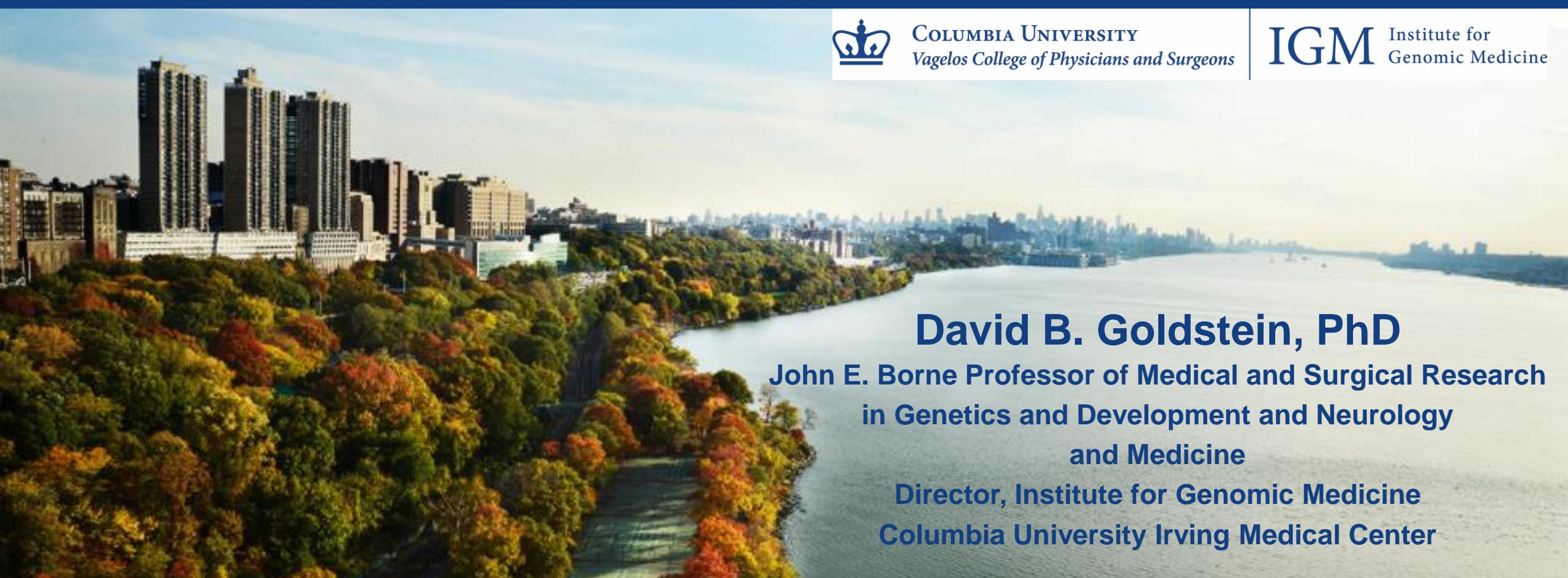


Precision Medicine 2021



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IGM Institute for
Genomic Medicine

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Disclosure Statement of Financial Interest

Founder of precision medicine companies Praxis Precision Medicines and Actio Biosciences .

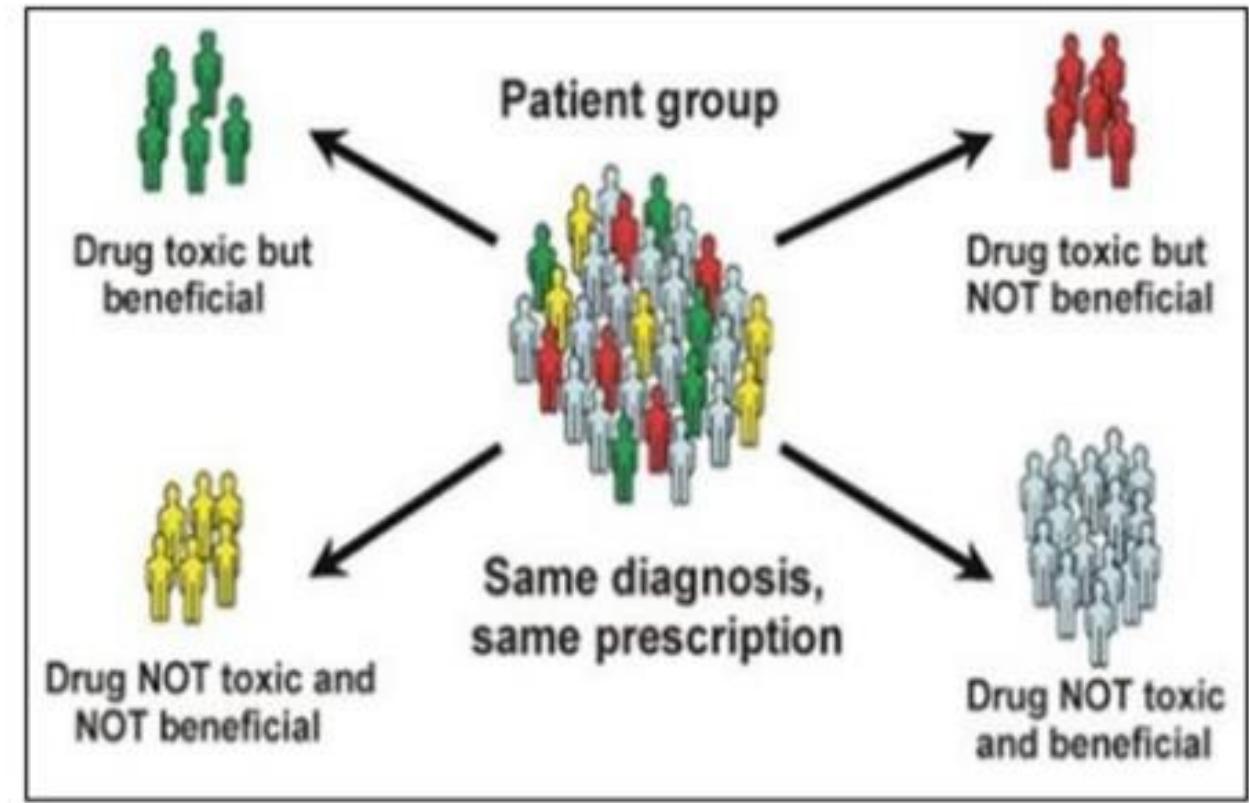


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Genetically Stratified Medicine

- Goal is to identify subgroups of patients with similar disease mechanisms and specific responses to medications and treatments
- WES is an important tool in the advancement of genetically stratified medicine
- Relies on widespread sequencing of cohorts of interest and a centralized system for enrollment, sequencing and storage of data



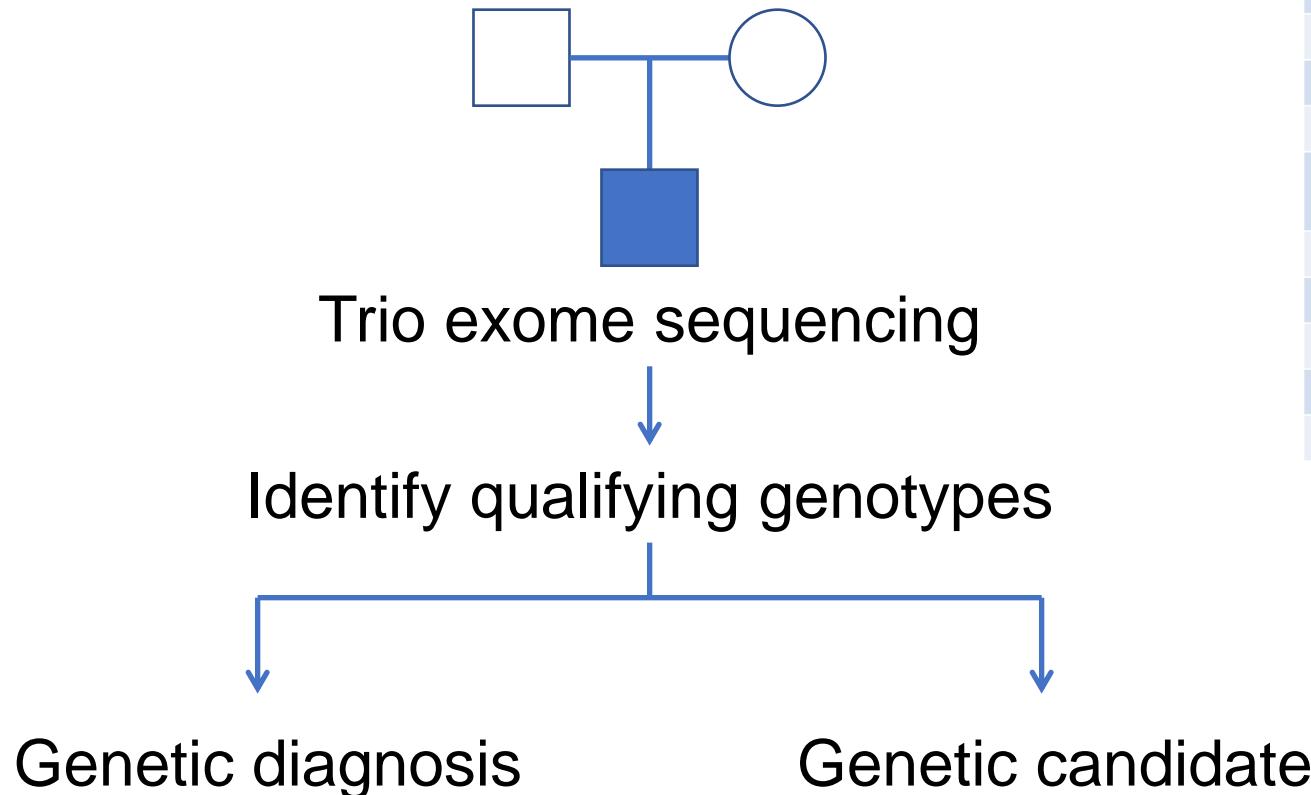
Source: https://www.who.int/medicines/areas/priority_medicines/Ch7_4Stratified.pdf?ua=1



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Sequencing for Rare Diseases



Study	Journal	N	Ascertainment	% resolved
Need 2012	J Med Genet	12	Mixture	50%
Yang 2013	NEJM	250	80% Neuro	25%
Calvo 2012	Sci Transl Med	42	Mitochondrial	24%
DeLigt 2013	NEJM	100	Severe ID	16%
Zhu 2014	Genetics in Medicine	119	Mixture	24%
Srivastava 2014	Annals of Neuro	78	Neuro	41%
Yang 2014	JAMA	2,000	Mixture	25%
Lee 2014	JAMA	814	Mixture	26%
Soden 2014	Sci Transl Med	119	Neuro	45%
Combined	-	3,534	Mixture	26%



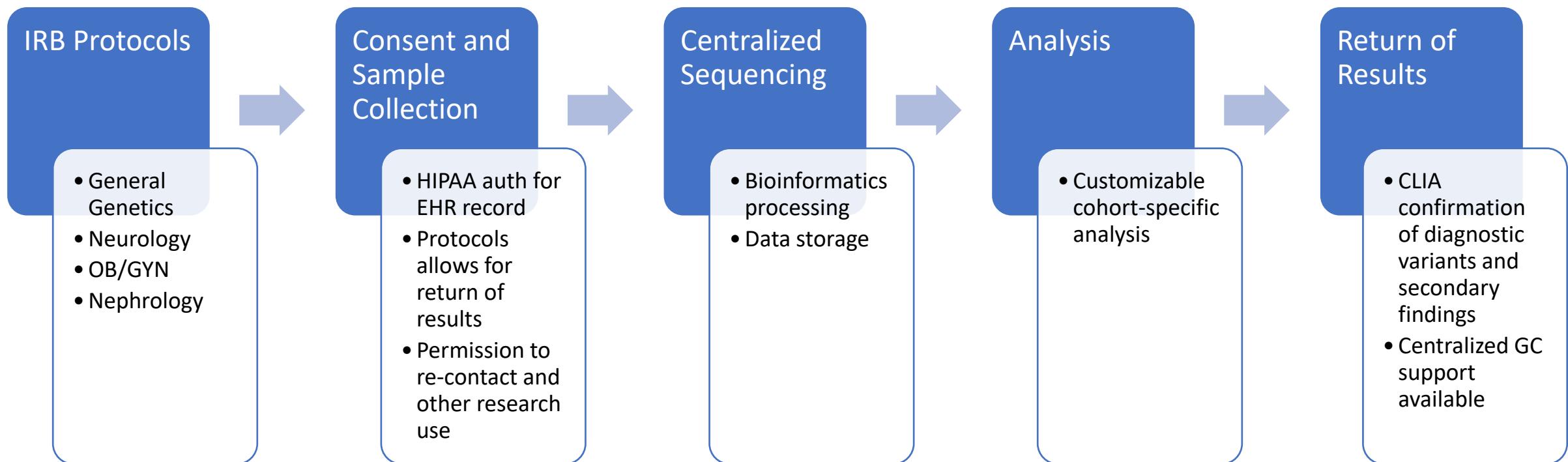
Ten Thousand patients sequenced to date at tertiary care center



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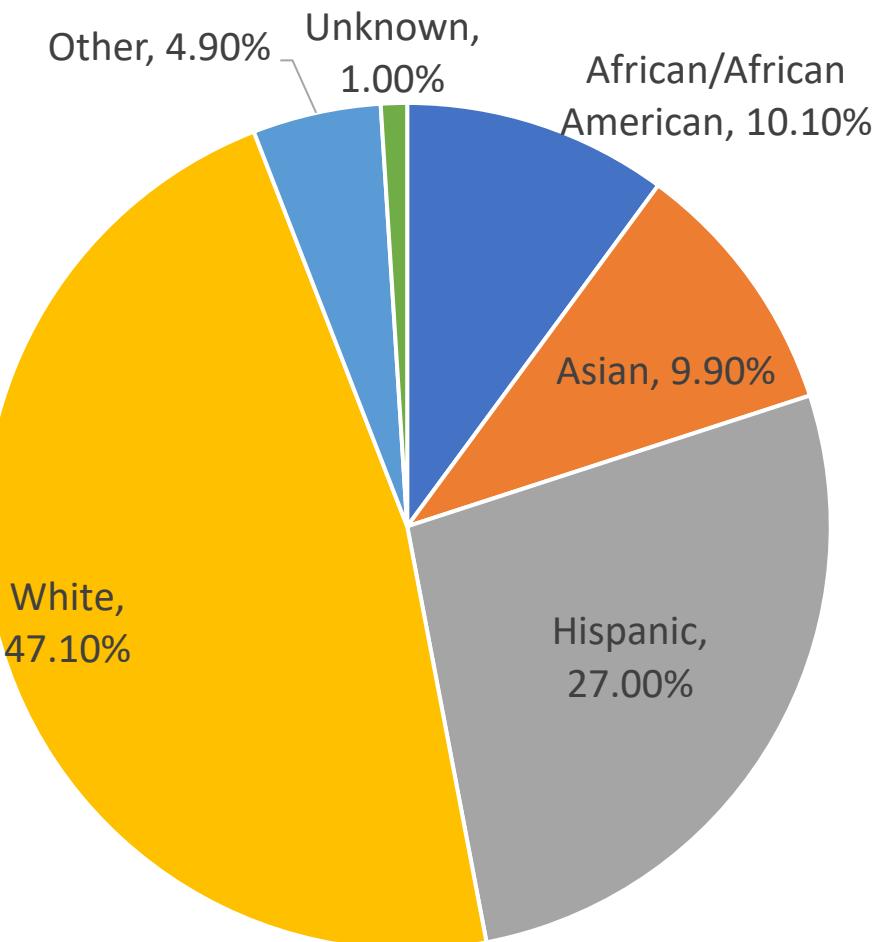
General Workflow



Diversity

- Protocols were developed to be as accessible as possible
 - Remote enrollments
 - Spanish translations
 - CUIMC's short form consent process
 - No cost to participant
- ~ 50% of study subjects identified from a group underrepresented in biomedical research

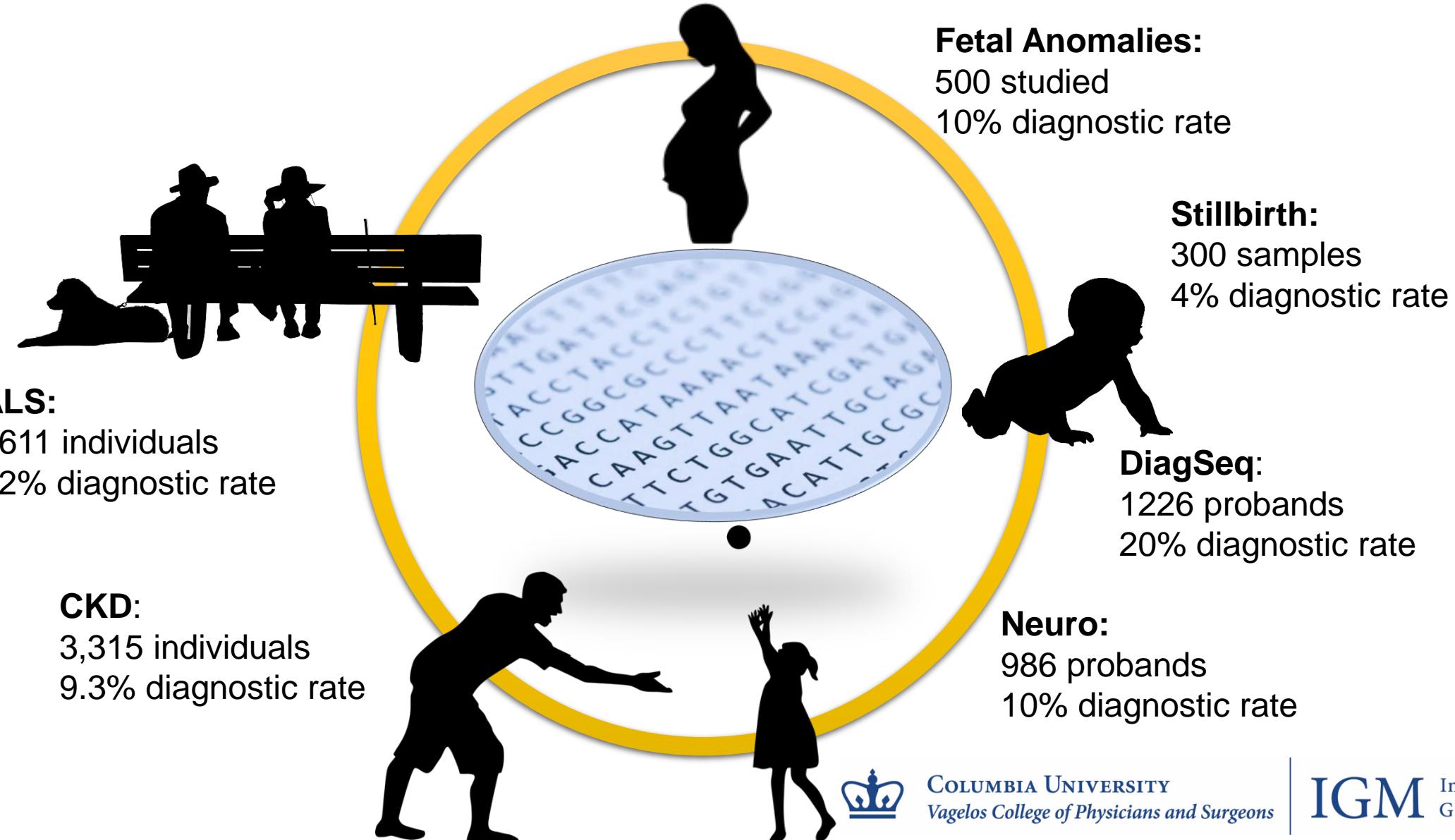
Race/Ethnicity of Cohort



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Utility of Genomics Throughout the Lifespan

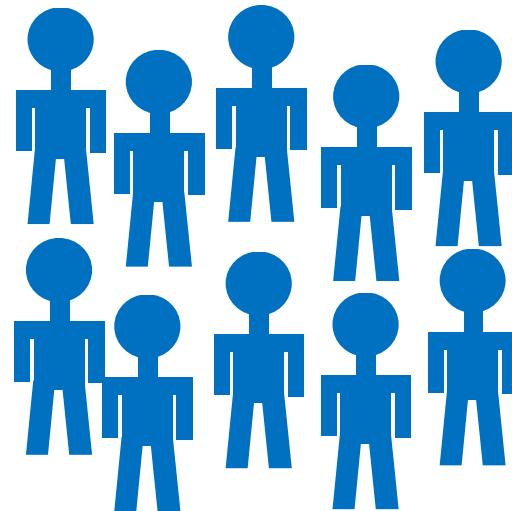


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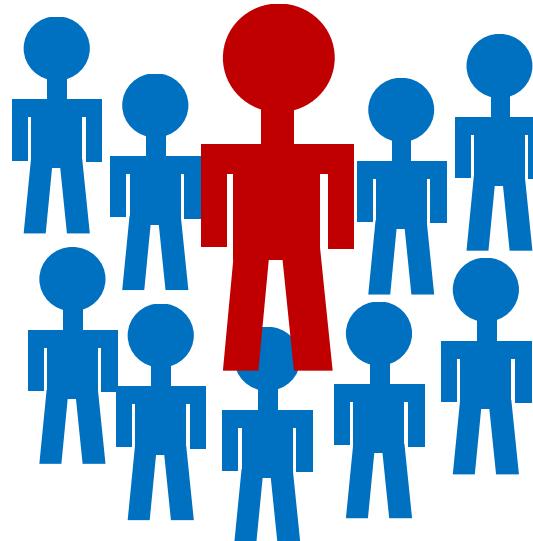
Diagnostic Utility of Exome Sequencing For Kidney Disease

ES of 3,315 individuals with all-cause CKD



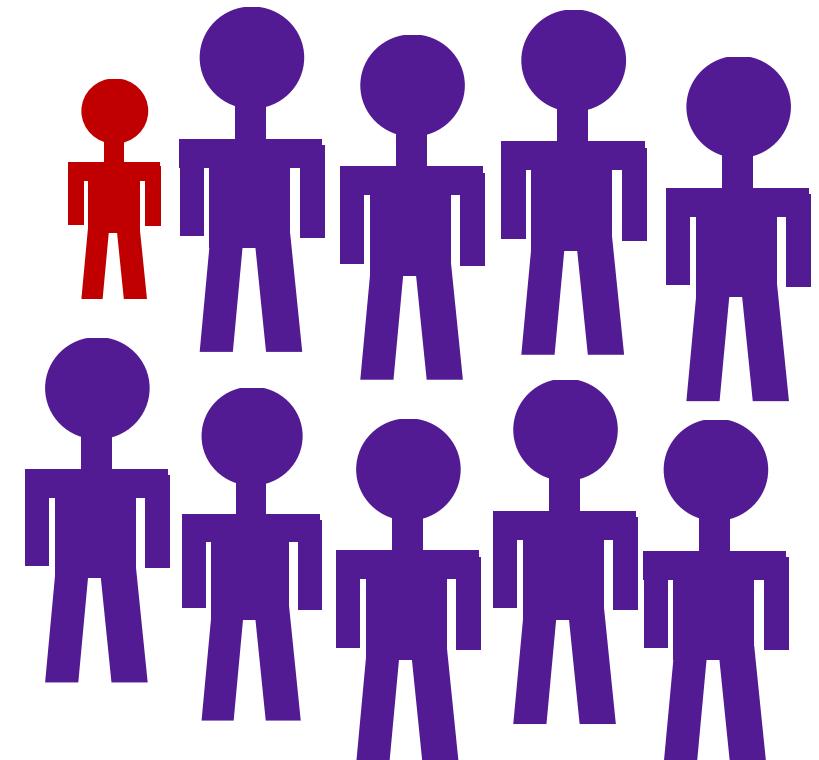
91.6% adults
35.6% non-white
European ethnicity

~1 in 10 (9.3%) have diagnostic findings



66 different single-gene etiologies
59% unique cases

In 89% of cases genetic findings inform clinical care



Spectrum of Schizophrenia Severity by Treatment Setting and Length of Stay

Community/Outpatient



Community Inpatient (10 days)



Schizophrenia Severity

State Inpatient (< 5 years)



State Inpatient (> 5 years)



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Burden of Rare Variants in Intolerant Genes Across Neuropsychiatric Disorders

Disease	Missense Variants	Loss-of-Function Variants
SETRS	OR 2.62*	OR 1.95**
Typical SCZ	OR 1.06	OR 1.26
Autism	OR 1.2	OR 1.8
Epilepsy	OR 1.1	OR 1.3

* $p = 1.64 \times 10^{-5}$

** $p = 3 \times 10^{-4}$

50% of SETRS patients vs. 26% of controls have a rare qualifying missense or LoF variant in the intolerant gene sets (**OR 2.9, 95% CI 1.86-4.52, $P = 1.2 \times 10^{-6}$**)



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Most Common Genetic Diagnoses

Diagnosis Gene	Proband Count	Cohort
<i>COL4A5</i>	35	CKD
<i>COL4A3</i>	17	CKD
<i>COL4A4</i>	14	CKD
<i>SCN1A</i>	12	Epilepsy, ID/DD/ASD
<i>NF1</i>	10	CKD, Epilepsy, ID/DD/ASD
<i>PKD1</i>	10	CKD
<i>SCN2A</i>	10	Fetal Anomaly, Epilepsy, ID/DD/ASD
<i>NF1</i>	9	Epilepsy, ID/DD/ASD
<i>TRPC6</i>	8	CKD
<i>NSD1</i>	7	Epilepsy, ID/DD/ASD
<i>UMOD</i>	7	CKD
<i>CACNA1A</i>	6	Epilepsy, ID/DD/ASD, Ataxia
<i>EYA1</i>	6	CKD, Fetal
<i>HNF1A</i>	6	CKD
<i>NPHS2</i>	6	CKD
		Fetal Anomaly, Epilepsy, Congenital
<i>COL4A1</i>	5	Anomaly
<i>PAX2</i>	5	CKD
<i>PTPN11</i>	5	CKD, ID/DD/ASD

- Identified a primary result in 568/4890 probands that fully or partially explains phenotype
- Genetic diagnoses were identified across multiple cohorts



Brown-Vialetto-Van Laere Syndrome

3 weeks pre-treatment



2 days of treatment



3 weeks of treatment



4 weeks of treatment



Cara Greene



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Transcriptomic Restoration

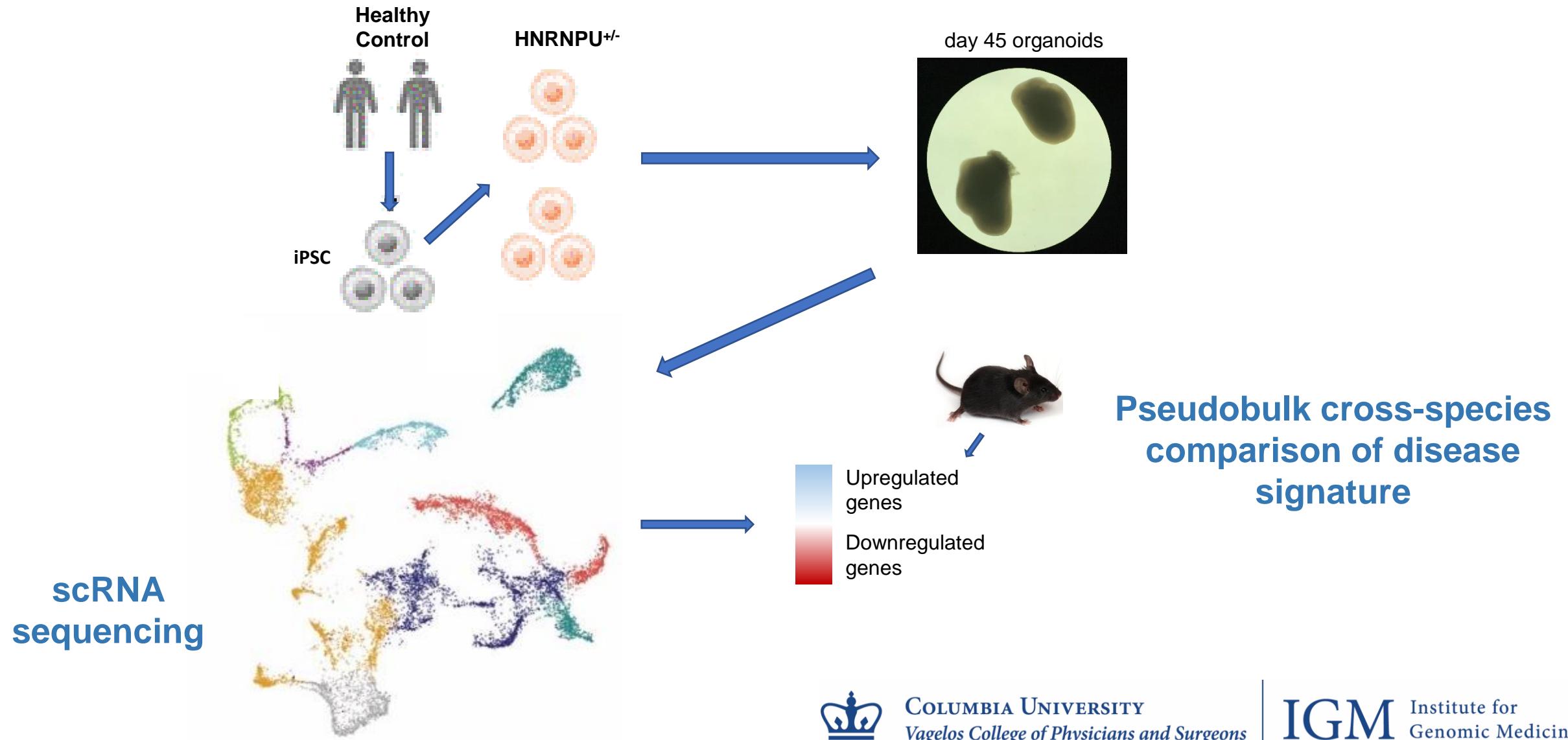
Developmental delay	<i>ACTL6B</i>	<i>CHD2</i>	<i>FOGX1</i>	<i>KAT6A</i>	<i>NACC1</i>	<i>POLR3A</i>	<i>SIM1</i>	<i>TBX1</i>
	<i>ADNP</i>	<i>CHD4</i>	<i>FOXP1</i>	<i>KAT6B</i>	<i>NFIX</i>	<i>POLR3B</i>	<i>SIX3</i>	<i>TCF20</i>
Autism spectrum disorder	<i>AFF2</i>	<i>CHD7</i>	<i>FOXP3</i>	<i>KDM5C</i>	<i>NKX2-1</i>	<i>POU3F3</i>	<i>SKI</i>	<i>TCF4</i>
	<i>AFF4</i>	<i>CREBBP</i>	<i>GATA2D2B</i>	<i>KDM6A</i>	<i>NR2F1</i>	<i>PQBP1</i>	<i>SMARCA2</i>	<i>TGIF1</i>
Epileptic encephalopathy	<i>ARID1A</i>	<i>CTCF</i>	<i>GLI2</i>	<i>KMT2A</i>	<i>NSD1</i>	<i>PRMT7</i>	<i>SMARCA4</i>	<i>THOC6</i>
	<i>ARID1B</i>	<i>CTDP1</i>	<i>GLI3</i>	<i>KMT2D</i>	<i>OTX2</i>	<i>PTF1A</i>	<i>SMARCB1</i>	<i>THRA</i>
Schizophrenia	<i>ARX</i>	<i>DDX3X</i>	<i>GTF2H5</i>	<i>KMT2E</i>	<i>PAX6</i>	<i>PURA</i>	<i>SNRPB</i>	<i>TWIST1</i>
	<i>ASXL1</i>	<i>DEAF1</i>	<i>HCFC1</i>	<i>KMT5B</i>	<i>PAX8</i>	<i>RAI1</i>	<i>SON</i>	<i>UPF3B</i>
BAZ2B	<i>ATRX</i>	<i>DNNMT3A</i>	<i>HDAC4</i>	<i>LARP7</i>	<i>PCGF2</i>	<i>RARB</i>	<i>SOX2</i>	<i>WAC</i>
	<i>AUTS2</i>	<i>DNNMT3B</i>	<i>HDAC8</i>	<i>MAF</i>	<i>PHF6</i>	<i>RAX</i>	<i>SOX3</i>	<i>YY1</i>
BCL11A	<i>BCL11A</i>	<i>EBF3</i>	<i>HNRNPK</i>	<i>MECP2</i>	<i>PHF8</i>	<i>RERE</i>	<i>SRCAP</i>	<i>ZBTB20</i>
	<i>BRPF1</i>	<i>EHMT1</i>	<i>HNRNPR</i>	<i>MED12</i>	<i>PHOX2B</i>	<i>SATB2</i>	<i>SUZ12</i>	<i>ZEB2</i>
CC2D1A	<i>BRWD3</i>	<i>EP300</i>	<i>HNRNPU</i>	<i>MEF2C</i>	<i>POGZ</i>	<i>SETBP1</i>	<i>TAF1</i>	<i>ZIC2</i>
	<i>CDK8</i>	<i>EZH2</i>	<i>HOXA1</i>	<i>MSL3</i>	<i>POLR2A</i>	<i>SETD5</i>	<i>TBL1XR1</i>	<i>ZNF711</i>
Epileptic encephalopathy	<i>ADNP</i>	<i>CHD1</i>	<i>DDX3X</i>	<i>HNRNPU</i>	<i>MBD5</i>	<i>NR2F1</i>	<i>SATB2</i>	<i>TBR1</i>
	<i>AFF2</i>	<i>CHD2</i>	<i>DEAF1</i>	<i>KANSL1</i>	<i>MECP2</i>	<i>NR3C2</i>	<i>SETBP1</i>	<i>TCF20</i>
Schizophrenia	<i>ARID1B</i>	<i>CHD3</i>	<i>DNNMT3A</i>	<i>KAT6A</i>	<i>MED12L</i>	<i>NR4A2</i>	<i>SETD1B</i>	<i>TCF4</i>
	<i>ARID2</i>	<i>CHD7</i>	<i>EBF3</i>	<i>KDM3B</i>	<i>MED13</i>	<i>NSD1</i>	<i>SETD2</i>	<i>TRRAP</i>
BAZ2B	<i>ARX</i>	<i>CHD8</i>	<i>EHMT1</i>	<i>KDM6B</i>	<i>MED13L</i>	<i>PHF21A</i>	<i>SETD5</i>	<i>TSHZ3</i>
	<i>ASH1L</i>	<i>CIC</i>	<i>EP300</i>	<i>KMT2A</i>	<i>MEF2C</i>	<i>POGZ</i>	<i>SIN3A</i>	<i>UPF3B</i>
BCL11A	<i>ASXL3</i>	<i>CNOT3</i>	<i>FMR1</i>	<i>KMT2C</i>	<i>MEIS2</i>	<i>RAI1</i>	<i>SMARCC2</i>	<i>WAC</i>
	<i>ATRX</i>	<i>CREBBP</i>	<i>FOGX1</i>	<i>KMT2E</i>	<i>MYT1L</i>	<i>RERE</i>	<i>SON</i>	<i>ZBTB20</i>
Epileptic encephalopathy	<i>AUTS2</i>	<i>CSDE1</i>	<i>FOXP1</i>	<i>KMT5B</i>	<i>NACC1</i>	<i>RFX3</i>	<i>SOX5</i>	<i>ZNF292</i>
	<i>BAZ2B</i>	<i>CTCF</i>	<i>HDAC4</i>	<i>LZTR1</i>	<i>NFIB</i>	<i>RORB</i>	<i>SRCAP</i>	<i>ZNF462</i>
Schizophrenia	<i>BCL11A</i>	<i>CUX2</i>	<i>HNRNPH2</i>					
Epileptic encephalopathy	<i>ARID1B</i>	<i>ASXL3</i>	<i>FOGX1</i>	<i>MBD5</i>	<i>MEF2C</i>	<i>ZEB2</i>		
	<i>ARX</i>	<i>CHD2</i>	<i>HNRNPU</i>	<i>MECP2</i>	<i>PURA</i>			
Schizophrenia								
Schizophrenia				<i>SETD1A</i>	<i>SP4</i>			



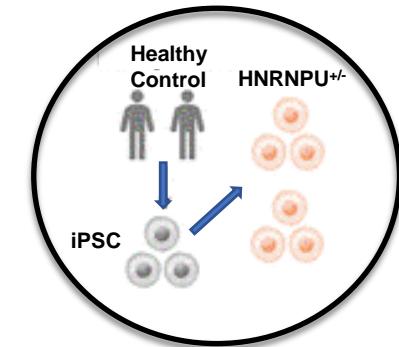
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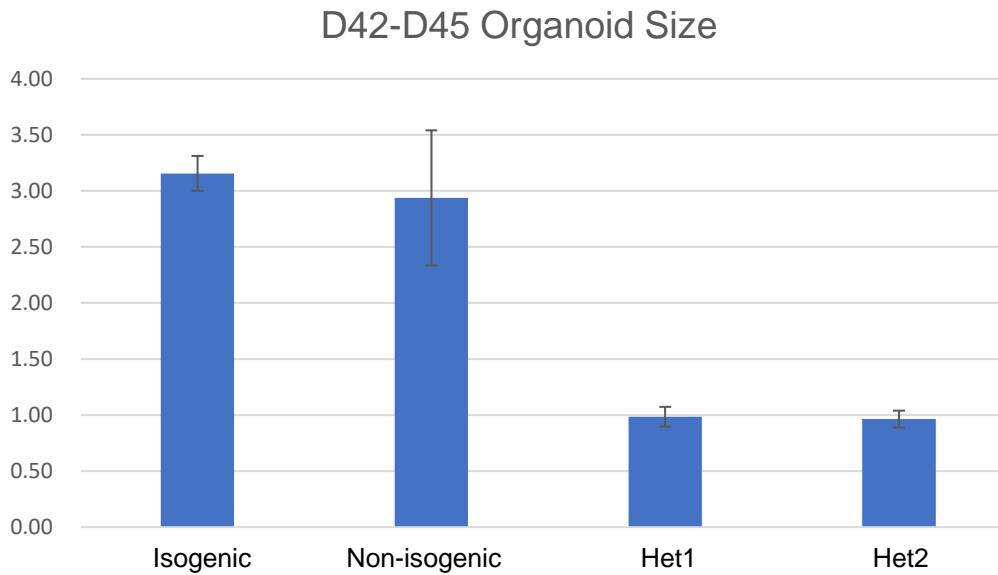
Modelling Human HNRNPU Dysregulation in Cortical Organoids



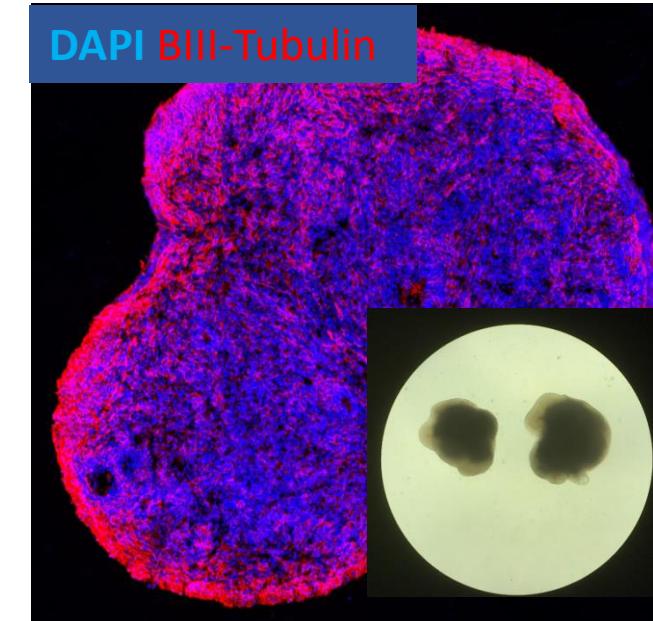
Impaired Growth in HNRNPU Cortical Organoids



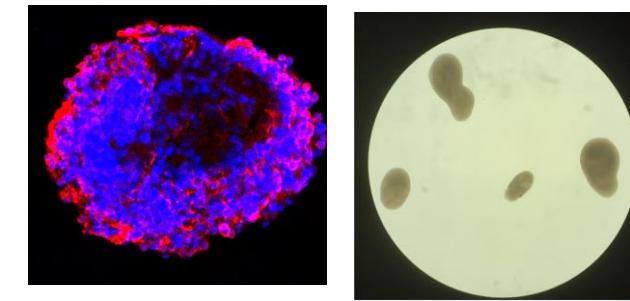
Wild-type and Mutant organoids generate significant neuronal populations in ~1.5 months



Isogenic Control (PGP1) – Day 42



HNRNPU^{+/} Clone 1 (D11) – Day 42



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Building a Precision Medicine Ecosystem Needs a Community



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