021

17

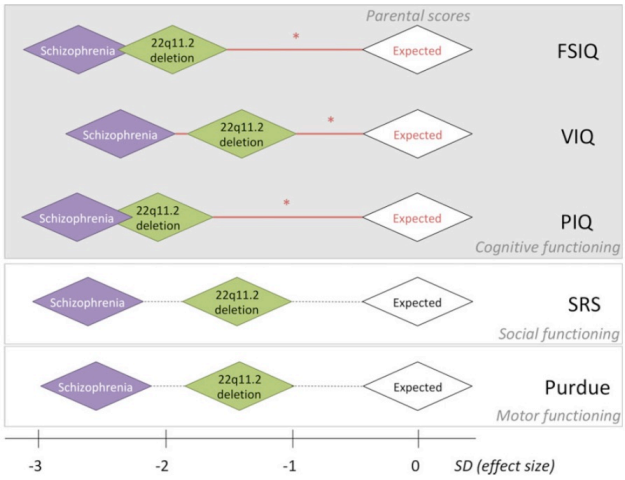


Fig. 1. Relative effect sizes of the *de novo* 22q11.2 deletion and schizophrenia in the context of within-family expectations on five-dimensional neurobehavioral traits. For each of five-dimensional neurobehavioral constructs studied, the within-family biparental mean score, indicated by the white diamonds, was set to be standard deviation (s.d.) of 0, representing the average expected score for adult probands with a *de novo* 22q11.2 deletion, based on the respective within-family parental scores. Red horizontal lines with an asterisk indicate significant effects of parental scores on the respective scores assessed in probands; non-significant correlations with parental scores are represented by dashed horizontal lines (details in Tables 1 and 3). Green diamonds are centered at the average estimated effect size (in s.d.) of the *de novo* 22q11.2 deletion on each phenotype, using results for the affected adult probands with the 22q11.2 deletion *and no psychotic illness*; thus, representing the estimated effect size of the 22q11.2 deletion. Purple diamonds are centered at the average estimated effect size (in s.d.) of those with the 22q11.2 deletion and schizophrenia, on each phenotype; thus, indicating the estimated additional effect size of schizophrenia expression. Details about these effect size s.d. are presented in this paper. For simplicity sake, the sizes of all diamond shapes were kept consistent; while pictorially representing general inter-individual variability, they do not represent confidence intervals. Individual within-family results that indicate the preserved relationship for FSIQ between probands with a *de novo* 22q11.2 deletion and their unaffected parents, regardless of cognitive level, are shown for FSIQ in Fig. 2.

18

Neuron

CellPress OPEN ACCESS 2022

Review

Can the "female protective effect" liability threshold model explain sex differences in autism spectrum disorder?

Joseph D. Dougherty,[1,2,3,*] Natasha Marrus,[2,3] Susan E. Maloney,[2,3] Benjamin Yip,[4] Sven Sandin,[5,9,10] Tychele N. Turner,[1,3] Din Selmanovic,[1,2] Kristen L. Kroll,[3,6] David H. Gutmann,[7] John N. Constantino,[2,3] and Lauren A. Weiss[8,*]

Marrus et al. Journal of Neurodevelopmental Disorders (2021) 13:39
https://doi.org/10.1186/s11689-021-09389-8

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Genetic counseling as preventive intervention: toward individual specification of transgenerational autism risk

Natasha Marrus[1*], Tychele N. Turner[2], Elizabeth Forsen[1], Drew Bolster[1], Alison Marvin[3], Andrew Whitehouse[4], Laura Klinger[5], Christina A. Gurnett[6] and J. N. Constantino[1]

Table 3 Summary of recurrence risk estimates for prospective parents relative to general population

Indicator of familial ASD liability	Relative recurrence risk	Source
Mother with ASD-affected sibling*	3	Bai D, et al. [18]
Father with ASD-affected sibling*	2	
Mother and father with upper quintile of QATs	1.85	Lyall K, et al. [19])
Either mother or father with upper quintile of QATs	1.52	
Mother with ASD-affected sibling* and elevated QATs	[~6.5]**	Second Generation Project

*Idiopathic ASD is assumed. For ASD with a known genetic cause, recurrence will vary based on that variant's inheritance and penetrance. For example, in Renpenning Syndrome, an X-linked disorder affecting males [54], a sister carrying the associated X-linked mutation has a 50% likelihood of having an affected son, who then has an estimated 38% likelihood of ASD [55].
**This estimate, based on dividing our observed second-generation offspring ASD prevalence (13%) by general population ASD prevalence (~2%), is highly preliminary, given it is derived from a small sample subject to bias from clinical ascertainment of ASD. Nevertheless, it confirms elevated transgenerational ASD risk in parents with two markers of aggregated ASD liability (having an ASD-affected sibling and elevated QATs) and highlights the need for future research in large, genetically informative samples examining joint interactions of predictors of transgenerational ASD risk

19

Constantino Molecular Autism (2021) 12:28
https://doi.org/10.1186/s13229-021-00434-w

Molecular Autism

COMMENTARY Open Access

New guidance to seekers of autism biomarkers: an update from studies of identical twins

John N. Constantino*

HERITABILITY OF **QUANTITATIVE** VARIATION
IS INVERSELY PROPORTIONAL TO SEVERITY
(in clinical range, heritability of variation in severity is 0.20 for SRS and 0.20 for ADOS)

UPPER LIMIT TO PRECISION OF GENOTYPE-PHENOTYPE ASSOCIATION IN **CLINICAL** CASES DUE TO IMPACT OF STOCHASTIC INFLUENCES

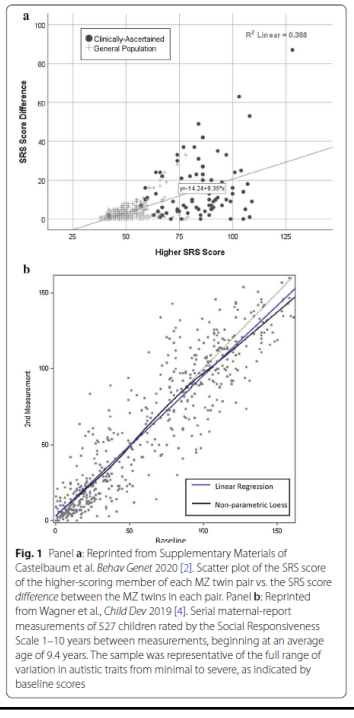
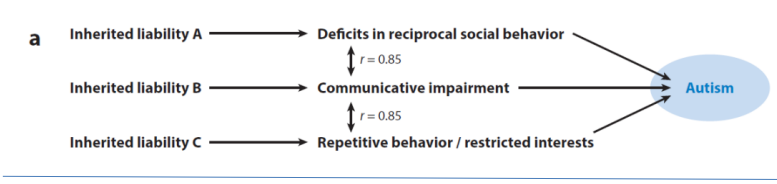


Fig. 1 Panel **a**: Reprinted from Supplementary Materials of Castelbaum et al. *Behav Genet* 2020 [2]. Scatter plot of the SRS score of the higher-scoring member of each MZ twin pair vs. the SRS score *difference* between the MZ twins in each pair. Panel **b**: Reprinted from Wagner et al., *Child Dev* 2019 [4]. Serial maternal-report measurements of 527 children rated by the Social Responsiveness Scale 1–10 years between measurements, beginning at an average age of 9.4 years. The sample was representative of the full range of variation in autistic traits from minimal to severe, as indicated by baseline scores

20



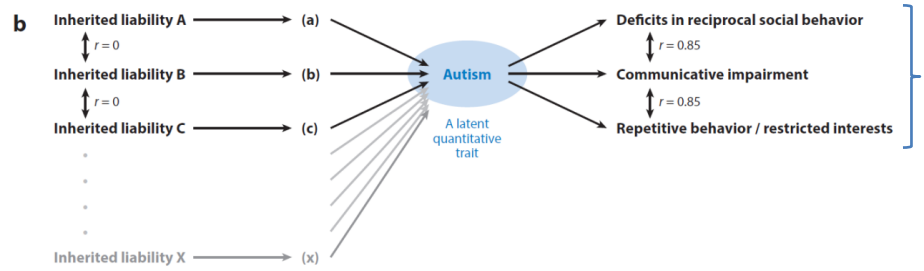
ANNUAL REVIEWS

2021

Annual Review of Clinical Psychology

Clinical and Translational Implications of an Emerging Developmental Substructure for Autism

John N. Constantino,[1] Tony Charman,[2] and Emily Jones[3]



c **Search for biomarkers relevant to the CAUSE of autism (versus epiphenomena or correlates of causal influences) MUST consider:**

i) characterizing A, B, C…X among controls
ii) correlations with A, B, C…X rather than "autism"
iii) biological associations in general population samples, in which stochastic influences appear to have a markedly lower confounding effect

d **Arbitrary dichotomizations of ASD populations will induce the same biases that confounded a generation of research that (for example) invoked categorical distinctions between Asperger Syndrome and Autistic Disorder.**

21

Dual Diagnosis

- Intellectual Disability
- Autism Spectrum Disorder
- Receptive / Expressive Language Delay
- Sensorimotor Impairment
  - Visual Impairment
  - Hearing Impairment
  - Physical Disability

X

- Aggression (Intermittent Explosive Disorder)
- Anxiety (Generalized Anxiety Disorder)
- Depression / SIB (Major Depressive Disorder)
- Substance Use Disorder
- Mood Instability (Bipolar Disorder)
- Psychosis (Schizophrenia)
- Personality Disorder
- Impulse Control Disorder (ADHD)
- Post-traumatic Stress Disorder

= 4 x 9 = 36…

22

Neuropsychiatric risk in children with intellectual disability of genetic origin: IMAGINE, a UK national cohort study

Jeanne Wolstencroft, Francesca Wicks, Ramya Srinivasan, Sarah Wynn, Tamsin Ford, Kate Baker, Samuel J R A Chawner, Jeremy Hall, Marianne B M van den Bree, Michael J Owen, IMAGINE Study, David Skuse, F Lucy Raymond*

www.thelancet.com/psychiatry **Vol 9 September 2022**

	Familial	de novo	p value
Emotional disorders	78/529 (14·7%)	40/492 (8·1%)	0·0010
Anxiety	77/529 (14·5%)	40/492 (8·1%)	0·0013
Depression	5/529 (0·9%)	1/492 (0·2%)	0·12
Behavioural disorders	101/529 (19·1%)	49/492 (10·0%)	<0·0001
Oppositional defiant disorder	96/529 (18·1%)	48/492 (9·8%)	0·0001
Conduct disorder	13/529 (2·5%)	4/492 (0·8%)	0·040
Hyperactivity disorder	145/529 (27·4%)	69/492 (14%)	<0·0001
Autism spectrum disorder	242/529 (45·7%)	141/492 (28·7%)	<0·0001

Data are n (%) or mean (SD). Threshold of significance corrected for multiple comparisons using the Bonferroni correction method α=0·002. General physical health was estimated using primary caregivers' ratings on the DAWBA (5 point Likert scale from very bad to very good). IMD quintile 1=most deprived, 5=least deprived. See appendix (p 29) for summary of n numbers. IMD=index of multiple deprivation. ABAS-3=Adaptive Behaviour Assessment System 3. SDQ=Strengths and Difficulties Questionnaire. DAWBA=Development and Well-Being Assessment. *Calculated using χ^2 test of independence. †Calculated using two-sample Kolmogorov–Smirnov test. ‡DAWBA skip rules affect number of responses. §The developmental quotient was calculated from primary caregivers' estimates of the child's mental age divided by their chronological age (0=low developmental level, 1=high developmental level).

***Table 3*: Copy number variant group participant characteristic comparison by variant inheritance**

23

Intervention relevant to both DD and BH

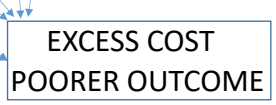
- Positive Behavior Support
- Functional Communication Training
- Case Management
- In-home support
- Psychopharmacologic Intervention
  - Impulse Control
  - Mood Stabilization
  - Behavioral Rigidity
  - Aggression

Summary Interventions that are commonly implemented in the IDD service sector (e.g., functional communication training and positive behavioral support planning) are capable of mitigating severe behavioral impairment, yet rarely invoked when dual diagnosis patients are seen in the psychiatric service sector. Conversely, state-of-the-art interventions for traumatic stress, pharmacotherapy, and psychotherapy have proven capable of improving behavioral impairments in IDD but are typically restricted to the psychiatric service sector, where there exist significant barriers to access for patients with IDD, including limitations imposed by diagnostic eligibility and practitioner experience. Bridging these gaps in knowledge and clinical capacity across the respective IDD and PS service sectors should be of very high priority in strategizing the care and support of IDD patients with serious co-occurring psychiatric conditions.

24

Consequences of non-comprehensive treatment

- Low impact on adaptive functioning
- Languishing in scenarios of inadequate support
- Ineffective expenditures over years of time
- Injury, Traumatic Experience
- Incarceration / Placement
- Emergency Room Visits
- Delays in maturation



25

Table 1 Glossary of terms

Glossary	
Adaptive function	"The child's performance across socialization, communication, and daily living domains" [9]. Deficits in adaptive function may be influenced by symptoms of a condition but differ from symptoms in that they relate to general aspects of maturity and homeostasis that allow an individual to direct the course of his/her own behavior, pursue goals, maintain safety, contribute to the community through work and social interaction, and engage in fulfilling interpersonal relationships
Functional behavior assessment	Involves evaluation of the behavior and of the antecedent and consequences associated with the behavior. An assessment analyzes the precipitants of the behavior and proposes hypotheses about factors that control the behavior. The information gathered guides the intervention by altering conditions so that the desired behaviors are shaped and reinforced [10]
Functional communication training	Functional communication training involves teaching a socially appropriate communicative response that serves the same function as a problem behavior and therefore serves as a substitute for problem behavior. A functional analysis is conducted to identify the environmental events that serve as reinforcers for the problem behavior and the conditions that evoke problem behavior. A socially appropriate communicative response is selected and taught with prompting and a schedule of reinforcement that results in the appropriate response replacing the problem behavior. An example of this would include training a child to say, "help please" when engaged in a difficult task rather than screaming [11•]
Neurotypical	Exhibiting or characteristic of typical neurological development; i.e. pertaining to individuals who are not affected by a neurodevelopmental disorder
Noncontingent reinforcement without extinction	Includes the delivery of a reinforcer on a time-based schedule that does not depend on the individual's adaptive or maladaptive behavior. For example, noncontingent reinforcement without extinction may involve allowing an individual to access preferred items every 30 s, irrespective of the individual's behavior, and without any specific contingency for the preferred item that would operate to extinguish a maladaptive behavior [12]

26

Table 2 Listing of selected clinical trials and systematic reviews, publication dates 2014–2019, documenting evidence for specific intervention modalities for ASD/ID and aggression, depression, or addictions

Title	Lead author; Year; Citation number in reference list	Intervention modalities
IDD and aggression		
Aggression in autism spectrum disorder: presentation and treatment options	Fitzpatrick et al. *Neuropsychiatric Disease and Treatment* 2016 [2]	-Functional behavioral assessment -Reinforcement strategies -Functional communication training
Shaping complex functional communication responses	Ghaemmaghami et al. *Journal of Applied Behavior Analysis* 2018 [36]	-Shaping -Functional communication training -Complex functional communication responses
Noncontingent reinforcement without extinction plus differential reinforcement of alternative behavior during treatment of problem behavior	Fritz et al. *Journal of Applied Behavior Analysis* 2017 [12]	-Noncontingent reinforcement without extinction -Differential reinforcement of alternative behavior
Meta-analysis of noncontingent reinforcement effects on problem behavior	Richman, et.al, *Journal of Applied Behavior Analysis* 2015 [38]	-Positive behavior support planning
Effects of mindfulness-based positive behavior support (MBPBS) training are equally beneficial for mothers and their children with autism spectrum disorder or with intellectual disabilities	Singh et al. *Frontiers in Psychology* 2019 [39]	-Mindfulness to reduce perceived psychological stress for both caregivers and children with IDD -Positive behavior support
Pharmacologic treatment of severe irritability and problem behaviors in autism: a systematic review and meta-analysis	Fung et al. *Pediatrics* 2016 [41]	-Risperidone -Aripiprazole
Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: a randomized clinical trial	Bearss et al., *JAMA* 2015 [42]	-Behavioral parent training

27

IDD and Depression		
Multidisciplinary assessment and treatment of self-injurious behavior in autism spectrum disorder and intellectual disability: integration of psychological and biological theory and approach	Minshawi et al. *J Autism Dev Disord* 2015 [47•]	-Applied behavior analysis (ABA)-based positive behavior supports -Psychopharmacologic intervention
Catatonia in Down syndrome: systematic approach to diagnosis, treatment and outcome assessment based on a case series of seven patients	Miles JH et al. *Neuropsychiatr Dis Treat* 2019 [52]	-Pharmacotherapy and electroconvulsive therapy (ECT)
Non-pharmacological interventions for adults with intellectual disabilities and depression: a systematic review	Hamers et al. *Journal of Intellectual Disability Research* 2018 [55]	-Cognitive behavioral therapy -Behavioral therapy -Exercise intervention -Social problem-solving skills program -Bright light therapy
Comparison of behavioral activation with guided self-help for treatment of depression in adults with intellectual disabilities: a randomized controlled trial	Jahoda et al. *Lancet Psychiatry* 2017 [56]	-Individual psychological interventions: BeatIt and StepUp

28

Table 2 (continued)

Title	Lead author; Year; Citation number in reference list	Intervention modalities
Adapting cognitive behavioral techniques to address anxiety and depression in cognitively able emerging adults on the autism spectrum	Kerns et al. *Cognitive and Behavioral Practice* 2016 [57]	-Cognitive behavioral therapy
IDD and addictions		
Acceptance and commitment therapy for problematic internet pornography use: a randomized trial	Crosby et al. *Behavior Therapy*. 2016 [60]	-Acceptance and commitment therapy
Efficacy of short-term treatment of internet and computer game addiction: a randomized clinical trial	Wölfling et al. *JAMA Psychiatry* 2019 [59]	-Short-term, manualized cognitive behavioral therapy, specifically adapted for internet/computer game addiction
Treating patients with co-occurring autism spectrum disorder and substance use disorder: a clinical explorative study	Helverschou et al. *Substance Abuse: Research and Treatment* 2019 [61]	-Cognitive behavioral therapy -Monthly ASD education and group supervision to therapists in substance use clinics
A feasibility randomized controlled trial of extended brief intervention for alcohol misuse in adults with mild to moderate intellectual disabilities living in the community; the EBI-LD study	Kouimtsidis et al. *Trials* 2017 [63]	-Manualized motivational enhancement therapy incorporating principles of CBT

29

Current Psychiatry Reports (2020) 22:9
https://doi.org/10.1007/s11920-020-1127-8

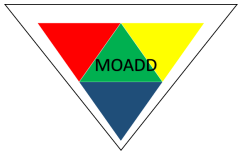
AUTISM SPECTRUM DISORDERS (ES BRODKIN, SECTION EDITOR)

Toward Actionable Practice Parameters for "Dual Diagnosis": Principles of Assessment and Management for Co-Occurring Psychiatric and Intellectual/Developmental Disability

John N. Constantino[1] · Shae Strom[1] · Michael Bunis[1] · Cy Nadler[2] · Teresa Rodgers[3] · Julia LePage[3] · Connie Cahalan[3] · Amber Stockreef[3] · Lucas Evans[3] · Rachel Jones[3] · Alyssa Wilson[4]

https://link.springer.com/article/10.1007/s11920-020-1127-8

Current Psychiatry Reports, February 2020 Issue



Missouri Alliance for Dual Diagnosis

30

MOADD Mobile App

Available on the App Store

31

Project ECHO®

Extension for Community Healthcare Outcomes

SCHOOL OF MEDICINE

- **Move knowledge, not people...**
- **Case-based learning**

- https://echoautism.org/moadd/

32

Identification of missed opportunity

(Biopsychosocial approach to person-centered support)

- Absence of history
- Fundamental lapses in migration of guardianship / decision-making
  - (near-complete "dis-integration" of therapeutic strategy of DMH and DSS)
- Incorporation of "identity" into a coherent positive behavior support plan
- Major gaps in application of evidence-base psychiatric intervention
  - Medication trials
  - Specific evidence-based psychotherapies
- Rift in alliance between guardians and intervention team
- Unintended recapitulation of trauma
- Neglect of functional communication training
- Underutilization of "co-registration" in DD and BH service streams

33

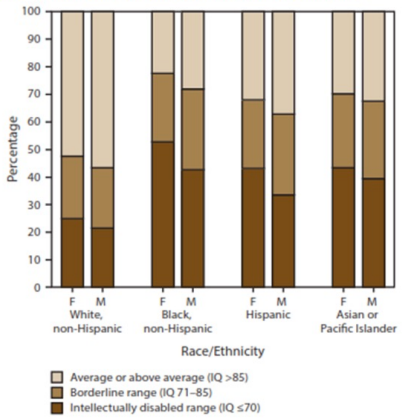
Equity and Parity

34

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Surveillance Summaries / Vol. 67 / No. 6 April 27, 2018

2018

FIGURE 2. Most recent intelligence quotient score as of age 8 years among children with autism spectrum disorder for whom test data were available, by sex and race/ethnicity — Autism and Developmental Disabilities Monitoring Network, nine sites,* United States, 2014



Abbreviations: ASD = autism spectrum disorder; F = female; IQ = intelligence quotient; M = male.
* Includes nine sites (Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, New Jersey, North Carolina, and Tennessee) that had intellectual ability data available for ≥70 of children who met the ASD case definition (n = 3,714).

ADDM Network Surveillance Data

- Overall ASD prevalence per 1,000 children aged 8 years became equal across race in 2006 birth cohort
- Disproportionate burden of cognitive impairment has been consistent across 2006, 2008, and 2010 birth cohorts. For the 2010 birth cohort, the percentages of children with ASD with IQ scores ≤70 were 49.8%, 33.1%, and 29.7% among Black, Hispanic, and White children, respectively (Maenner et al., 2021)
- Most recent median age of diagnosis: 50 months; 44 months for children with IQ<70

Key References

Baio et al., MMWR Surveill Summ. 2018 Apr 27;67(6):1-23.
Maenner et al., MMWR Surveill Summ. 2020 Mar 27;69(4):1-12.
Maenner et al., *MMWR Surveill Summ. 2021 Dec 3;70(11):1-16.*
Constantino et al. Pediatrics 2020 Sep;146(3):e20193629.

35

Constantino et al., in press *J Am Acad Child Adolesc Psychiatry*

Table 1. Selected Characteristics of the STL study sample at baseline (I), at follow-up in the 4th year of life (II and III, as a function of supplemental intervention), and in comparison to two contrast samples (IV and V).

	I. All ASD Toddlers for whom the respective data elements were available: St. Louis site						II. Toddlers who received supplemental intervention and whose cognitive status was evaluated at >18 months follow-up *						III. Toddlers who completed follow-up cognitive assessments but did not receive ASD-specific developmental intervention services: St. Louis site						IV. Contrast sample of later-diagnosed Black children with Autism from the parent study, MH 100027, 3:1 matched to the toddlers in group II by core early childhood ASD symptoms ascertained by ADI-r *			V. Contrast sample of toddlers enrolled in MH 100027 at Emory University in Atlanta (Emory participants were not assessed using the Raven's Progressive Matrices at follow-up					
	Baseline			Follow up			Baseline			Follow up			Baseline			Follow up			Follow up			Baseline			Follow up		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Age at Diagnosis (in months)	52	29.6	5.4																42	87.4	51.8	157	25.4	4.2			
Age at Vineland-3	50	28.9	5.2	20	48.1	6.2	14	29.4	5.5	14	48.6	5.7	6	28.0	6.0	6	46.7	7.5	41	109.8	50.9	157	25.9	5.1	27	49.6	18.5
Vineland Composite Score	50	65.6	12.0	20	65.0	13.2	14	65.4	14.8	14	65.6	12.9	6	71.2	7.8	6	63.3	15.1	41	71.3	9.1	135	62.4	12.4	27	65.6	11.6
Vineland Communication	50	57.0	18.7	20	60.3	21.8	14	54.8	21.9	14	59.3	21.8	6	71.2	7.0	6	62.5	23.5	41	72.3	12.3	135	61.4	13.5	27	62.0	17.0
Vineland Daily Skill	50	73.5	15.8	20	71.9	13.2	14	74.1	17.6	14	72.6	11.3	6	77.3	11.5	6	70.3	18.0				135	53.9	21.8	27	67.1	16.9
Vineland Socialization	50	66.7	12.0	20	63.5	16.3	14	67.9	13.3	14	65.8	13.4	6	66.5	15.5	6	58.0	22.2				135	67.8	15.7	27	67.6	12.0
Vineland Motor Skill	50	82.3	12.3	20	77.5	17.9	14	81.9	16.4	14	82.0	12.3	6	82.0	9.4	6	67.0	25.3				132	68.6	14.0	27	72.4	10.5
Age at Mullen	41	30.8	6.3	20	49.9	7.6	13	29.5	4.03	12	49.6	7.5	6	26.5	6.3	6	49.5	9.2				131	27.9	5.1	28	49.6	5.4
Mullen Early Learning Composite Score	40	57.2	14.3	19	61.1	15.2	13	53.6	8.37	12	60.7	14.0	6	61.0	9.7	6	64.0	18.9				131	57.9	11.4	28	57.8	16.4
Raven*				5	84.0	12.1													16	86.3	23.5						
iQ Proxy (DAS/Raven/Mullen/PPVT)																			41	77.4	20.3						
Age at ADIR				16	49.0	5.2				12	48.9	4.5				4	49.3	7.6							16	46.9	3.4
ADIR Social				16	16.3	7.1				12	17.8	6.1				4	11.8	9.1							16	13.8	5.2
ADIR Communication				16	11.8	3.1				12	11.3	2.2				4	13.3	5.2							15	17.1	5.6
ADIR Repetitive Behavior				16	4.2	1.0				12	4.5	2.3				4	3.0	2.2							15	11.3	3.2

* Randomly selected from a pool of Black ASD participants enrolled in MH100027 at older ages, and matched 3:1 to early-diagnosed subjects on ADIR Social and RRB

* Average of 5 hours per week for 9 months

--"Intervention group" was substantially more impaired at baseline and gained an average of 7 points on Mullen
--One third of the children in both groups improved substantially on Mullen over the course of follow-up
--On Vineland Composite, 1 out of 5 controls improved (the others LOST ground); 5 out of 12 intervention kids improved.

36

The Youth Mental Health Crisis

Ken Burns Presents Hiding in Plain Sight
June 2022

"You've got problems with access, the quality of care isn't what it should be, the cost…is insurmountable, there is a whole range of difficulties.

Most of the people who will benefit from mental health care are not in the health care system that we have.

I don't think that would be true for cancer, heart disease, arthritis, or asthma"

Thomas Insel, MD (2022)
Former Director, U.S. National Institute of Mental Health

37

Evidence-based mental health care meeting criteria for "medical necessity"

Requires transdisciplinary implementation, often requiring case management, family and/or social service support

Maternal-Child (2GEN) Mental Health

Treatment of Maternal Depression, Prevention of traumatic life events and their consequences

Parent-Child Interactional Therapies

Reduction in enduring patterns of disruptive / aggressive behavior

Cognitive Behavioral Therapy

Resolution of depression and anxiety, and the prevention of suicide

Psychopharmacology

Symptom improvement: ADHD, psychosis, anxiety, OCD, depression, cycling mood disorders

Substance Use Disorder Treatment

Offsetting risk for chronic addiction

Dialectical Behavioral Therapy

Prevention of catastrophic loss of life (suicide, homicide)

38

Federal Mental Health Parity Legislation

- 1996 Mental Health Parity Act (MPHA)
- 2008 Mental Health Parity and Addiction Equity Act (MHPAEA)
- 2020 Strengthening Behavioral Health Parity Act (SBHPA)

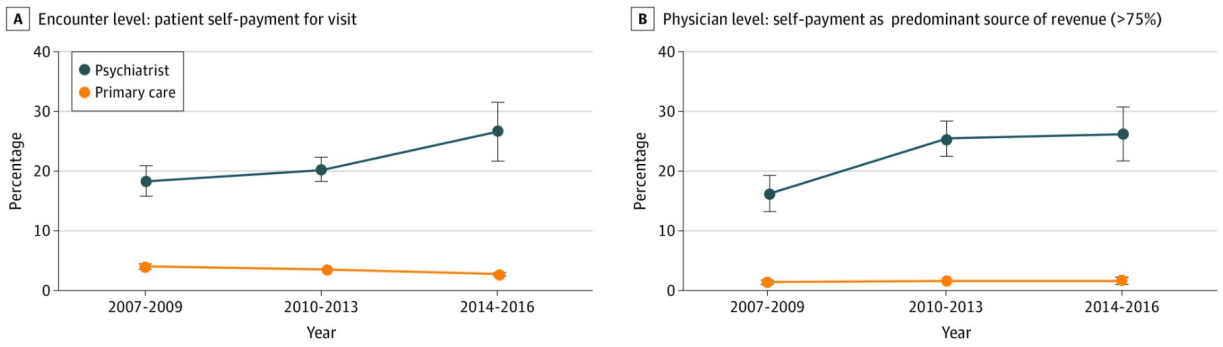
Children's Healthcare of Atlanta

39

Patient self-payment and mental health parity

"Network Adequacy": A Non-Quantitative Treatment Limitation (NQTL) according to the 2020 *Strengthening Behavioral Health Parity Act* (SBHPA, H.R. 7539)

Self-pay contrast between medical and psychiatric care as signature ("smoking gun") of violation of mental health parity…



Benjenk I, Chen J. (2020) Trends in Self-payment for Outpatient Psychiatrist Visits. JAMA Psychiatry 77:1305-1307

40

Children's Healthcare of Atlanta

Children's Board approved a **$0.6B endowment to subsidize new** Behavioral and Mental Health programs in perpetuity for its population.

In 2022, the Legislature of the State of Georgia unanimously passed H.B. 1013 to enforce federal mental health parity law

41

TRANSLATIONS

Bridging the Divide Between Health and Mental Health: New Opportunity for Parity in Childhood

John N. Constantino, MD

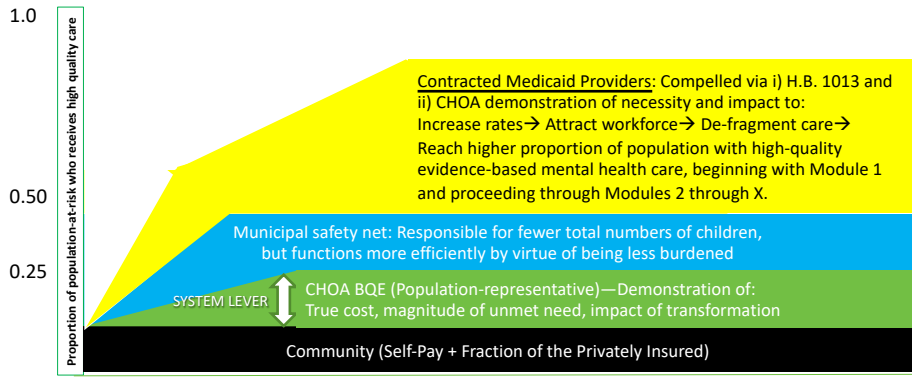
J Am Acad Child Adolesc Psychiatry, 2023

FIGURE 1 Parameterizing Nonquantitative Treatment Limitations

	Psychiatric Diagnosis	*How often does this condition occur in the population of the insurance pool?*	*Which evidence-based interventions are medically indicated for this condition?*	*How often should this service be rendered to keep the population mentally healthy?*	*Is the service occurring as often as would be expected for known prevalence*	*Are there adequate numbers of providers in-network to meet the need?*	*Does the insurer cover the cost of this service?*
	Diagnostic Indication for Medically-Necessary (Evidence-based) Service	**Annual Incidence (Per 1,000 Covered Lives)**	**Medically-Necessary Evidence-Based Service**	**Expected Encounters/Yr Per 1,000 Covered Lives**	**Proportion of expected encounters per 1,000 covered lives ACTUALLY DELIVERED**	**Proportion of provider slots (work RVUs) necessary to meet expected demand that are actually available**	**Proportion of true cost of service, inclusive of care coordination, that is covered by insurer**
Example:	Major Depressive Disorder, F32	71	Management of established patient, CPT 99214	426	?	?	?

42

Path to Ecosystem Transformation, GA Child Mental Health



In descending order of acuity x public health impact:

Module 1: Suicide Recovery (CAMS)
Module 2: Comprehensive Treatment at Earliest Origin: PTSD, Disruptive Preschool Behavior
Module 3: Parental Mental Health Care
Module 4: Comprehensive Treatment at Earliest Origin: Mood / Anxiety Disorder
Module 5: Early Substance Use Disorder
.
.
Module X: (covered at poor quality): Inpatient Hospitalization

43

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Kristen Lyall, PhD (Drexel)
Dan Geschwind, MD PhD (UCLA)

THANK YOU

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Children's Healthcare of Atlanta
EMORY UNIVERSITY

44