The Integration of Genomics into Acute Care Psychiatry

Precision Medicine on the Inpatient Child and Adolescent Psychiatry Service

UC San Diego/Rady Children's Autism Research and Practice Seminar

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No Conflicts of Interest to Disclose

Overview

I. Genetics of Autism and Other Neurodevelopmental Disorders

II. Genetic Testing in Child and Adolescent Psychiatry: An Inpatient Experience

III. Genetic Testing Implementation at RCHSD and RCIGM

I. Genetics of Autism and Other Neurodevelopmental Disorders

Neurodevelopmental Disorders (NDDs)

Autism Spectrum Disorders

- Social communication deficits
- Restrictive and repetitive behaviors, interests, activities

Global Developmental Delay

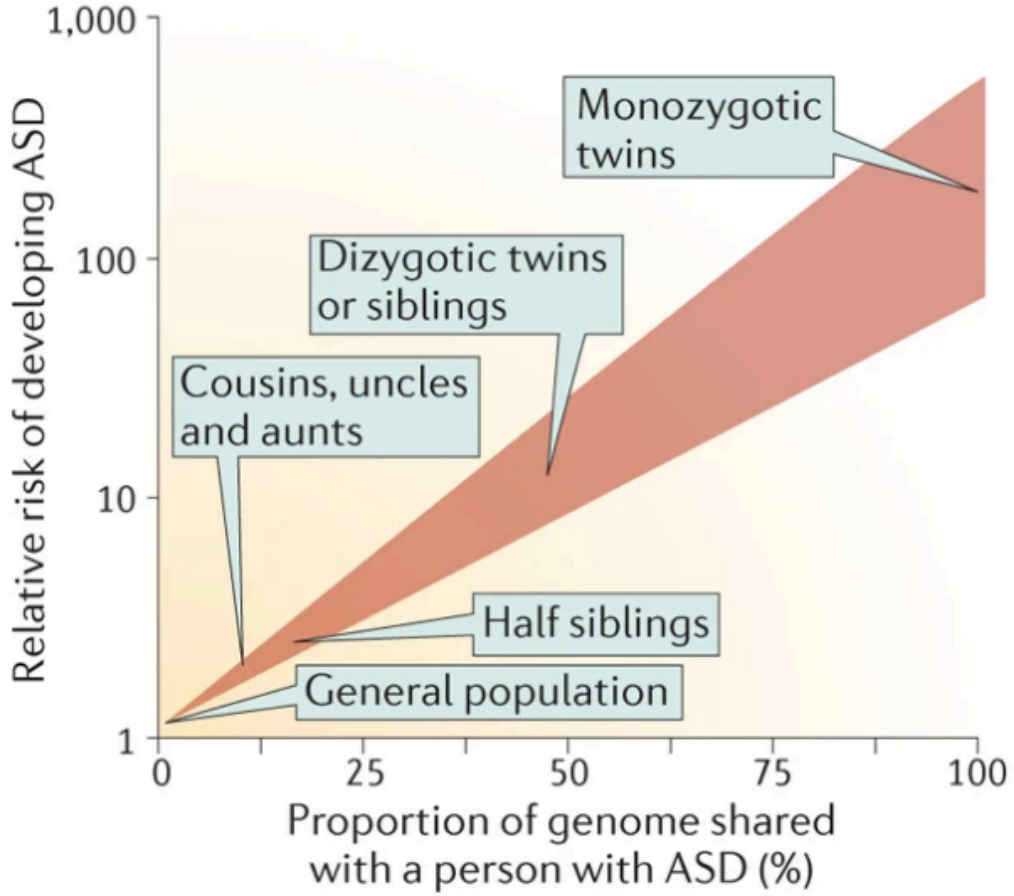
- Not reaching developmental milestones on time
- <5 years old

Intellectual Disability

- Deficits in intellectual and adaptive functioning

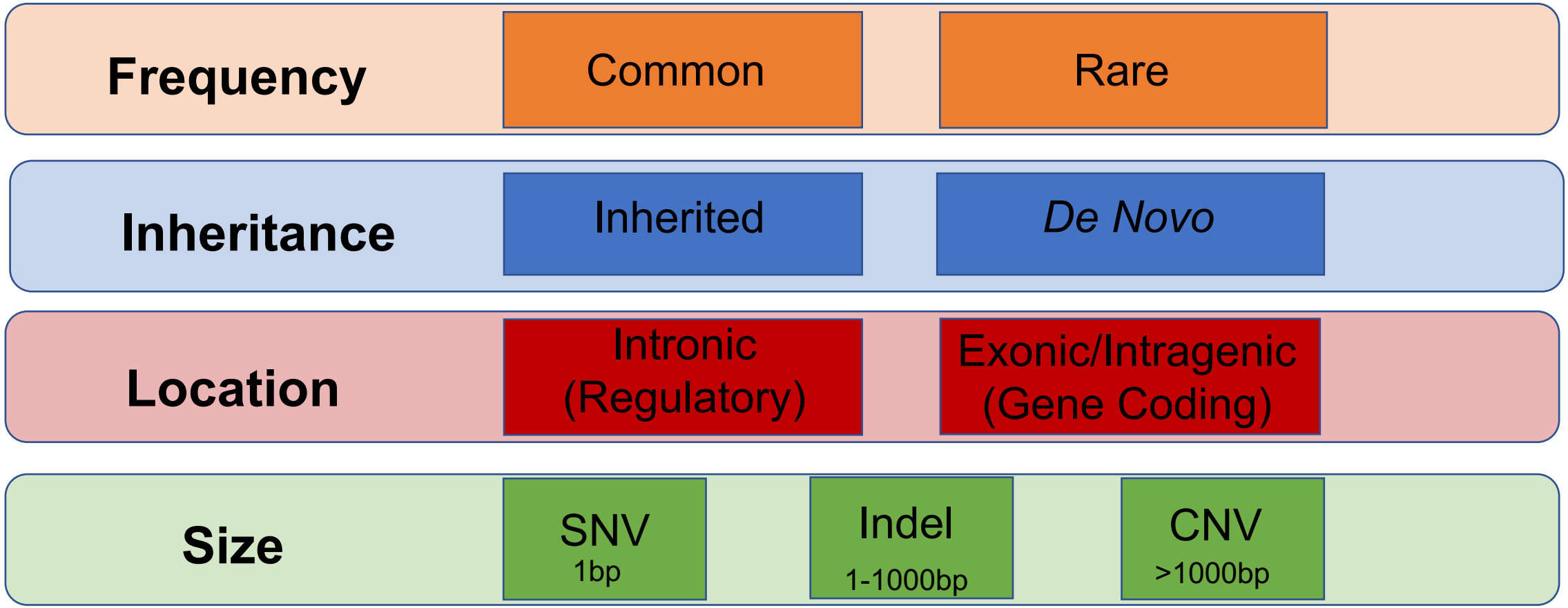
(…and ADHD, Schizophrenia, Tourette Syndrome…)

Neurodevelopmental Disorders Are Largely Genetic Disorders

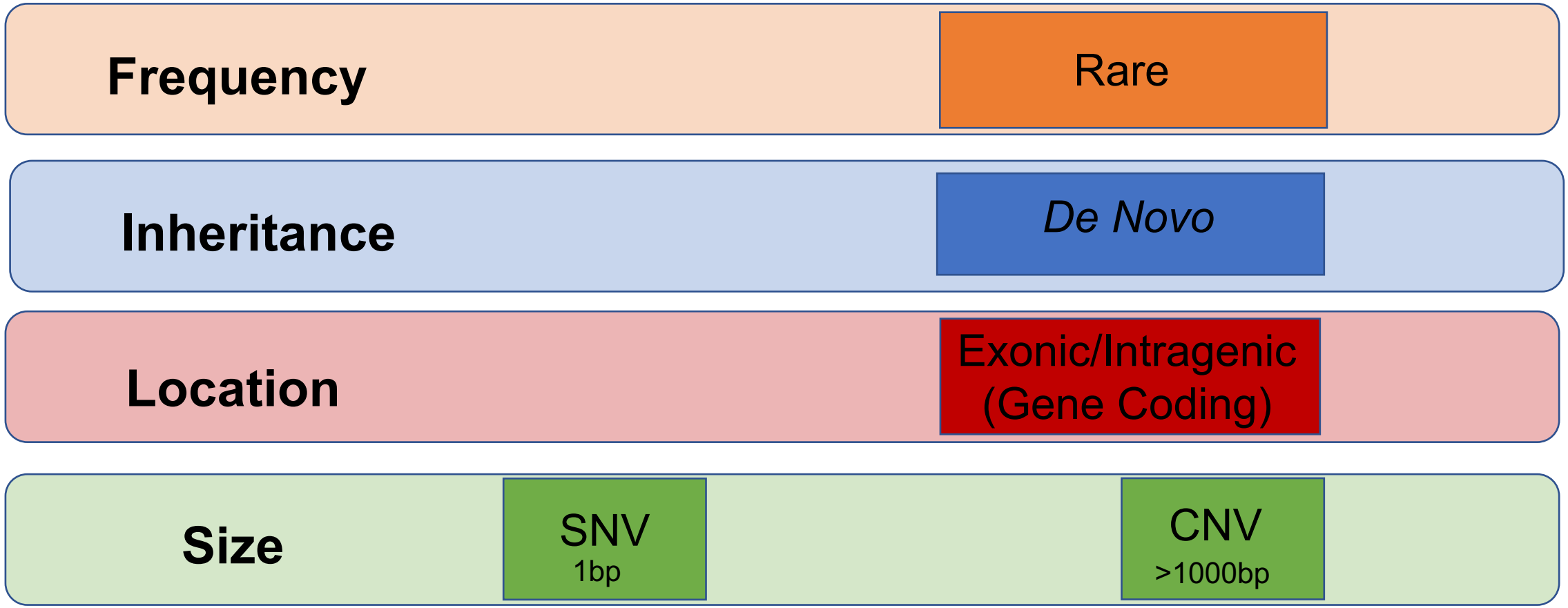


Bourgeron. Nat Rev Neurosc. 2015

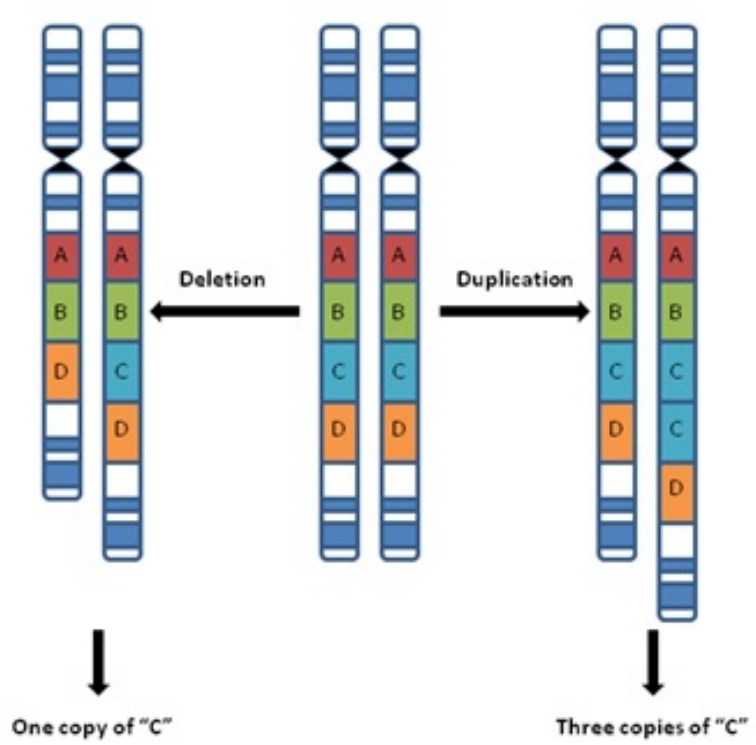
Human Genetic Variation Can Be Classified Multiple Ways



Rare, De Novo, Intragenic Variants May Have Largest *Individual* Contribution to Genetic Risk for NDDs



Pathogenic Copy Number Variants Are Detected in 15-20% of Individuals with NDDs



http://readingroom.mindspec.org/wp-content/genetics_CNV.jpg

Abnormality	ASD penetrance* (rate of ASD in carriers; %)	Neuropsychiatric pleiotropy‡ (associated neuropsychiatric phenotypes)	Somatic pleiotropy‡ (associated somatic phenotypes)
Del1q21.1	8 (REF. 129)	ID[130], ADHD[129], schizophrenia[131]	Microcephaly[129], heart defect[132], eye abnormalities[129], short stature[129], epilepsy[129]
Dup1q21.1	36 (REF. 133)	ID[133], schizophrenia[133]	Epilepsy[133,134], macrocephaly[133], heart defect[133]
Del2q23.1	100 (REF. 135)	ID[135], ADHD[135], language disorder[136], motor delay[136]	Epilepsy[135,136], obesity[136], brachycephaly[136], microcephaly[136], short stature[136]
Del2q37	25–42 (REFS 137,138)	ID[139], ADHD[138]	Epilepsy[137], short stature[139], obesity[139], heart defect[137]
Del3q29	27 (REFS 63,140)	ID[63], speech delay[63], language disorder[63], anxiety disorders[63], schizophrenia[63], bipolar disorder[63]	Gastrointestinal problems[63], heart defect[63], feeding problems[63], recurrent ear infections[63], abnormal dentition[63]
Del5q14.3	43 (REFS 141,142)	ID[141], absent speech[141]	Epilepsy[141,142], capillary malformation[141,142]
Dup7q11.23	41 (REF. 143)	ID[143], ADHD[144,145], anxiety disorders[145,146], oppositional defiant disorders[145], speech delay[134,145]	Epilepsy[143], macrocephaly[145], brachycephaly[147], dilatation of ascending aorta[145,147], patent ductus arteriosus[147], chronic obstipation[147], kidney abnormalities[147]
Del8p23	Unknown	ID[148], ADHD[138]	Heart defect[148], congenital diaphragmatic hernia[148]
Dup15q11–q13	69 (REF. 149)	ID[150], ADHD[151]	Epilepsy[134,152], heart defect[134], muscle hypotonia[153], short stature[153]

Vorstman et al. Nat Rev Genet. 2017

ARTICLE

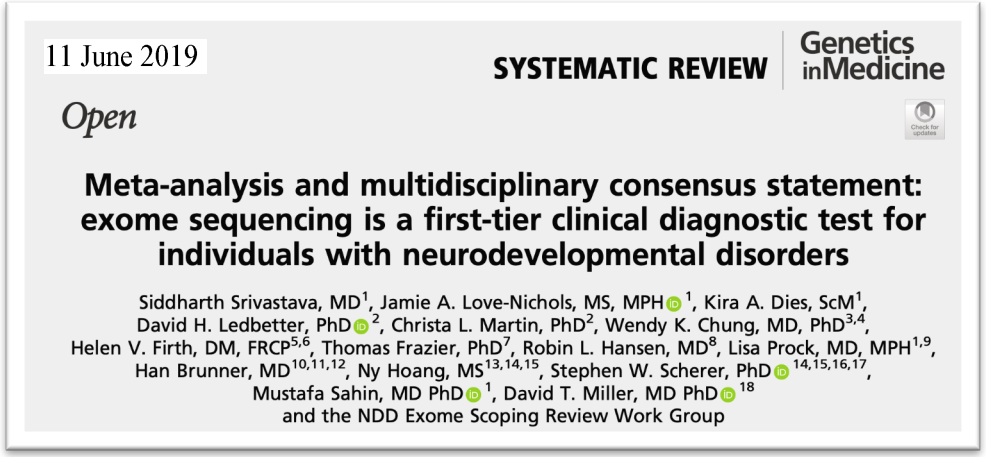
Consensus Statement: Chromosomal Microarray
Is a First-Tier Clinical Diagnostic Test for Individuals
with Developmental Disabilities or Congenital Anomalies

The American Journal of Human Genetics *86*, 749–764, May 14, 2010

Over 100 Genes Are Now Associated with ASD and NDDs through Whole Exome Sequencing (SNVs)

	ASD predominant (ASD_P) 53 genes			ASD & NDD (ASD_{NDD}) 49 genes		
Gene expression regulation 58 genes	***ASH1L***	*KMT2C*	*RFX3*	***ADNP***	*IRF2BPL*	*SETD5*
	CELF4	*KMT2E*	*RORB*	***ANKRD11***	*MBD5*	*SIN3A*
	CHD8	***KMT5B***	*SATB1*	***ARID1B***	***MED13L***	*TBL1XR1*
	DEAF1	*LDB1*	*SKI*	*ASXL3*	*MYT1L*	*TCF4*
	EIF3G	*MKX*	*SMARCC2*	*BCL11A*	*NACC1*	*TCF7L2*
	ELAVL3	*NCOA1*	*TBR1*	***CHD2***	*NSD1*	*TCF20*
	HDLBP	*PAX5*	*ZMYND8*	*CREBBP*	*NR3C2*	***TLK2***
	KDM5B	*PHF2*		***CTNNB1***	*PHF12*	*TRAF7*
	KDM6B	*PHF21A*		*DNMT3A*	***POGZ***	*TRIP12*
				FOXP1	*PPP2R5D*	*VEZF1*
				FOXP2	*RAI1*	*WAC*
Neuronal communication 24 genes	***ANK2***	*GRIA2*	*SCN1A*	*CACNA1E*	*KCNQ3*	***SLC6A1***
	AP2S1	*KCNMA1*	*SHANK2*	*GABRB2*	*LRRC4C*	*STXBP1*
	CACNA2D3	***NRXN1***	***SHANK3***	*GABRB3*	*PRR12*	***SYNGAP1***
	DIP2A	***PTEN***		***GRIN2B***	***SCN2A***	
	DSCAM	*PPP1R9B*				
Cytoskeleton 9 genes	*CORO1A*	*GFAP*	*PTK7*	*DYNC1H1*	***DYRK1A***	*TAOK1*
	DPYSL2	*MAP1A*	*SPAST*			
Other 11 genes	***GIGYF1***	*PPP5C*	*TM9SF4*	*GNAI1*	*HECTD4*	
	KIAA0232	*SRPRA*	*TRIM23*			
	NUP155	*TEK*	*UBR1*			

Satterstom et al. Cell. 2020.



11 June 2019

SYSTEMATIC REVIEW | Genetics inMedicine

Open

Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders

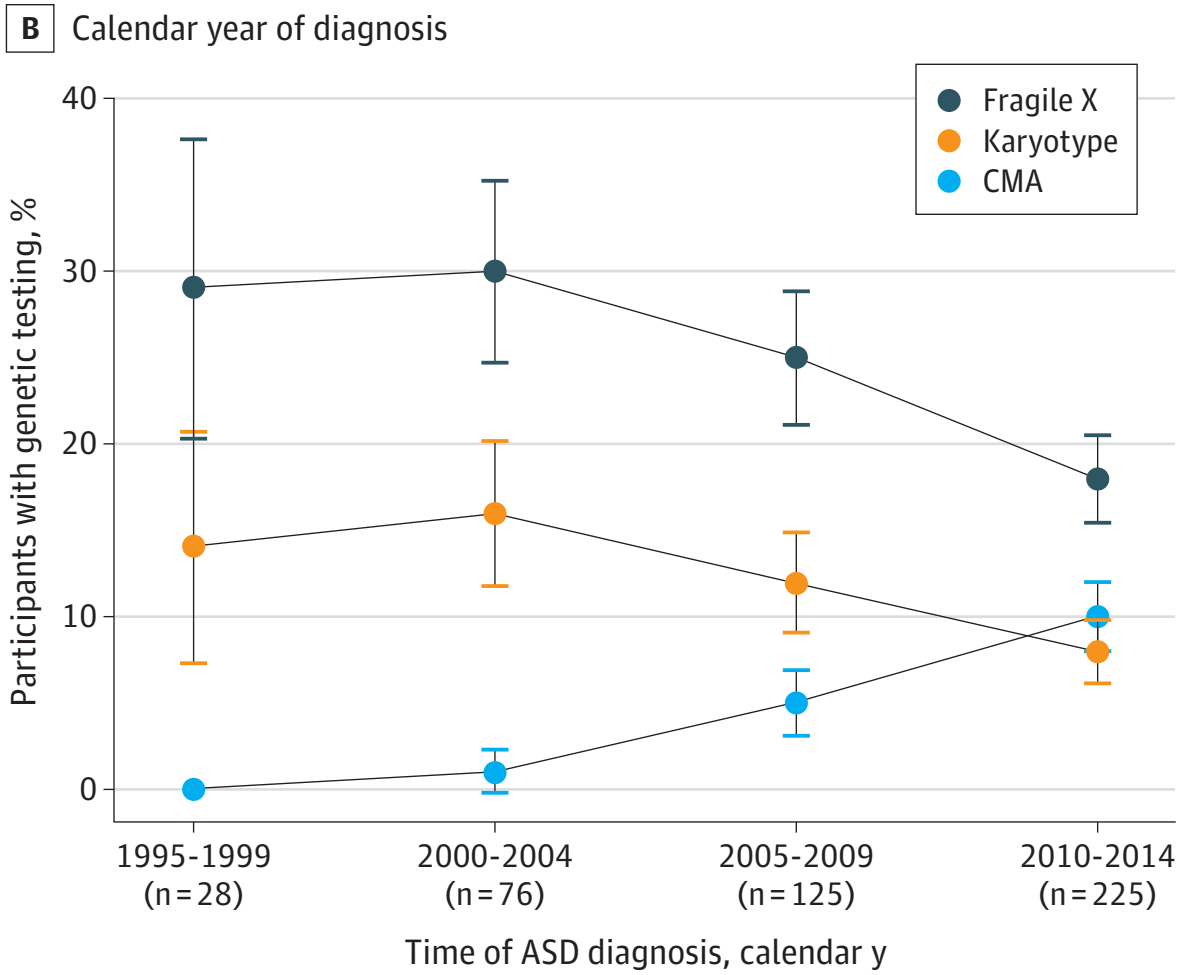
Siddharth Srivastava, MD[1], Jamie A. Love-Nichols, MS, MPH[1], Kira A. Dies, ScM[1], David H. Ledbetter, PhD[2], Christa L. Martin, PhD[2], Wendy K. Chung, MD, PhD[3,4], Helen V. Firth, DM, FRCP[5,6], Thomas Frazier, PhD[7], Robin L. Hansen, MD[8], Lisa Prock, MD, MPH[1,9], Han Brunner, MD[10,11,12], Ny Hoang, MS[13,14,15], Stephen W. Scherer, PhD[14,15,16,17], Mustafa Sahin, MD PhD[1], David T. Miller, MD PhD[18] and the NDD Exome Scoping Review Work Group

36% Diagnostic Yield

Why Do We Order Genetic Tests for NDDs?

- ✓ Answer the question “why?”
  - Diagnostic clarity (End the diagnostic odyssey)
  - Increase empowerment
- ✓ Allow for medical monitoring and prognosis
- ✓ Provide reproductive counseling
- ✓ Guide medical and ?psychiatric care
- ✓ Connect families with community support
- ✓ Allow families to partake in advocacy
- ✓ Identify relevant research studies to families

We are Failing to Act on these Guidelines



Daniel Moreno-De-Luca, MD, MSc
Brian C. Kavanaugh, PsyD
Carrie R. Best, MPH
Stephen J. Sheinkopf, PhD
Chanika Phornphutkul, MD
Eric M. Morrow, MD, PhD

JAMA Psychiatry September 2020 Volume 77, Number 9

II. Genetic Testing in Child and Adolescent Psychiatry: An Inpatient Experience

Why Genetic Testing on an Inpatient CAP Service? It All Began as a Fellow…

- **Clinical observation:** many very sick children with NDDs on our service with no history of genetic testing
  - Ex: 10yo M with mild ID, severe TS, ADHD, OCD, and situs inversus
- Number of patients with NDDs on our inpatient service in 2016: **125**
- Number of patients who received <u>any</u> genetic testing on our inpatient service in 2016: **2**

Multi-level Support and Buy-in are Vital

Mark DeAntonio

Inpatient Child Psychiatry

Mike Enenbach

Sheryl Kataoka

Training Director

Julian Martinez

Medical Genetics

Naghmeh Dorrani

Genetic Counseling

Hane Lee

Bioinformatics

A Genetics Education Initiative

What Should a Psychiatrist Know About Genetics?:

Review and Recommendations From the Residency Education Committee of the International Society of Psychiatric Genetics

John I. Nurnberger Jr, MD,PhD[a,*], **Jehannine Austin, PhD**[b], **Wade H. Berrettini, MD,PhD**[c], **Aaron D. Besterman, MD**[d], **Lynn E. DeLisi, MD**[e], **Dorothy E. Grice, MD**[f], **James L. Kennedy, MD**[g], **Daniel Moreno-De-Luca, MD**[h], **James B. Potash, MD,MPH**[i], **David A. Ross, MD,PhD**[j], **Thomas G. Schulze, MD**[k], and **Gwyneth Zai, MD,PhD**[g]

J Clin Psychiatry 80:1, January/February 2019

- ✓ Understand
- ✓ Counsel
- ✓ Consent
- ✓ Order
- ✓ Return Results
- ✓ Consult
- ✓ Refer

Genetic Testing Indications

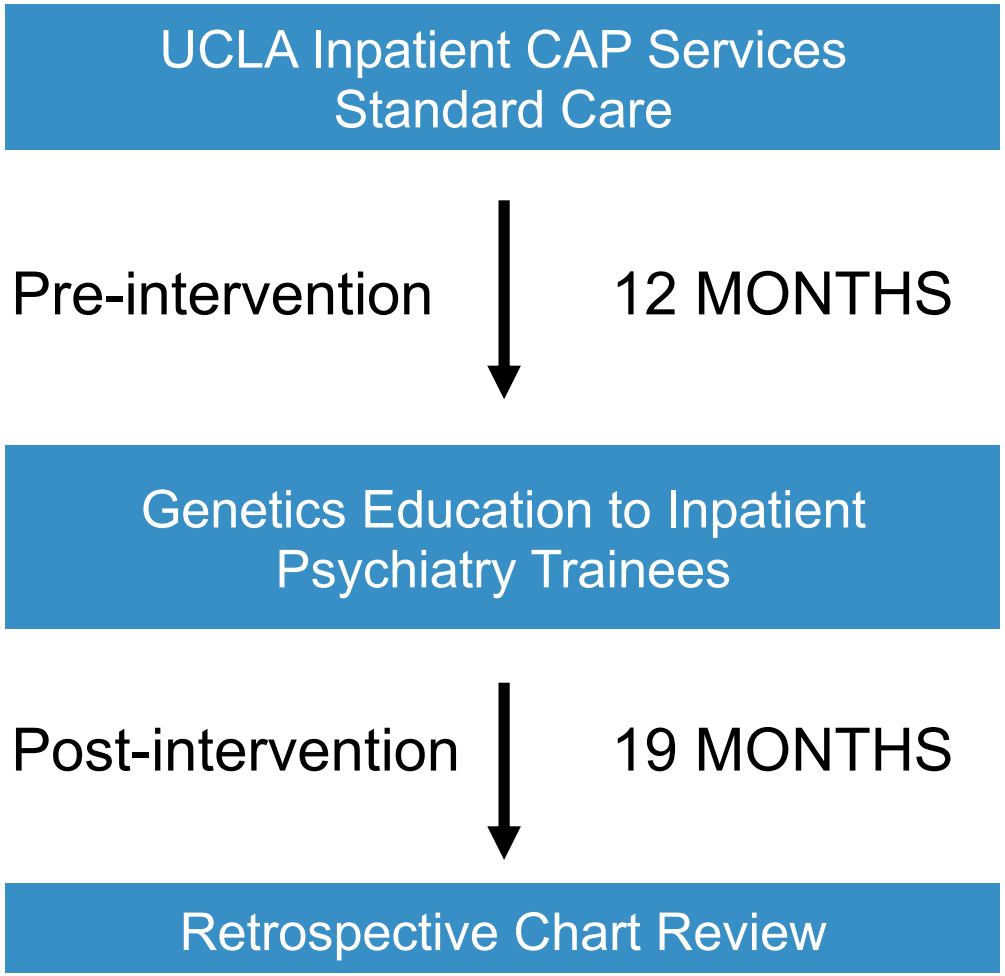
Absolute Indications

- Intellectual Disability
- Developmental Delay
- Autism Spectrum Disorders
- Childhood-Onset Schizophrenia

Relative Indications

- Childhood Epilepsy
- Severe Psychopathology + Congenital Malformations
- High family burden of severe psychopathology

Inpatient Genetic Testing Study



Results of Retrospective Analysis

Eligible Patient Overview

- ✓ 125 patients pre-education,
- ✓ 197 patients post-education
- ✓ Age Range: 6-17yo
- ✓ Male: 78.3%
- ✓ Tested: ID: 39.1%, ASD 69.6%, COS 8.7%

The Feasibility and Outcomes of Genetic Testing for Autism and Neurodevelopmental Disorders on an Inpatient Child and Adolescent Psychiatry Service

Aaron D. Besterman, Joshua Sadik, Michael J. Enenbach, Fabiola Quintero-Rivera, Mark DeAntonio, and Julian A. Martinez-Agosto

Autism Research 13: 1450–1464, 2020

Genetic Testing Rates

- ✓ Pre-Intervention: 2/125 (1.6%)
- ✓ Post-Intervention: 21/197 (10.7%)

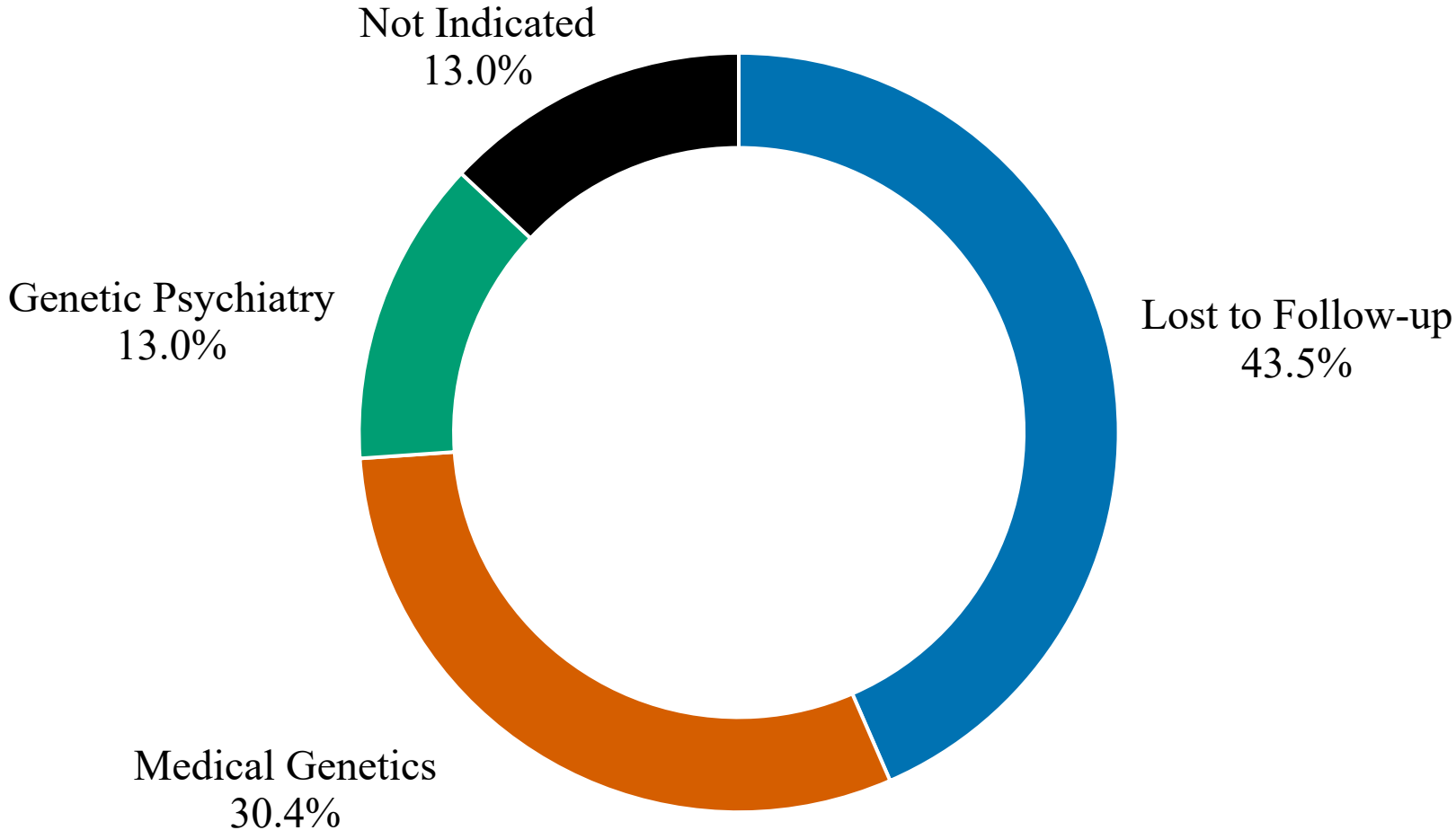
Diagnostic Yield (FX: 18, CMA: 23, WES: 6)

- ✓ Pathogenic/Likely Pathogenic: 1/23 (4.3%)
- ✓ Variant of Unknown Significance: 8/23 (34.8%)

Interpreting and Addressing Low Yield

- Small sample size
- “Unexpected” phenotype (Impulse Control Disorders)
- Poorly studied patient population (High VUS rate)
- High common variant contribution (family history)
- Only ¼ of patients received WES

Outpatient Follow-up Was a Challenge



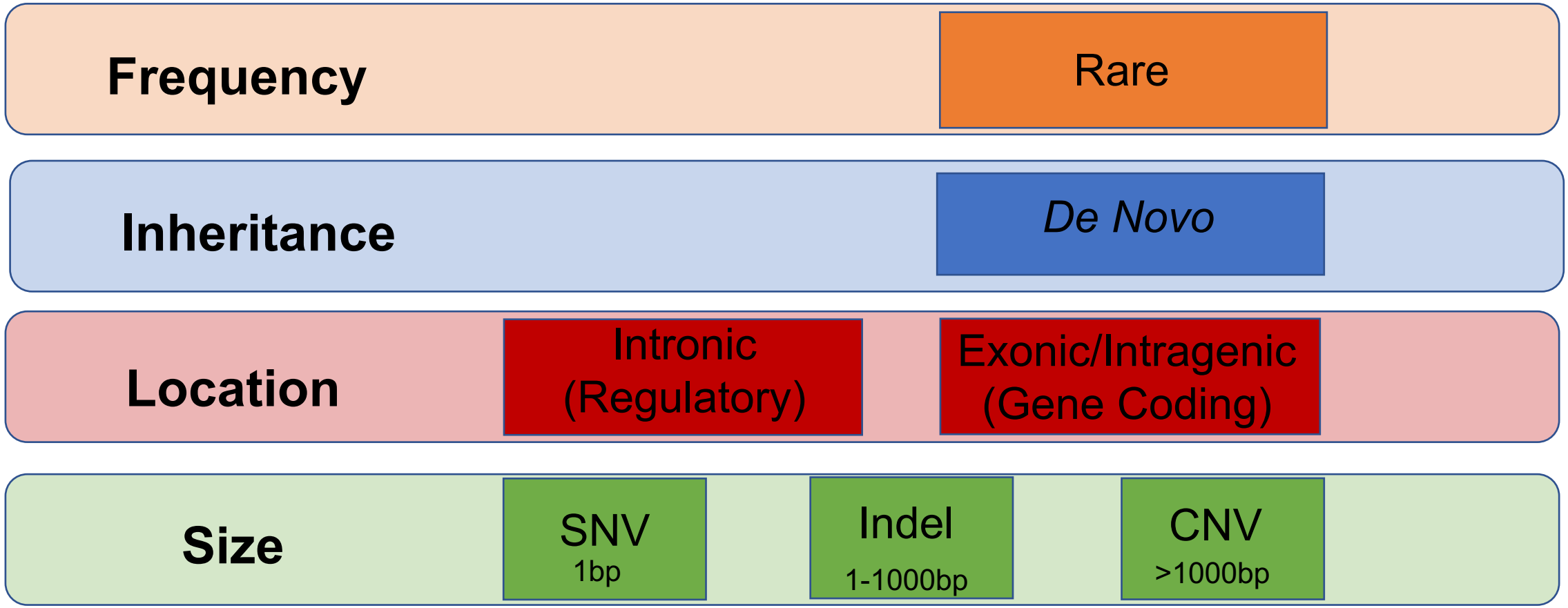
Unexpected Benefit to Inpatient Testing

- 39.1% of patients who received testing on inpatient were URMs
- 7.7% of patients who received testing elsewhere were URMs

Inpatient testing has the potential to increase access to genetic services for URMs

III. Genetic Testing Implementation in Child Psychiatry at RCHSD and RCIGM

RCIGM Performs Whole Genome Sequencing (WGS), Which Can Detect Most Variants of Interest for NDD Diagnoses



Rady Children's Institute Genomic Medicine

Rapid WGS
Is Ideal for an Acute Care Setting

DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5]* Neil Andrew Miller,[1,2,4]* Sarah Elizabeth Soden,[1,2,4]* Darrell Lee Dinwiddie,[1,2,3,4,5]* Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4] Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5]†

www.ScienceTranslationalMedicine.org 3 October 2012 Vol 4 Issue 154 154ra135

Turn around time in 3-7 days!

Average length of stay for psychiatry inpatient: 3-7 days!

npj | Genomic Medicine

www.nature.com/npjgenmed

ARTICLE OPEN

The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants

Josh E. Petrikin[1,2,3], Julie A. Cakici[4], Michelle M. Clark[4], Laurel K. Willig[1,2,3], Nathaly M. Sweeney[4,5], Emily G. Farrow[1,2,3], Carol J. Saunders[1,3,6], Isabelle Thiffault[1,3,6], Neil A. Miller[1], Lee Zellmer[1], Suzanne M. Herd[1], Anne M. Holmes[2], Serge Batalov[4], Narayanan Veeraraghavan[4], Laurie D. Smith[1,3,7], David P. Dimmock[4], J. Steven Leeder[2,3] and Stephen F. Kingsmore[4]

npj Genomic Medicine (2018) 6

Rady Children's Institute
Genomic Medicine

RCHSD and RCIGM Provide a Unique Environment for Success

Traditional Barriers to Genetic Testing for NDDs

1. Diagnostic Odyssey
   - Step-wise outpatient testing/authorization
   - Many visits, many years
2. Outpatient facilities are not equipped to provide blood draws for patients with severe agitation
3. Underrepresented minorities may have less access to genetic services for NDDs
4. High loss to follow-up with standard “slow” testing approaches
5. Difficult to access team of professionals with expertise in psychiatry + genetics to use results to inform clinical care

Inpatient rWGS Solution

1. Can detect most variants of interest in 1 test
2. Trained, professional staff can safely draw blood samples
3. Any child who gets admitted and is eligible can get genetic testing as part of their medical work-up
4. Minimize loss to follow-up with rapid turn-around time
5. Explore impact of genetic test result on clinical care with input from RCIGM collaborators

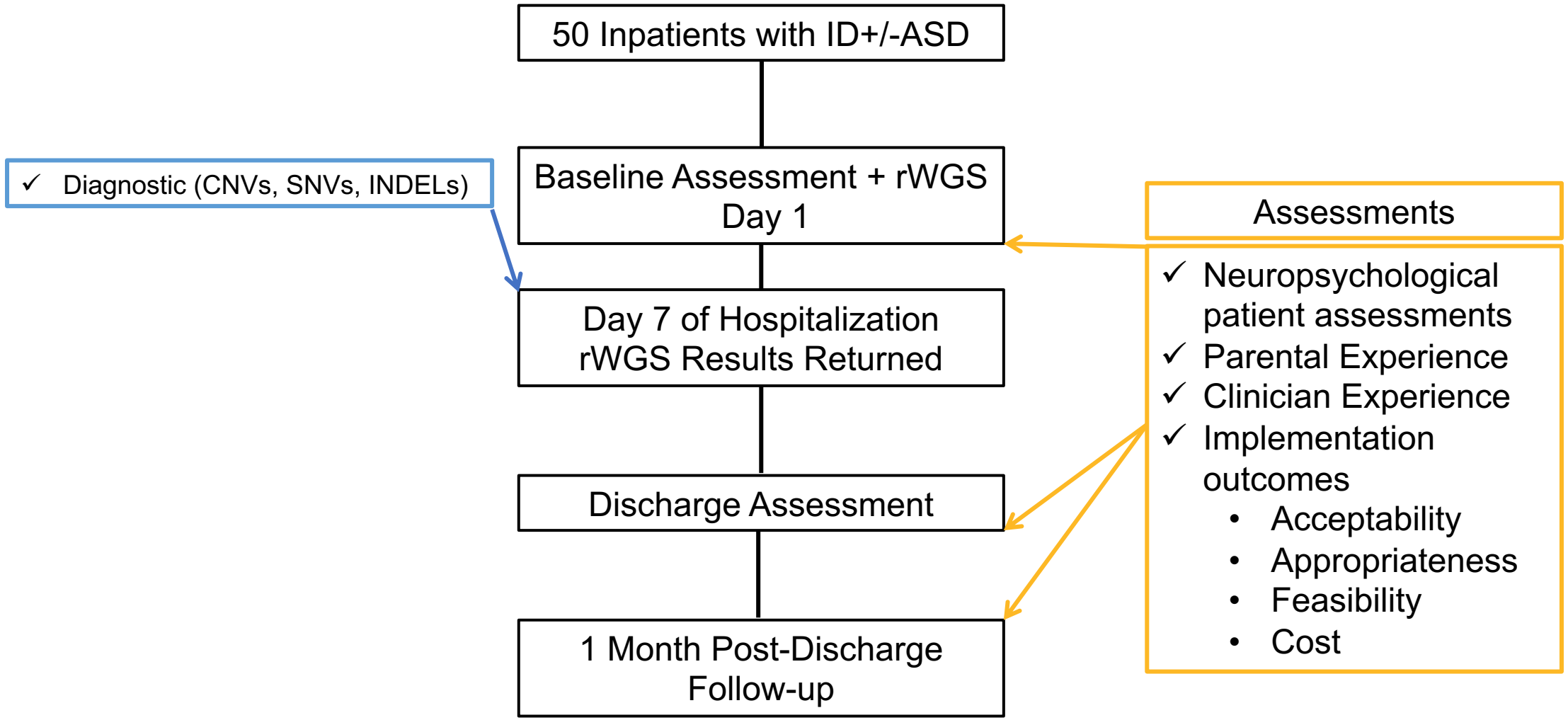
Genomics can Guide Precision Psychiatric Care for Some Patients with NDDs

- **Smith-Magenis Syndrome**
  - 17p11.2 deletion or RAI1 mutation with inverted melatonin secretion and sleep cycle
  - Treat with morning beta-blocker and evening melatonin
- **15q13.3 deletion syndrome**
  - ID syndrome with severe aggression and deleted α7NChR
  - Reduced aggression and psychotropic burden with galantamine

Additional Potential Benefits of rWGS on Inpatient CAP Service

- Improve family experience of hospitalization (e.g. everything is being done) and understanding of child's illness
- Prepare for dissemination into less acute areas of psychiatry and other indications (e.g. schizophrenia – diagnostic yield 5-10%)
- Educate psychiatry trainees in genomic medicine

Prospective, Observational Hybrid Clinical Effectiveness/Implementation Study



Thank You!

UCLA

- Families!
- Julian Martinez
- Mark DeAntonio
- Michael Enenbach

RCHSD/RCIGM

- Stephen Kingsmore
- Charlotte Hobbs
- Nicole Stadnick
- Greg Aarons

Funding and Support

- T32 UCLA Intercampus Medical Genetics Training Program
- Savant Fellowship in Developmental Neurogenetics
- AACAP Junior Investigator Award
- UCLA CART and IDDRC
- RCIGM