

Clinical Information Required by Testing Labs

Jim Weber

August 19, 2024

PreventionGenetics was acquired
by Exact Sciences in 2021.

I am no longer employed by Exact,
but I do still own some Exact stock.

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BS Chemistry, UW-Madison 1974

PhD Biochemistry, UC-Berkeley 1980

Postdoc, UW-Madison 1980-1982

Walter Reed Army Institute of Research,
Wash DC, Malaria Vaccines, 1982-1986

Marshfield Clinic Research Foundation,
NIH-funded Research, 1986-2004

PreventionGenetics, Founder and President,
2004-2021

Adjunct Faculty, UW-Madison, 2019-



What Happens After the Specimen Leaves the Hospital

Shipping



DNA Extraction

Quantitation and Shearing

Sequencing

Processing in Cloud

alignment to reference sequence

identification of variants



Analysis





Average Numbers of Variants by Interpretation Category

Interpretation	Exome	Genome
Pathogenic	2	3
Likely Pathogenic	2	3
Uncertain	100	5,000
Likely Benign	200	10,000
Benign	25,000	3M

Name: Dorothy Smith Sex: Female
DOB: Aug 19, 2024 Test: WGS

POSITIVE

Heterozygous for Pathogenic and
Uncertain Variants in *PKHD1*

The pathogenic and uncertain
variants in the *PKHD1* gene are in
trans phase (from parental
sequencing) and are likely to be the
primary cause of the patient's kidney
disease.



Clinical Features (HPO terminology)

Autosomal Recessive Polycystic Kidney Disease (*PKHD1*)

polycystic kidney dysplasia
respiratory failure
oligohydramnios
hepatomegaly
hypertension
dehydration

Noonan Syndrome (*RAF1*)

abnormal pulmonary valve morphology
hypertrophic cardiomyopathy
atrial septic defect
short neck
webbed neck
low-set, posteriorly rotated ears
scapular winging

Clinical Information *Required* by the Lab



Clinical Features

Pregnancy history

fetal clinical features

gestational age

Family history

clinical features of parents/sibs

previous miscarriages/stillbirths

Suspected diagnoses

Previous genetic testing in patient

or family members

Family ancestry

consanguinity

Lab results, even normal results

CLINICAL INFORMATION (CHECK ALL THAT APPLY)		
<p>PRE/PERINATAL</p> <input type="checkbox"/> Abnormality of septum pellucidum <input type="checkbox"/> Absent septum pellucidum <input type="checkbox"/> Cavum septum pellucidum <input type="checkbox"/> Choroid plexus cyst (CPC) <input type="checkbox"/> Absent nasal bone <input type="checkbox"/> Congenital heart defect <input type="checkbox"/> Intracardiac echogenic focus (IEF) <input type="checkbox"/> Cystic hygroma <input type="checkbox"/> Increased nuchal translucency, Size (mm): _____ <input type="checkbox"/> Pleural effusion <input type="checkbox"/> Pericardial effusion <input type="checkbox"/> Generalized edema <input type="checkbox"/> Fetal ascites <input type="checkbox"/> Hydrops fetalis <input type="checkbox"/> Diaphragmatic hernia <input type="checkbox"/> Absent stomach bubble <input type="checkbox"/> Omphalocele <input type="checkbox"/> Gastroschisis <input type="checkbox"/> Echogenic bowel <input type="checkbox"/> Fetal pyelectasis/hydronephrosis <input type="checkbox"/> Decreased fetal movement <input type="checkbox"/> Encephalocele <input type="checkbox"/> Myelomeningocele/Spina bifida <input type="checkbox"/> Sacrococcygeal teratoma <input type="checkbox"/> Intrauterine growth retardation (IUGR) <input type="checkbox"/> Small for gestational age (SGA) <input type="checkbox"/> Oligohydramnios <input type="checkbox"/> Polyhydramnios <input type="checkbox"/> Short long bones <input type="checkbox"/> Small thorax <input type="checkbox"/> Fetal demise <input type="checkbox"/> Prematurity, Gestational Age: _____ <input type="checkbox"/> Other: _____	<p>STRUCTURAL BRAIN ABNORMALITIES / IMAGING</p> <input type="checkbox"/> Abnormal/delayed myelination <input type="checkbox"/> Abnormality of basal ganglia <input type="checkbox"/> Abnormality of brainstem <input type="checkbox"/> Abnormality of white matter: <input type="checkbox"/> Periventricular <input type="checkbox"/> Other: _____ <input type="checkbox"/> Abnormality of cerebral ventricles: <input type="checkbox"/> Colpocephaly <input type="checkbox"/> Hydrocephalus <input type="checkbox"/> Ventriculomegaly <input type="checkbox"/> Abnormality of corpus callosum morphology: <input type="checkbox"/> Agenesis <input type="checkbox"/> Complete <input type="checkbox"/> Partial <input type="checkbox"/> Aplasia/hypoplasia <input type="checkbox"/> Aplasia/hypoplasia of cerebellar vermis <input type="checkbox"/> Aplasia/hypoplasia of cerebellum <input type="checkbox"/> Arnold-Chiari malformation: <input type="checkbox"/> Type I <input type="checkbox"/> Cerebral atrophy/hypoplasia <input type="checkbox"/> Cerebral calcification <input type="checkbox"/> Holoprosencephaly <input type="checkbox"/> Intraventricular hemorrhage <input type="checkbox"/> Preterm Intraventricular hemorrhage <input type="checkbox"/> Iron deposition <input type="checkbox"/> Leukodystrophy <input type="checkbox"/> Neuronal migration abnormality <input type="checkbox"/> Cortical gyration <input type="checkbox"/> Gray matter heterotopia <input type="checkbox"/> Other: _____	<input type="checkbox"/> Delayed fine motor development <input type="checkbox"/> Delayed gross motor development <input type="checkbox"/> Developmental regression <input type="checkbox"/> Gait disturbance Specify: _____ <input type="checkbox"/> Global developmental delay <input type="checkbox"/> Hyperactivity <input type="checkbox"/> Incoordination <input type="checkbox"/> Intellectual disability <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe/profound <input type="checkbox"/> Learning disability <input type="checkbox"/> Language impairment <input type="checkbox"/> Absent speech <input type="checkbox"/> Apraxia <input type="checkbox"/> Articulation difficulties <input type="checkbox"/> Delayed speech and language development <input type="checkbox"/> Expressive <input type="checkbox"/> Receptive <input type="checkbox"/> Dysarthria <input type="checkbox"/> Echolalia <input type="checkbox"/> Loss of speech <input type="checkbox"/> Memory impairment <input type="checkbox"/> Obsessive-compulsive behavior <input type="checkbox"/> Self-injurious behavior: <input type="checkbox"/> Biting <input type="checkbox"/> Head-banging <input type="checkbox"/> Skin picking <input type="checkbox"/> Sensory processing disorder/ neurodevelopmental abnormality <input type="checkbox"/> Sleep disturbance <input type="checkbox"/> Stereotypy <input type="checkbox"/> Recurrent hand flapping <input type="checkbox"/> Stereotypical hand wringing <input type="checkbox"/> Other: _____
	<p>DEVELOPMENTAL/BEHAVIORAL</p> <input type="checkbox"/> Aggressive/violent behavior <input type="checkbox"/> Anxiety <input type="checkbox"/> Attention-deficit hyperactivity disorder <input type="checkbox"/> Autistic behavior <input type="checkbox"/> Autism/autism spectrum disorder <input type="checkbox"/> Cognitive impairment	<p>NEUROLOGICAL</p> <input type="checkbox"/> Abnormality of nervous system <input type="checkbox"/> Ataxia <input type="checkbox"/> Athetosis

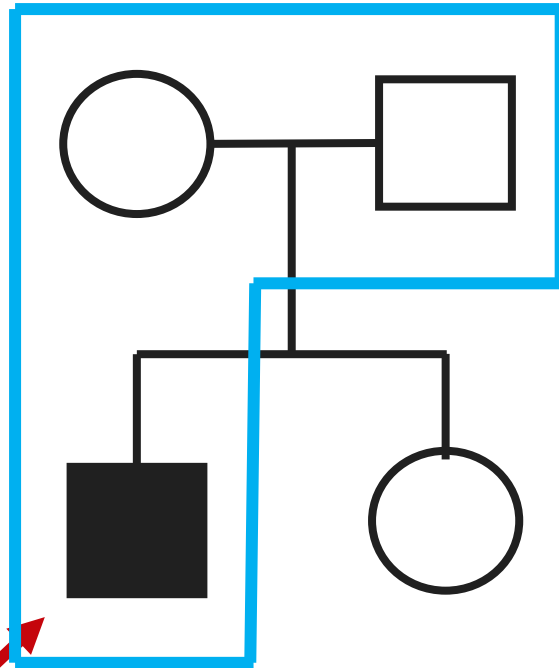
Importance of Trios

WES Test Yields

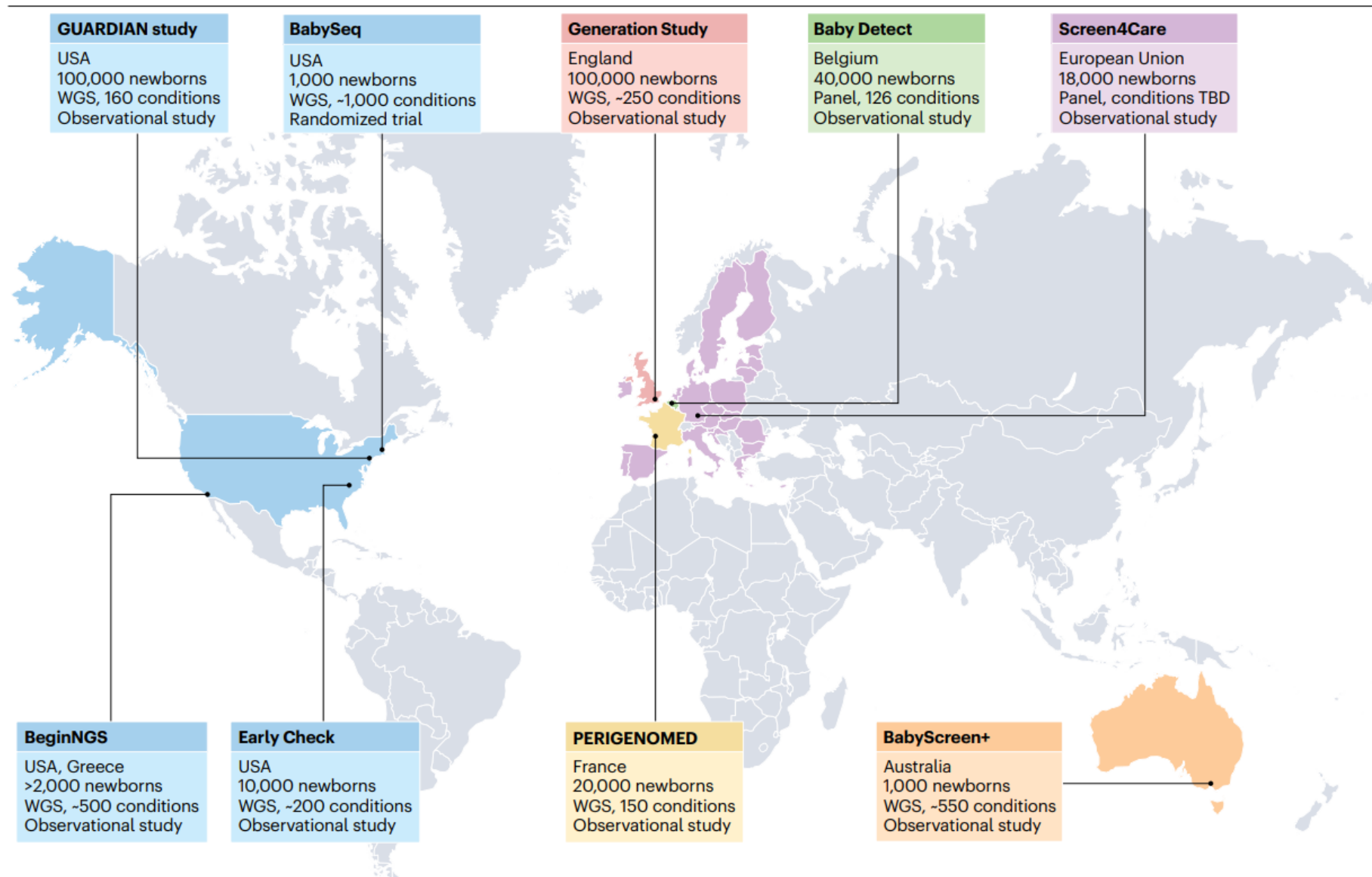
Reference (PMID)	Singleton	Trio
25326637	22%	31%
25356970	21%	37%
26633542	24%	31%

Other Factors

- Ideal to perform WGS on both parents and baby.
- Targeted testing of parents is another option.
- Delayed shipment of parental DNA is problematic.



Baby in NICU



PMID: 37386126

International Consortium on Newborn Sequencing
<https://www.iconseq.org/>



Importance of Sequence Retention and Reanalysis

Periodic reanalysis of raw sequence data improves test yield due to new:

- analysis methods
- disease genes
- clinical information
- variant interpretation
- polygenic indices

Reanalysis requires retention of raw sequence data


Don't rely on labs to retain data, but store it in patient EHR.

Data should be retained indefinitely even after dies.

Storage is relatively simple.

PMIDs: 29323667, 31216405, 34283395, 38819824

References

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- Lee et al. JAMA 2014 PMID:25326637
 - Farwell et al. Genetics in Medicine 2015 PMID:25356970
 - Retterer et al. Genetics in Medicine 2016 PMID:26633542
 - Stark and Scott Nature Reviews Genetics 2023 PMID: 37386126
 - Wright et al. Genetics in Medicine 2018 PMID:29323667
 - Liu et al. NEJM 2019 PMID:31216405
 - Ji et al. Molecular Diagnosis and Therapy 2021 PMID: 34283395
 - Surl et al. JAMA Network Open 2024 PMID:38819824

