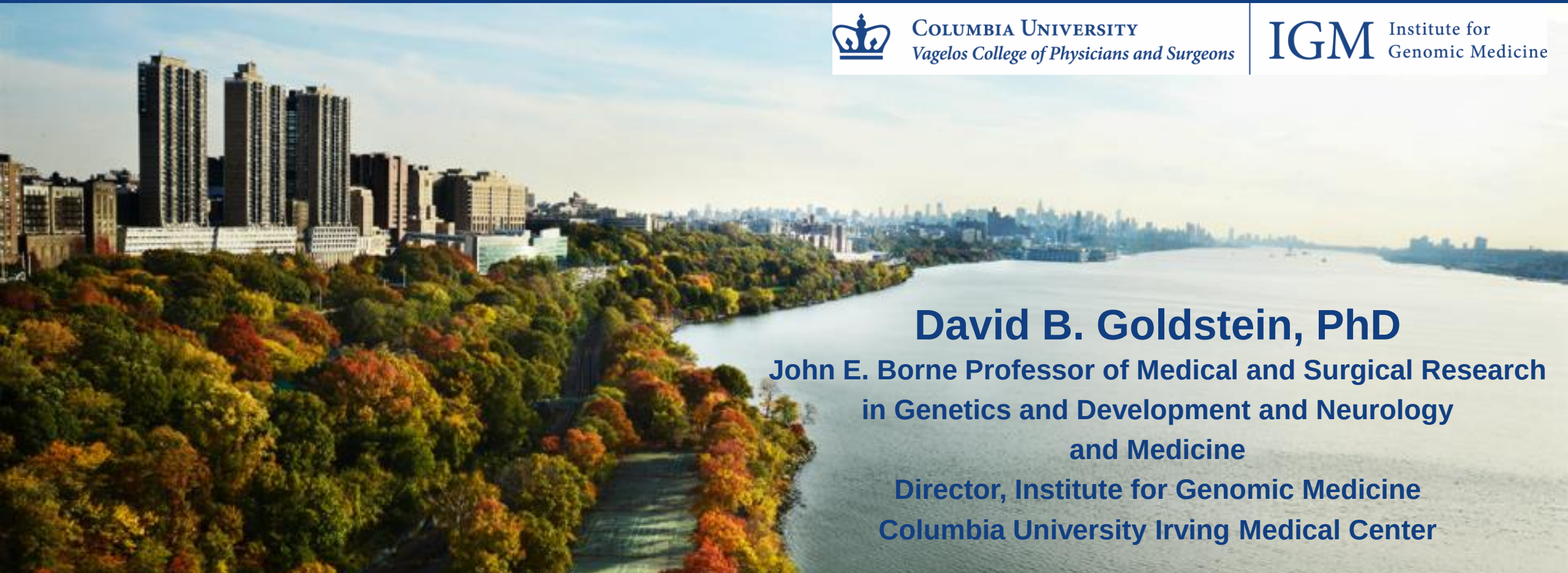
Precision Medicine 2021



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Vagelos College of Physicians and Surgeons

IGM Institute for Genomic Medicine

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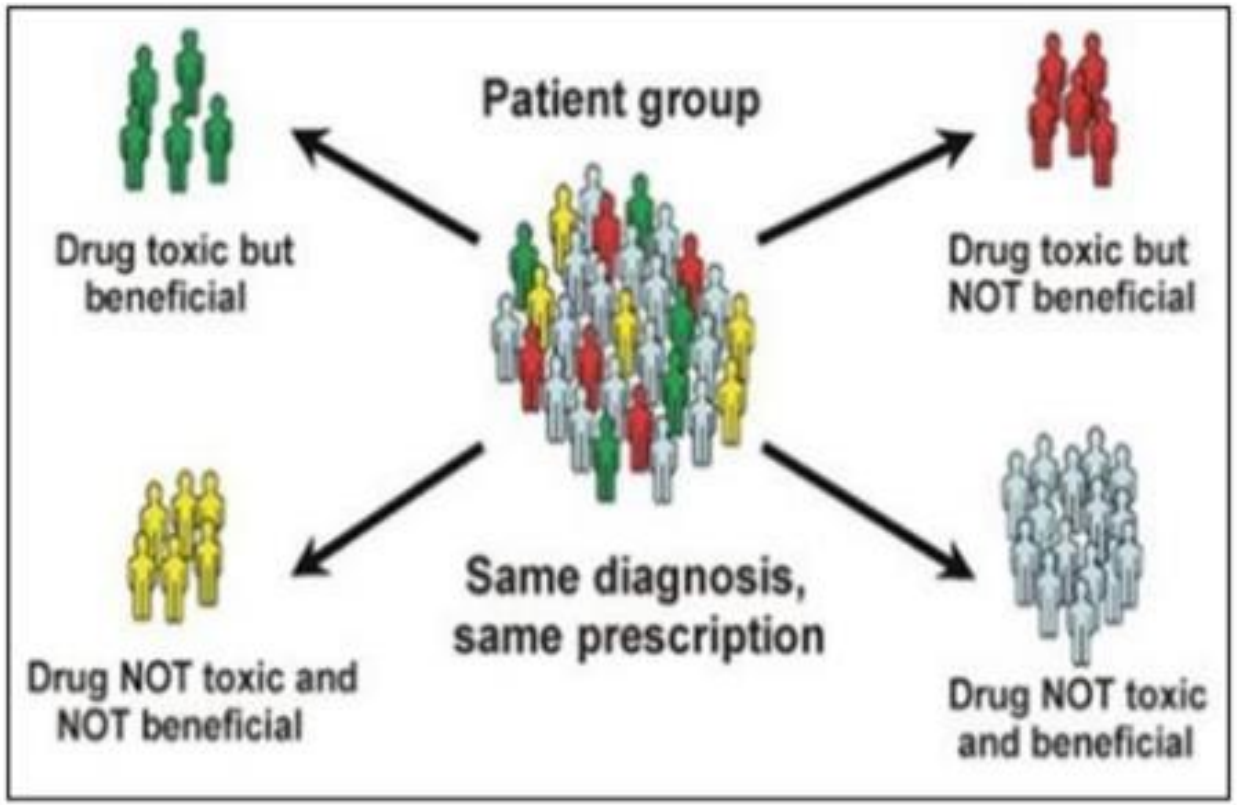
Disclosure Statement of Financial Interest

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

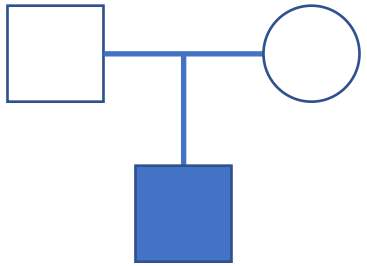
Genetically Stratified Medicine

- 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

Sequencing for Rare Diseases



Trio exome sequencing

Identify qualifying genotypes

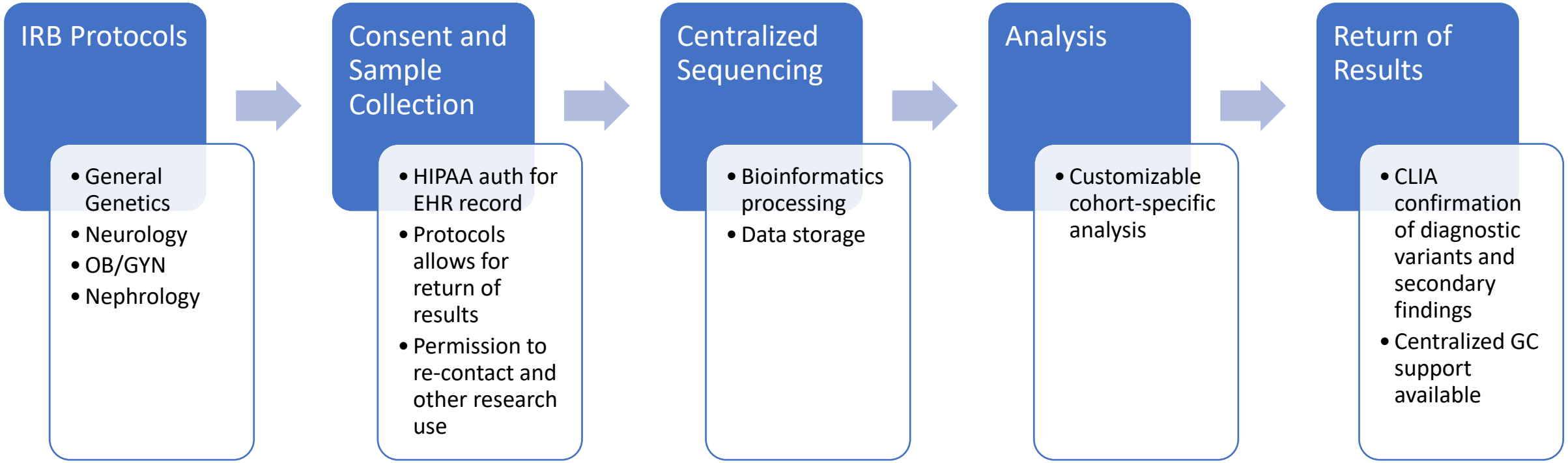
Genetic diagnosis

Genetic candidate

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%**

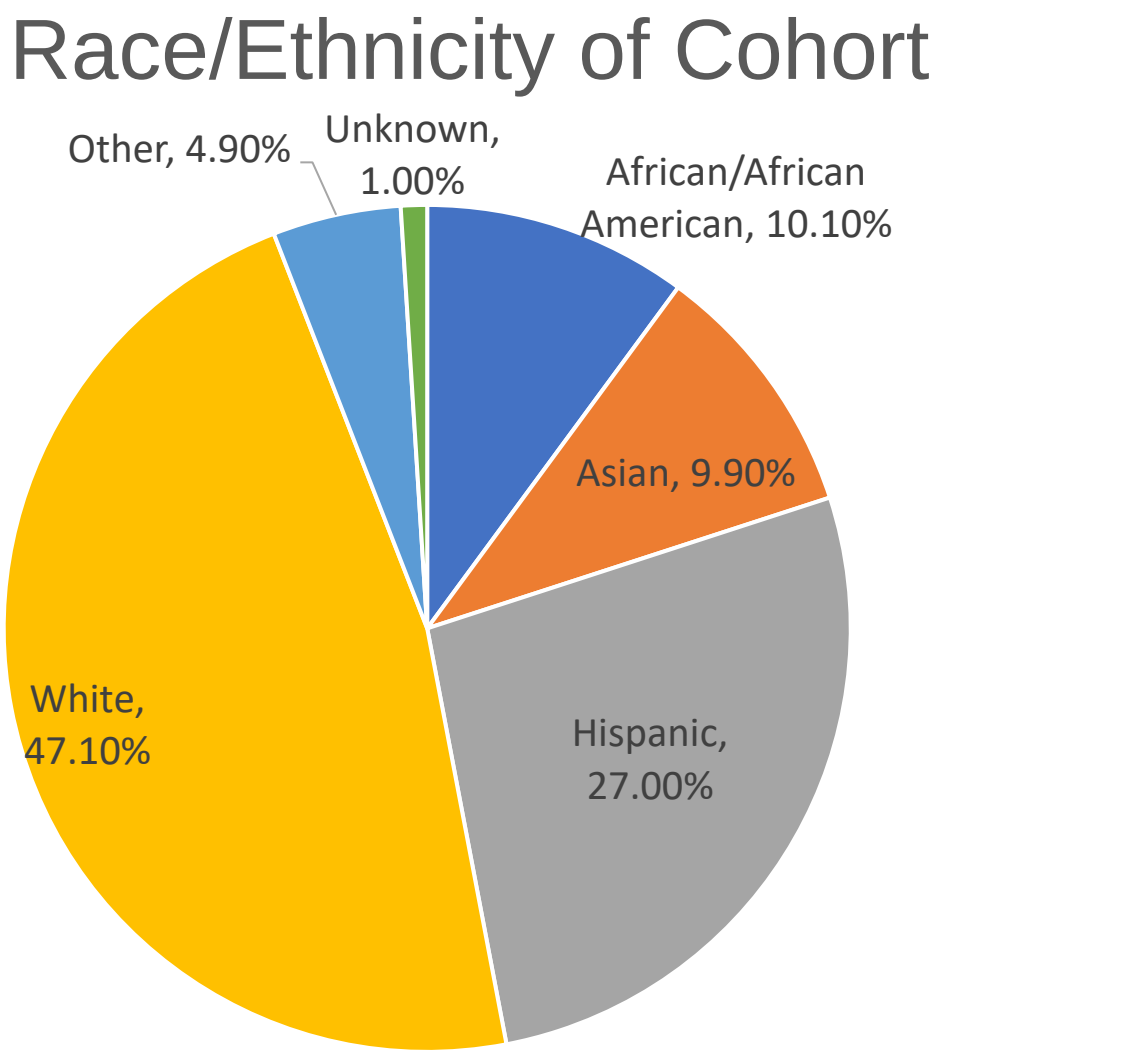
Ten Thousand patients sequenced to date at tertiary care center

General Workflow

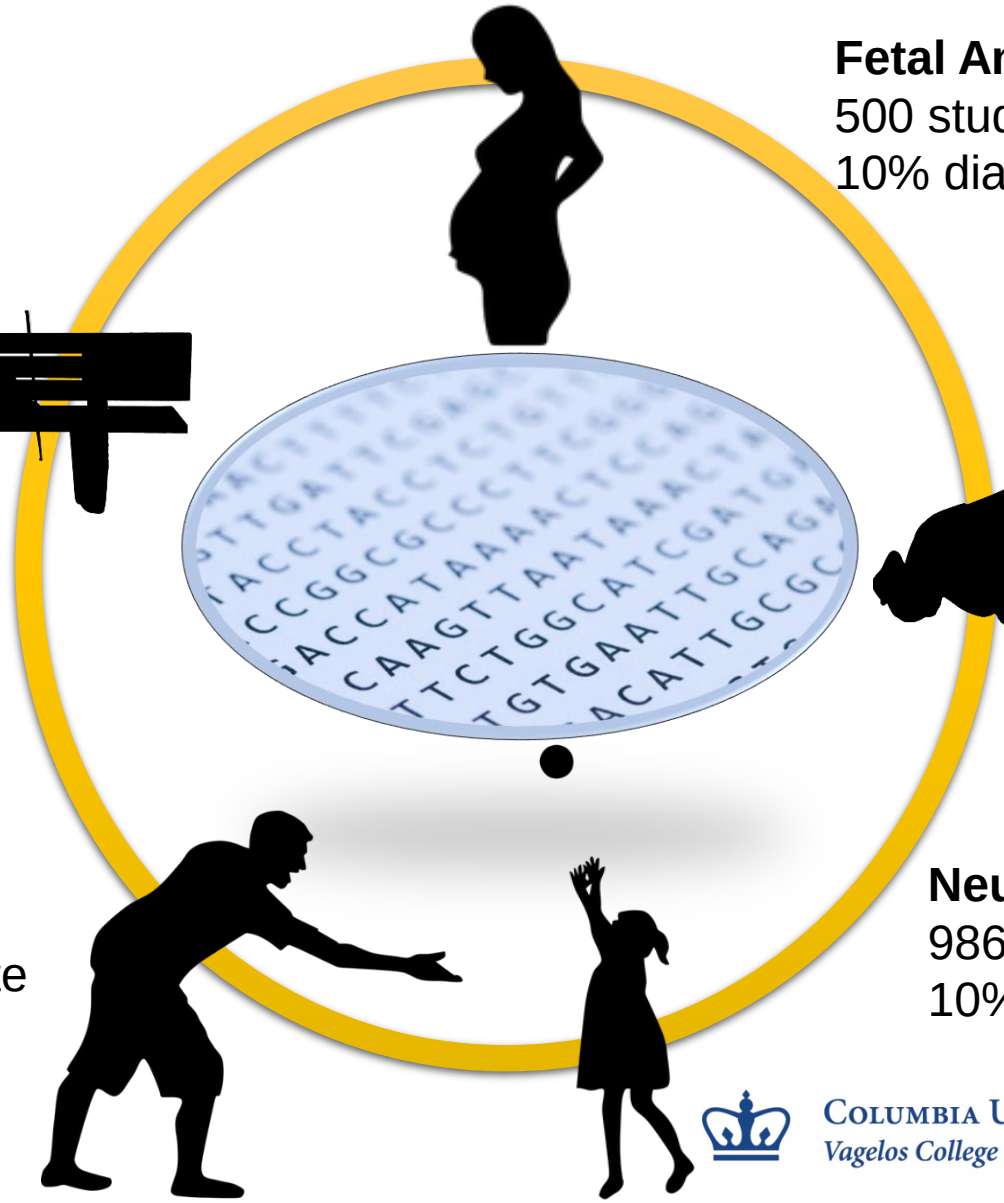


Diversity

- 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



Utility of Genomics Throughout the Lifespan



Fetal Anomalies:
500 studied
10% diagnostic rate

Stillbirth:
300 samples
4% diagnostic rate

DiagSeq:
1226 probands
20% diagnostic rate

Neuro:
986 probands
10% diagnostic rate

CKD:
3,315 individuals
9.3% diagnostic rate

ALS:
5611 individuals
12% diagnostic rate

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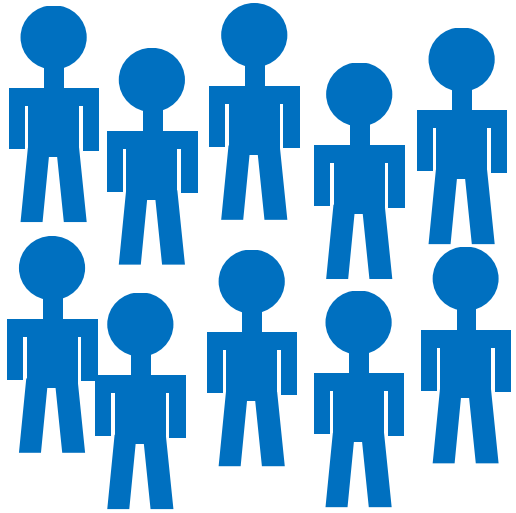
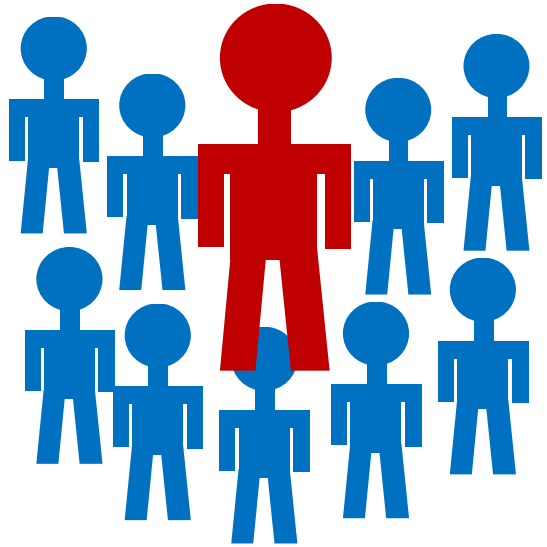
Diagnostic Utility of Exome Sequencing For Kidney Disease

ES of 3,315 individuals with all-cause CKD



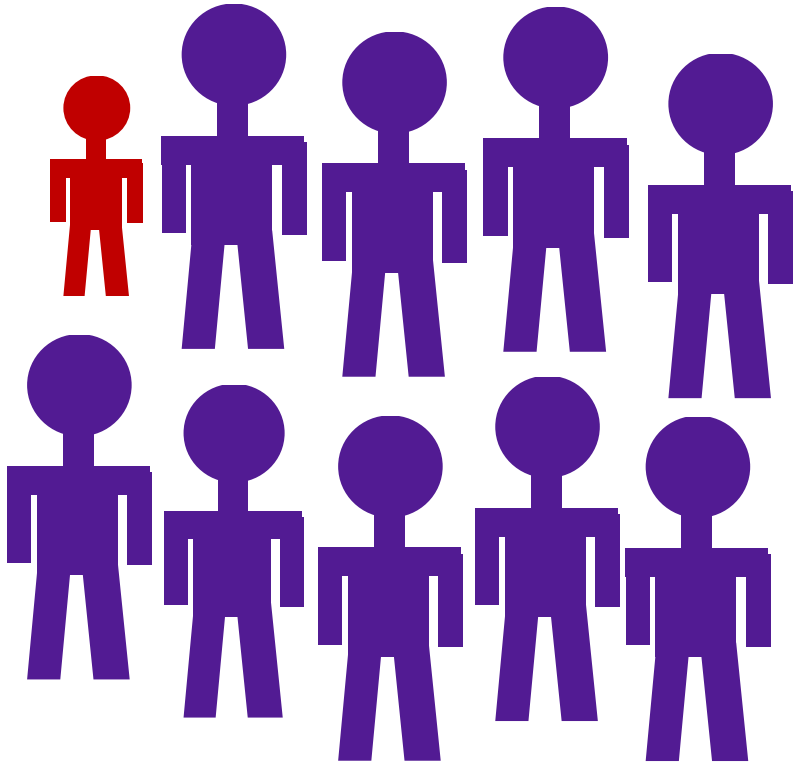
91.6% adults
35.6% non-white
European ethnicity

~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



Groopman et al., *NEJM* 2019

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Spectrum of Schizophrenia Severity by Treatment Setting and Length of Stay

Community/Outpatient

Community Inpatient (10 days)

State Inpatient (< 5 years)

State Inpatient (> 5 years)

Schizophrenia Severity

- Mild
- Moderate
- Severe
- SETRS

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* = 1.64x10^{-5}
****p* = 3x10^{-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* = 1.2x10^{-6}**)

Most Common Genetic Diagnoses

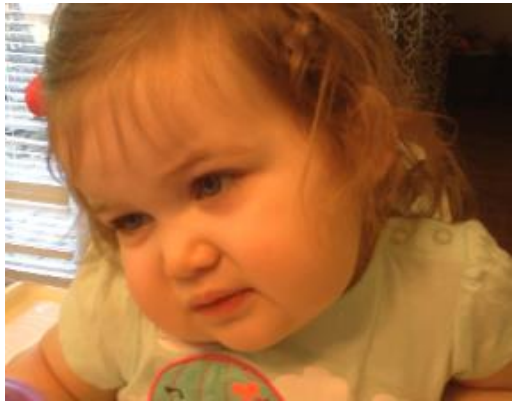
Diagnosis Gene	Proband Count	Cohort
COL4A5	35	CKD
COL4A3	17	CKD
COL4A4	14	CKD
SCN1A	12	Epilepsy, ID/DD/ASD
NF1	10	CKD, Epilepsy, ID/DD/ASD
PKD1	10	CKD
SCN2A	10	Fetal Anomaly, Epilepsy, ID/DD/ASD
NF1	9	Epilepsy, ID/DD/ASD
TRPC6	8	CKD
NSD1	7	Epilepsy, ID/DD/ASD
UMOD	7	CKD
CACNA1A	6	Epilepsy, ID/DD/ASD,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

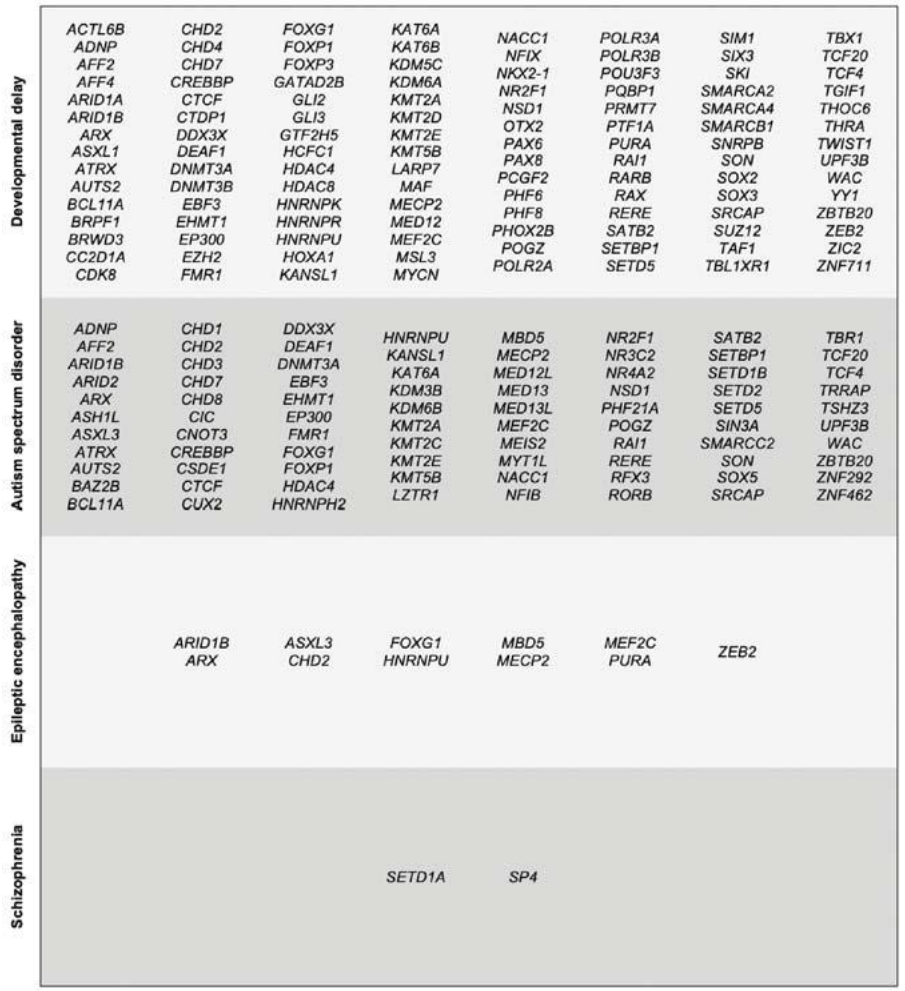


3 weeks of treatment

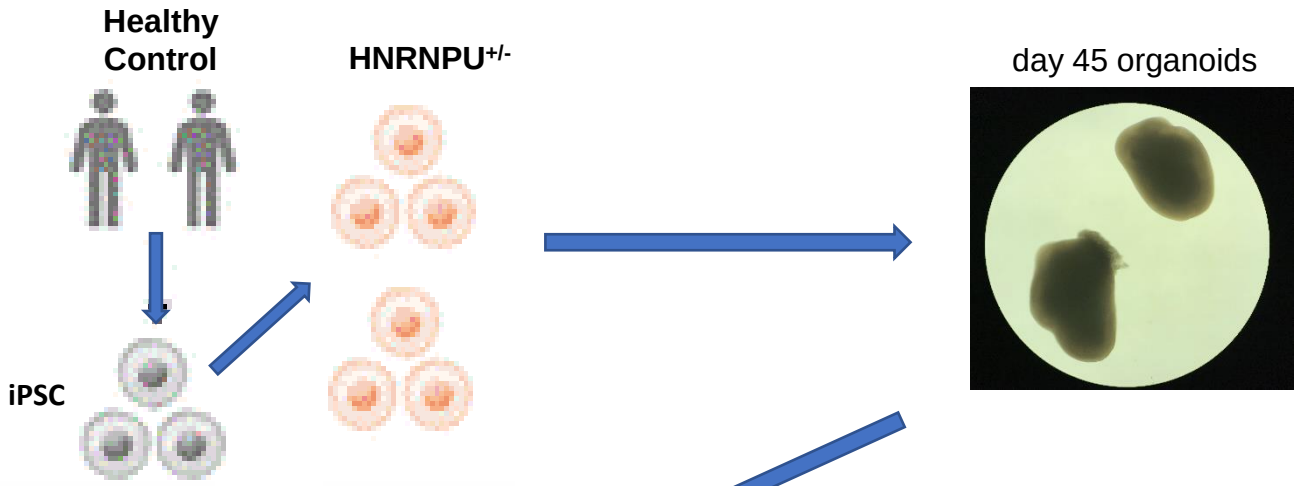
4 weeks of treatment

Cara Greene

Transcriptomic Restoration



Modelling Human HNRNPU Dysregulation in Cortical Organoids



scRNA sequencing

Upregulated genes

Downregulated genes

Pseudobulk cross-species comparison of disease signature

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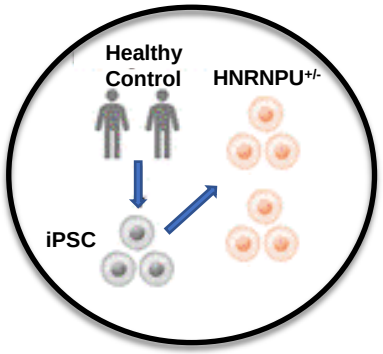
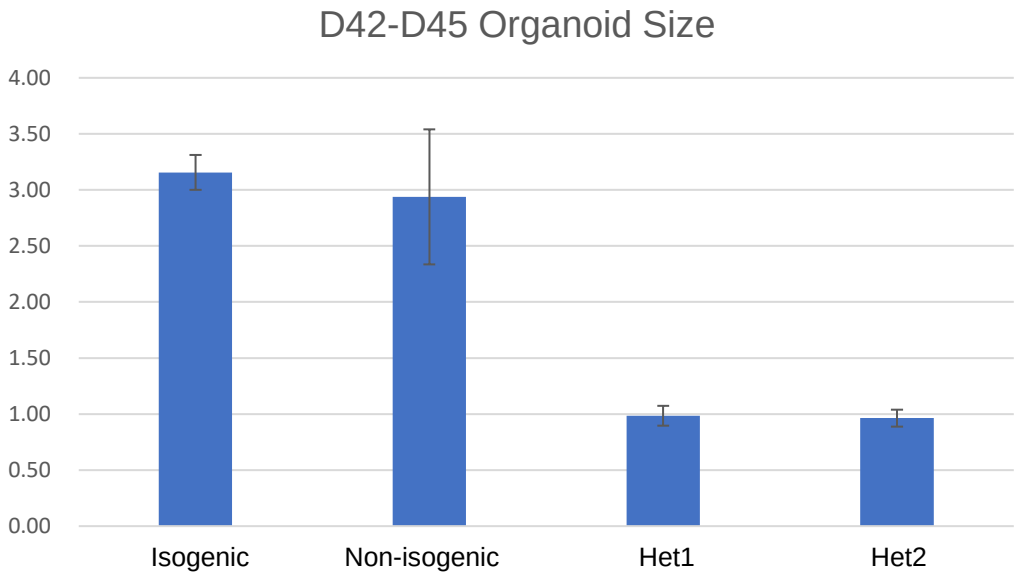
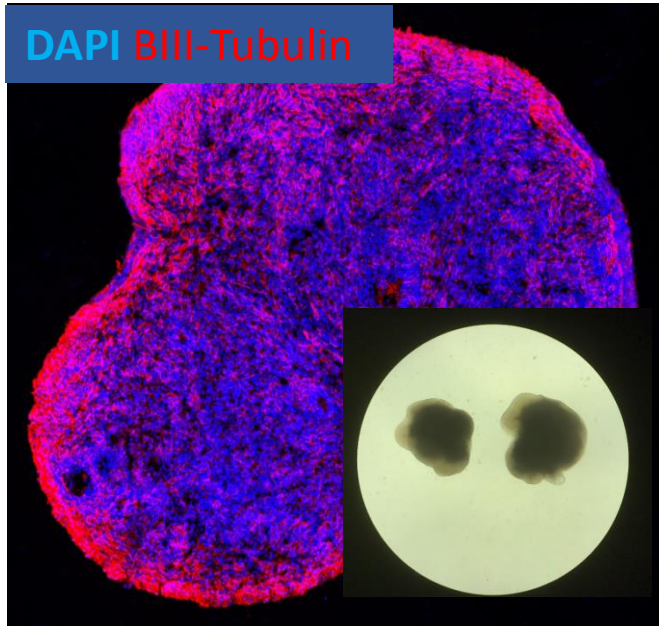
Impaired Growth in HNRNPU Cortical Organoids



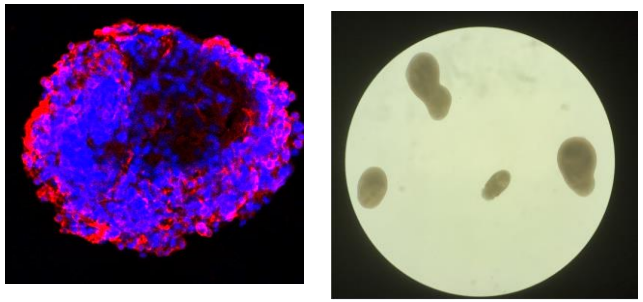
Wild-type and Mutant organoids generate significant neuronal populations in ~1.5 months



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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