BabySeq™

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Partners HealthCare Center for Personalized Genetic Medicine
Broad Institute and Harvard Medical School

G2P GENOMES *to People*

PARTNERS HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE

BCM Baylor College of Medicine

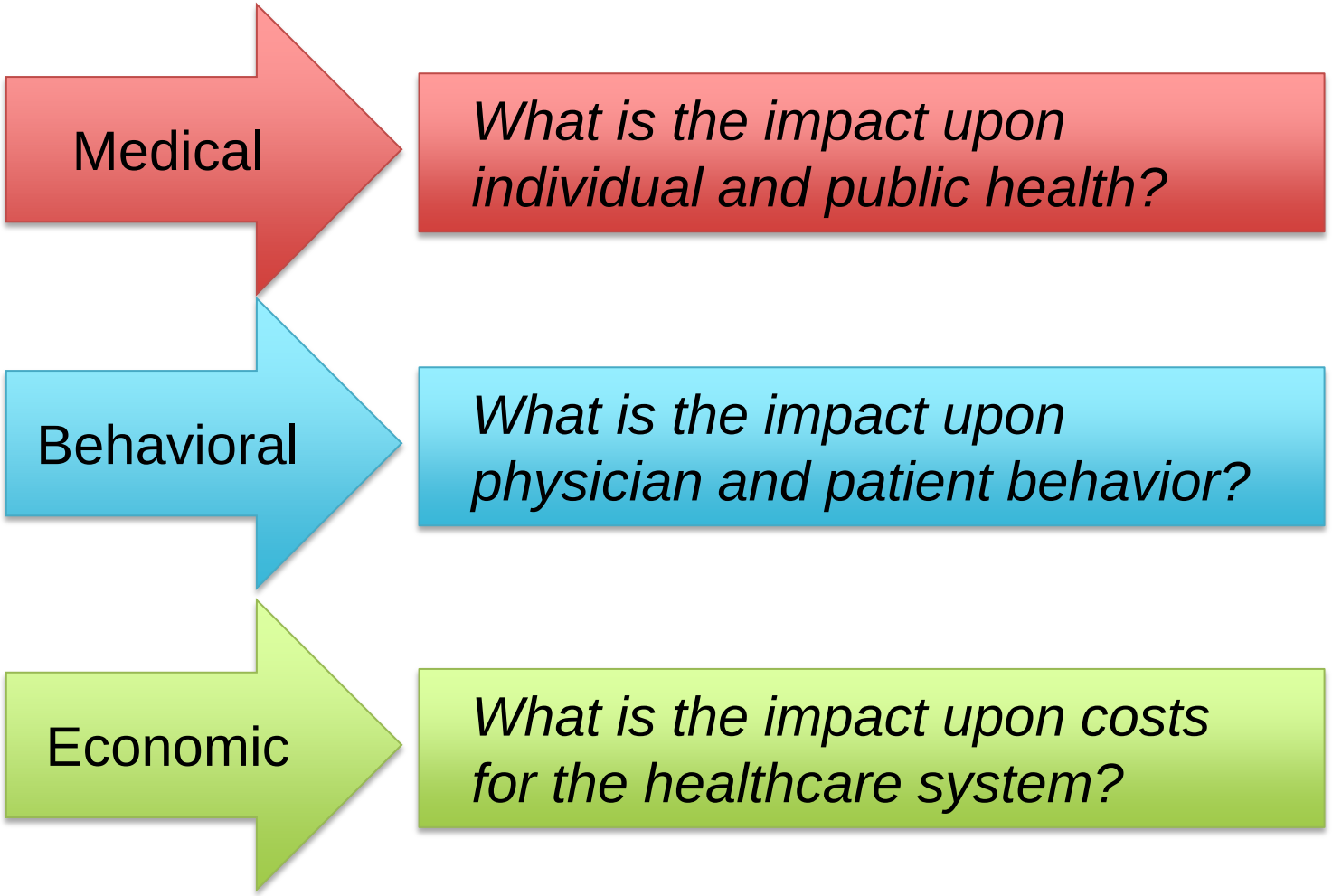
BWH

VE RI TAS

Disclosures

Research Grants:	NIH, DOD, Broad Institute
Compensated Speaking/Advisory:	AIA, Helix, Illumina, Invitae, Prudential, Roche
Equity:	Genome Medical, Inc.
Uncompensated Research Collaboration:	Pathway, 23andMe

Genomes2People Research is Examining the Clinical Utility of Genomics



The REVEAL Study

The PGen Study

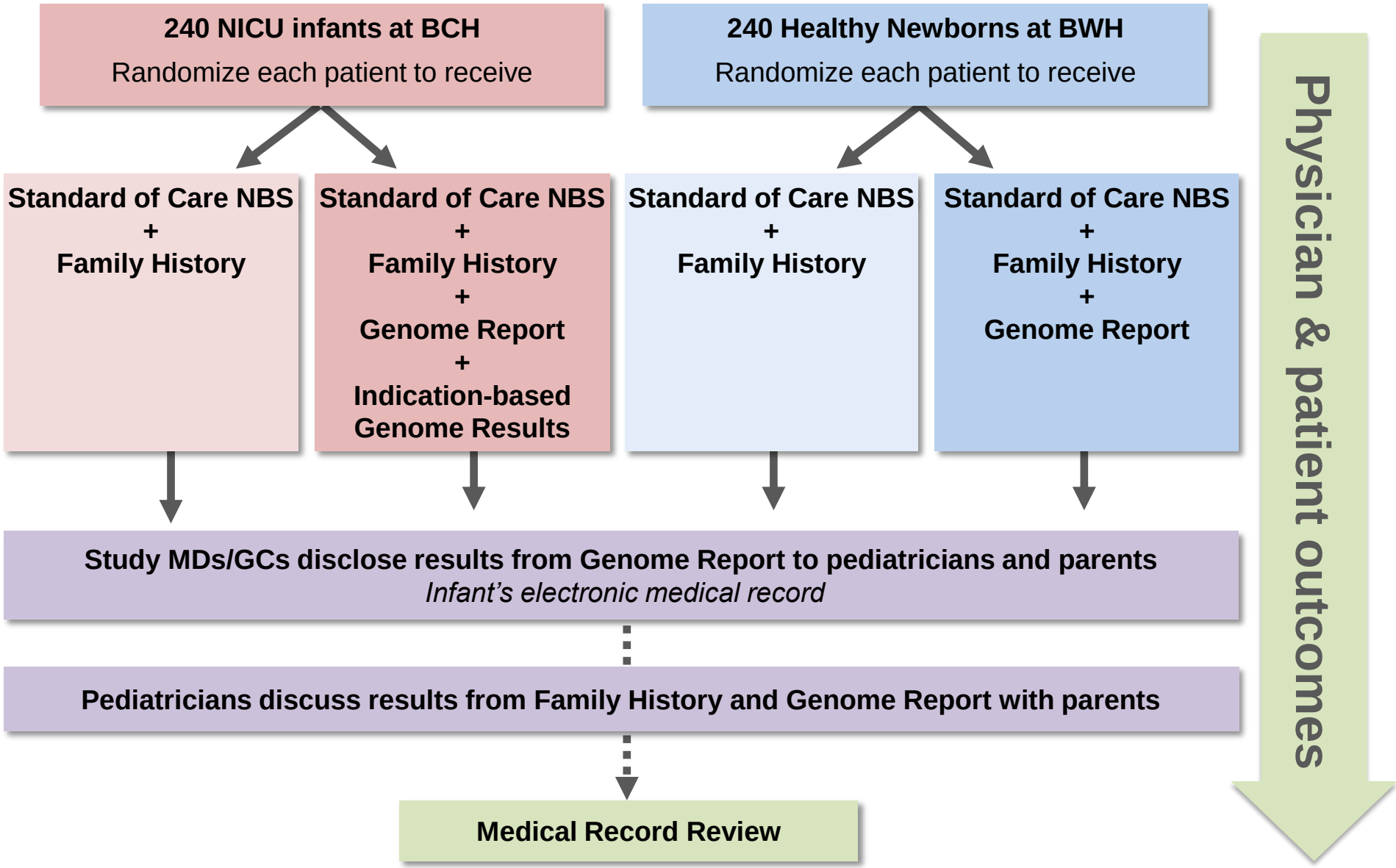
The MedSeq Project

The BabySeq Project

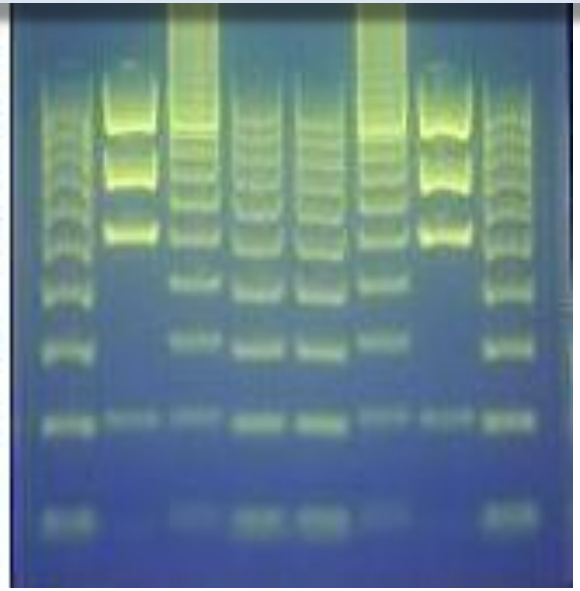
The PeopleSeq Consortium

The MilSeq Project

The BabySeq Project



Hypothetically:
Are parents interested in newborn sequencing?

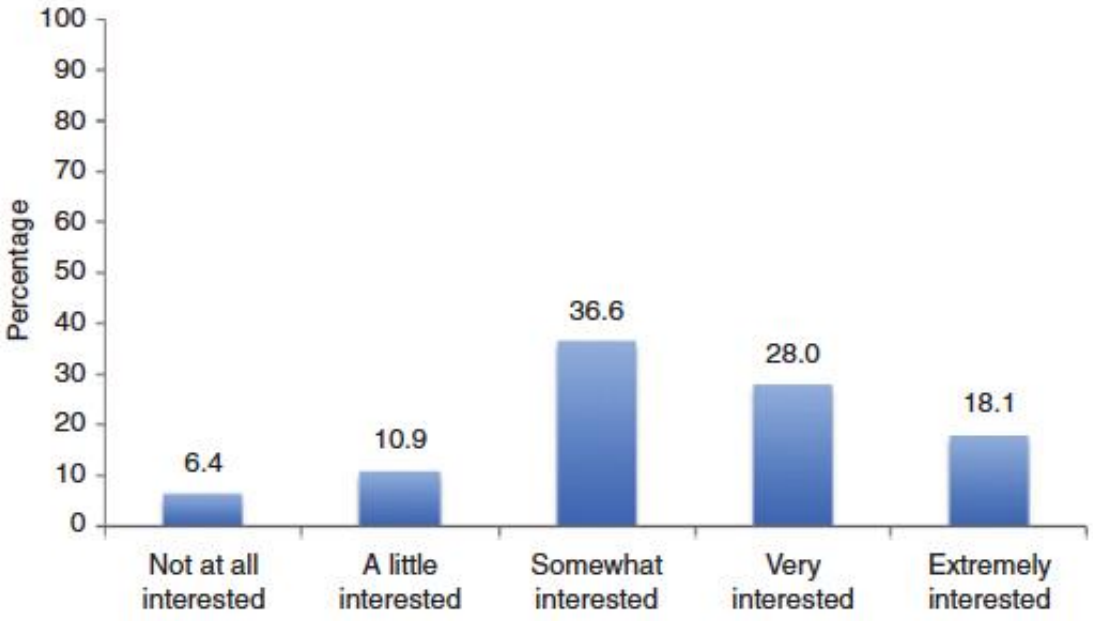


BRIEF REPORT | Genetics inMedicine

Parents are interested in newborn genomic testing during the early postpartum period

[Q2]

Susan E. Waisbren, PhD[1–3], Danielle K. Bäck, BS[3,4], Christina Liu, BS[4], Sarah S. Kalia, ScM, CGC[4], Steven A. Ringer, MD, PhD[3,5], Ingrid A. Holm, MD, MPH[1,3,6] and Robert C. Green, MD, MPH[3,4,7]



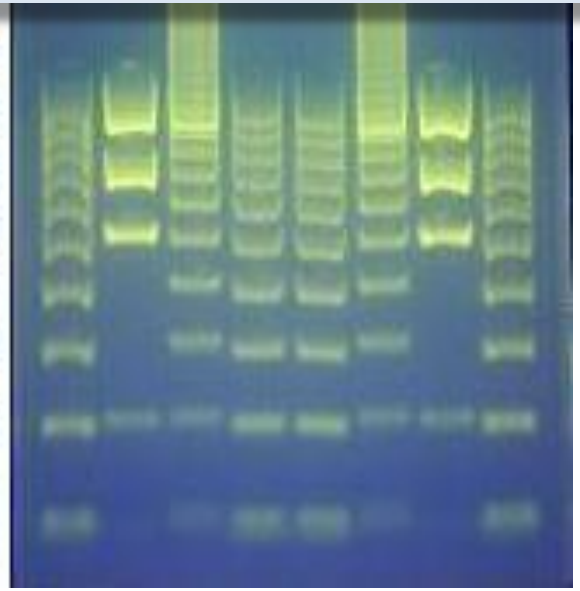
sting for their newborns. None refused con-
ening. Married participants and those with
heir infant were less interested in newborn
012 and $P = 0.030$, respectively). Degree of
fathers was discordant (at least two catego-
of couples.

newborn genomic testing was high among
rns, and the majority of couples had similar
ing parents about genomic sequencing did
ewborn screening.

e publication 00 Month 2014

n genomic testing; newborn screening;

BabySeq:
What categories should be reported?



Reporting Strategies in BabySeq

Well newborn nursery

NICU

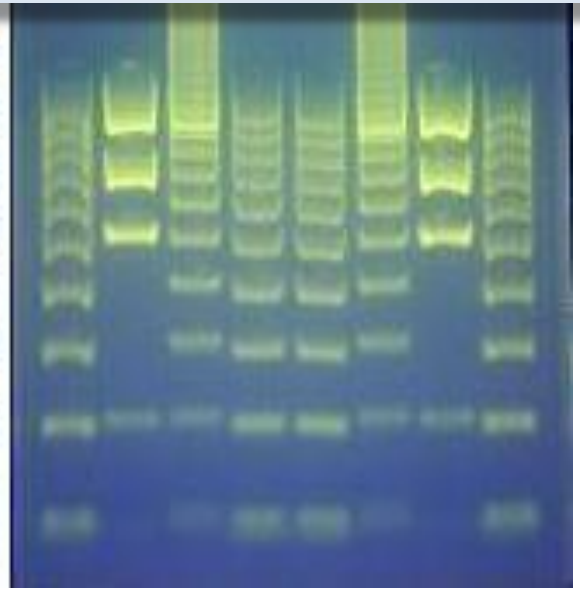
Newborn Genome Sequencing Report

- Risk for childhood-onset disease
- Carrier status for childhood-onset disease
- Pharmacogenomic (relevant to pediatrics)

Indication Based Analysis

- Genes associated with the infant's clinical features
- Option to query PGx variants related to the infant's care

How should the report be framed?



MedSeq Project Genome Report

One-Page Summary

- Disease-causing variants in 4600+ genes
- Carrier variants
- Pharmacogenomic variants
- Blood groups

- Additional Pages…
  - Structured variant data
  - Variant evidence
  - Disease/inheritance
  - Supporting references

McLaughlin et al. *BMC Med Gen*, 2014
Vassy, et al. *Public Health Genomics* 2015

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http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

Name: **John Doe**
DOB: **01/23/45**
Sex: **Male**
Race: **Caucasian**
Accession ID: **0123456789**
Specimen: **Blood, Peripheral**
Received: **01/23/45**
Family #: **F12345**
Referring physician: **John Smith, M.D.**
Referring facility: **Double Helix Hospital**

GENERAL GENOME REPORT

RESULT SUMMARY

A. MONOGENIC DISEASE RISK: 2 VARIANTS IDENTIFIED

This test identified 2 genetic variant(s) that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease (Inheritance)	Phenotype	Gene Variant	Classification
A1. Episodic ataxia type II (Autosomal Dominant)	Poor coordination and balance	CACNA1A p.Arg2156GlyfsX32	Pathogenic
A2. Hypertrophic cardiomyopathy (Autosomal Dominant)	Progressive heart failure	MYBPC3 p.Thr146AsnfsX7	Pathogenic

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorder(s).

Disease	Phenotype	Gene Variant	Classification	Carrier Phenotype*
B1. Cystic fibrosis	Chronic lung and digestive disease	CFTR c.1585-1G>A	Pathogenic	Infertility (moderate evidence)
B2. Myotonia congenita	Muscle disease	CLCN1 p.Arg894X	Pathogenic	Latent myotonia (case report only)
B3. Usher syndrome type II	Hearing loss and retinitis pigmentosa	USH2A p.Gly204ArgfsX12	Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's children to be affected, the partner of this individual would also need to be tested for these variants. Other biologically related family members may also be carriers of these variants.*Carriers for some recessive disorders may be at risk for certain mild phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

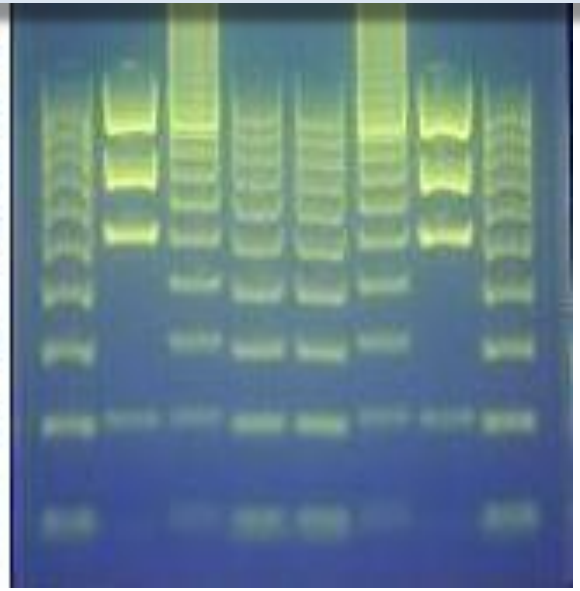
Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.
C3. Digoxin	Increased serum concentration of digoxin.
C4. Metformin	Typical glycemic response to metformin.
C5. Simvastatin	Lower risk of simvastatin-related myopathy.

D. BLOOD GROUPS

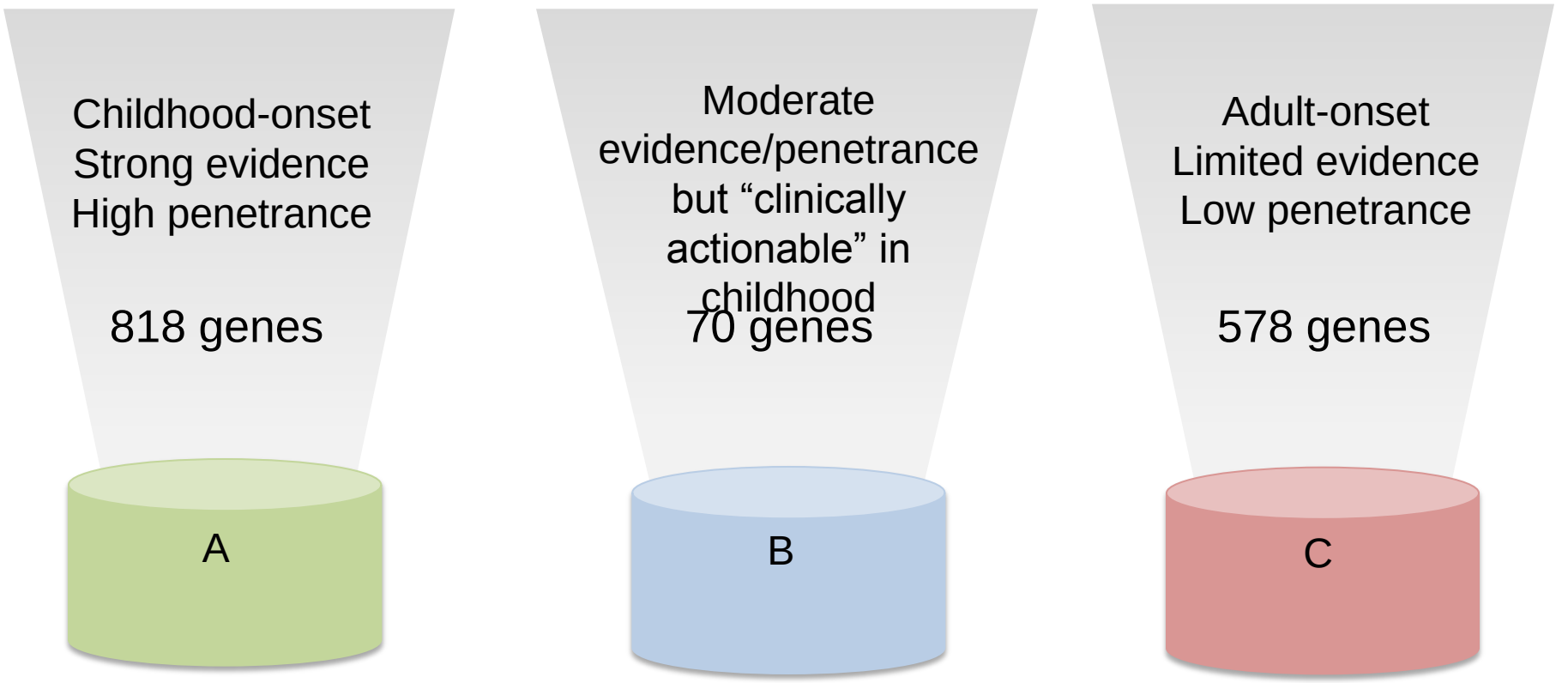
This test identified the ABO Rh blood type as O positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the

BabySeq:
What genes should be reported?



The first 1500 genes curated for BabySeq

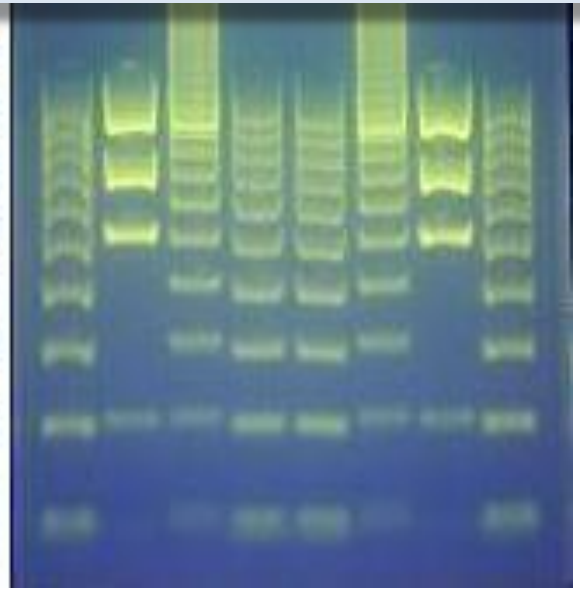


Will be reported

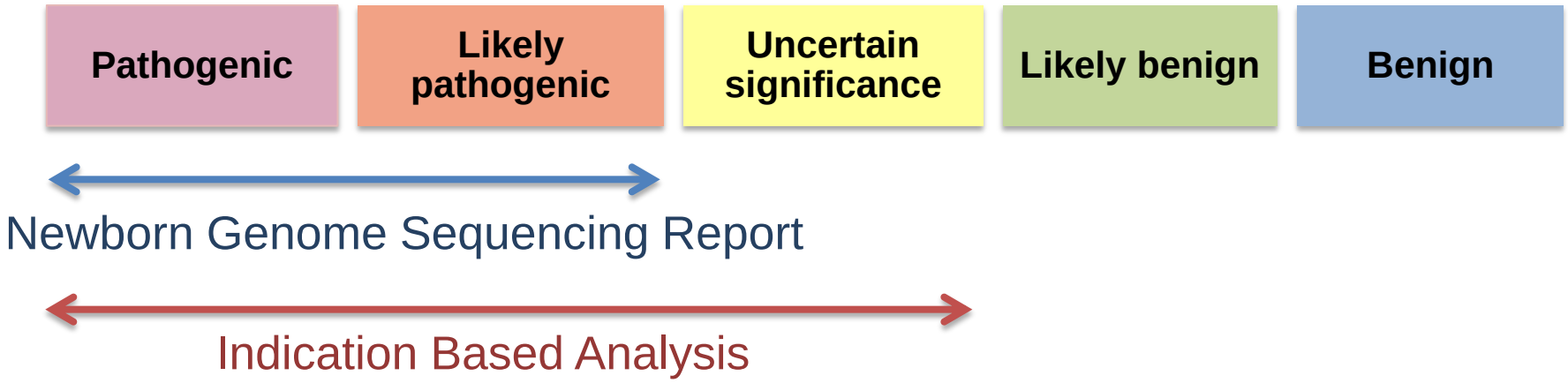
Will be reported based on actionability in childhood

Will not be reported

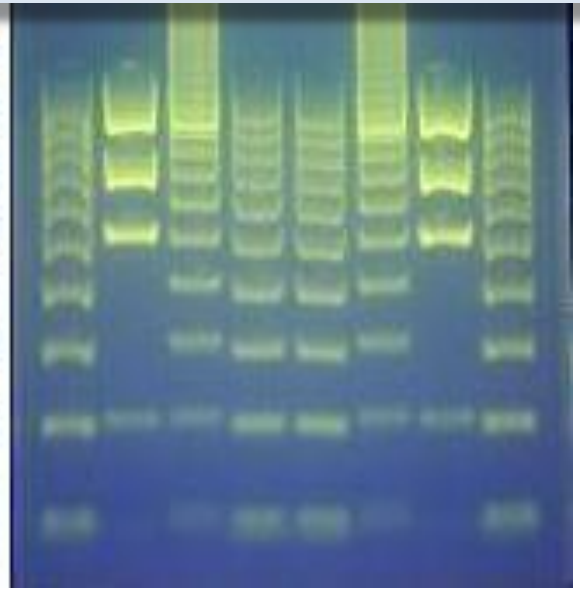
BabySeq:
What variants should be reported?

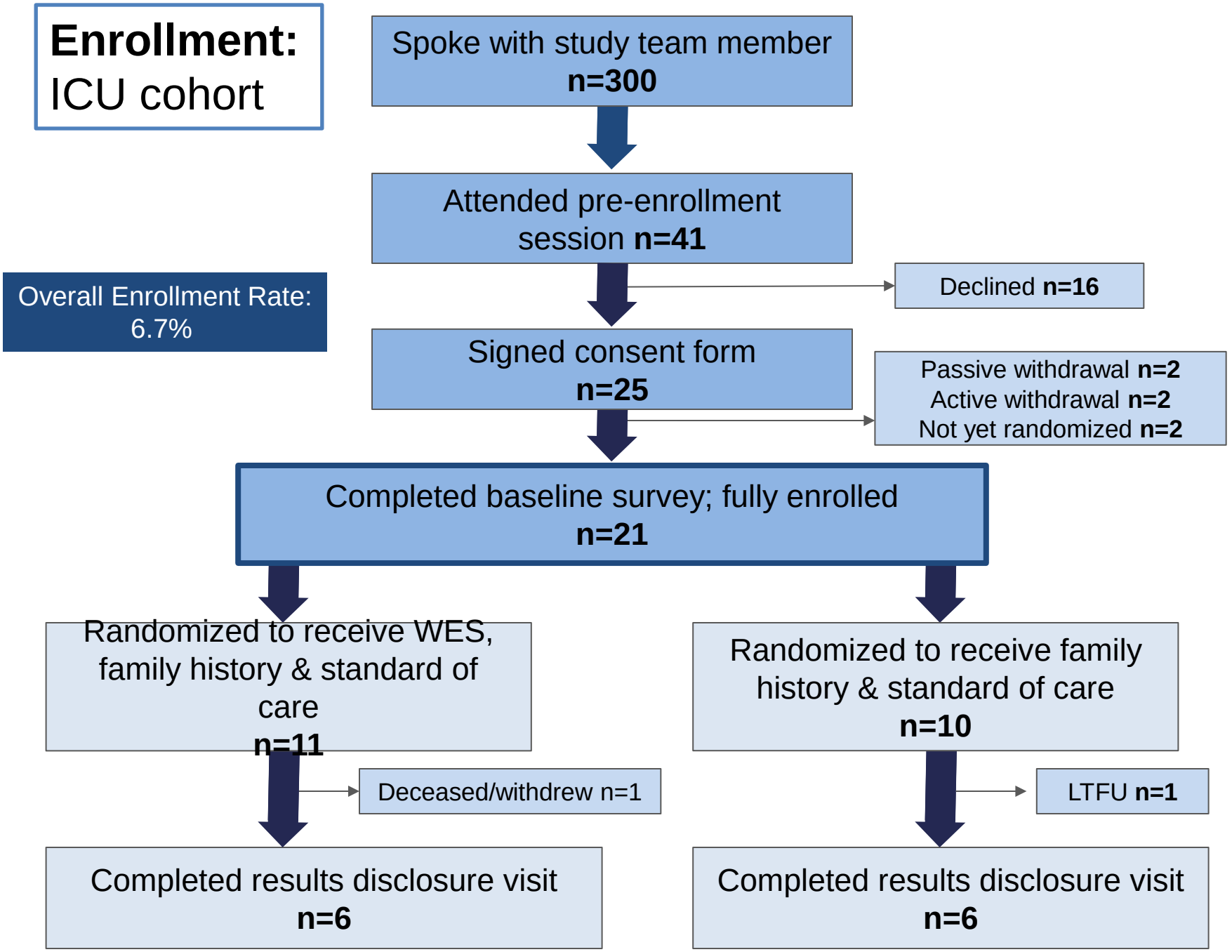


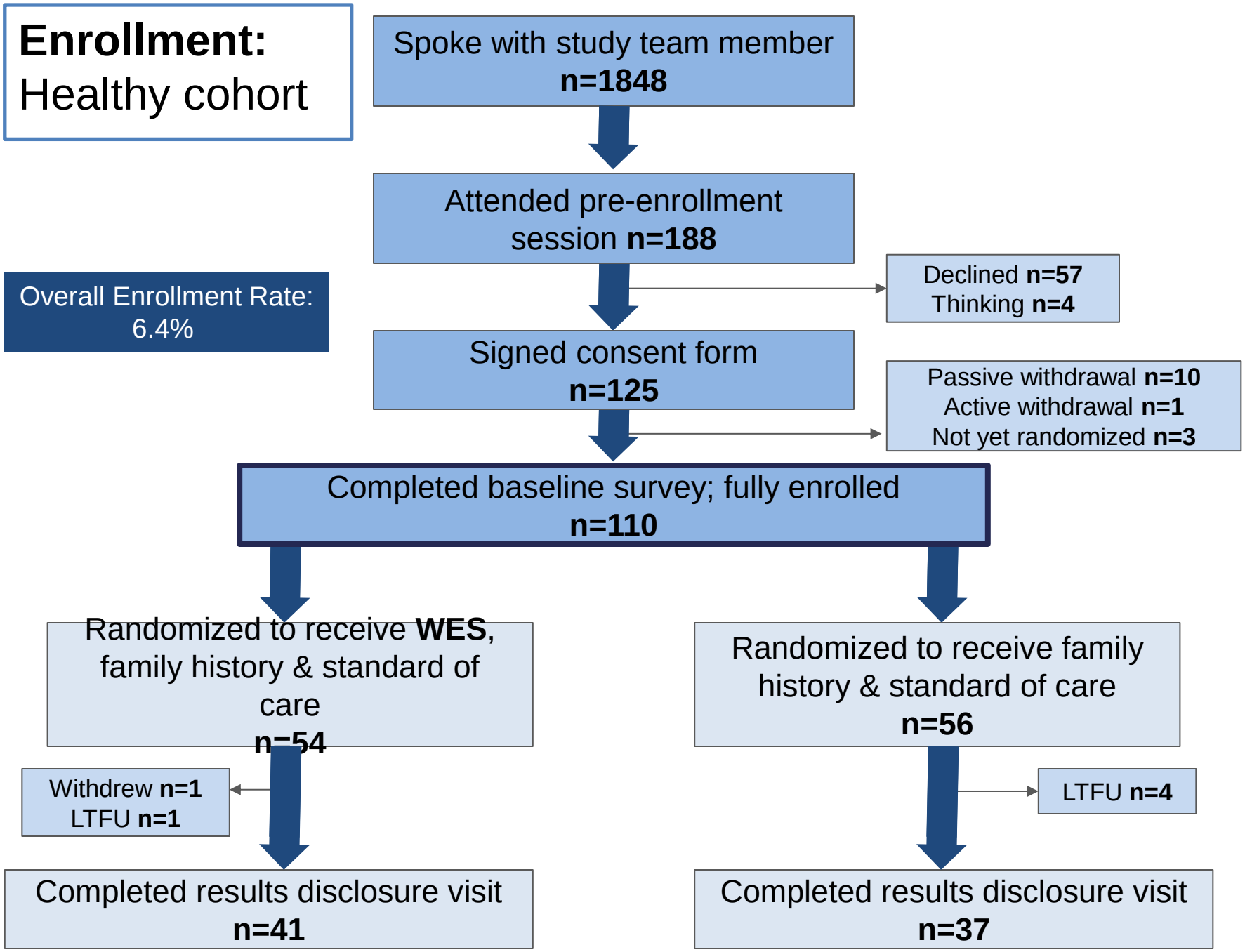
Criteria for including a variant in a BabySeq report



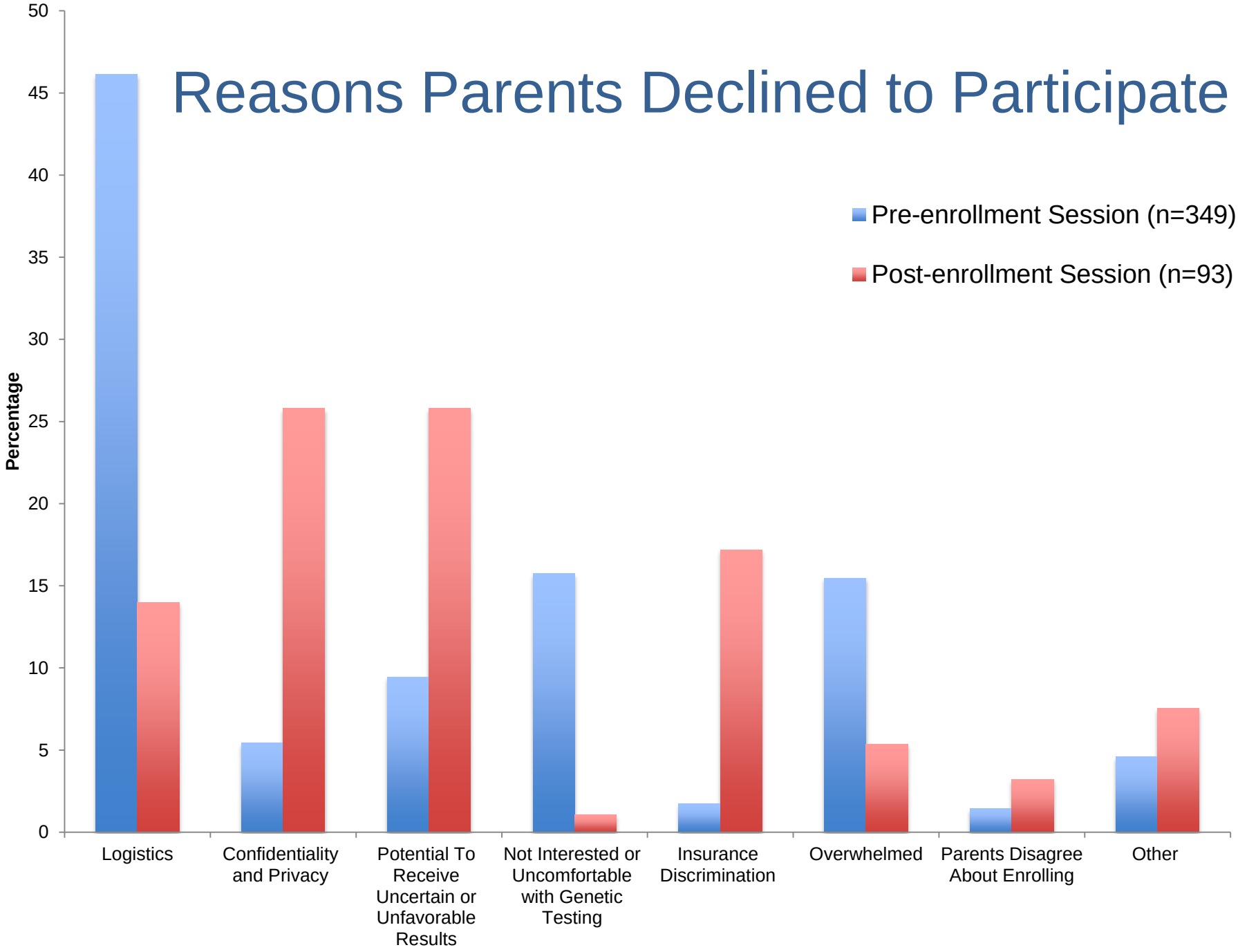

Recruitment Status for BabySeq


Enrollment:
ICU cohort
Spoke with study team member
n=300
Attended pre-enrollment session n=41
Declined n=16
Overall Enrollment Rate: 6.7%
Signed consent form
n=25
Passive withdrawal n=2
Active withdrawal n=2
Not yet randomized n=2
Completed baseline survey; fully enrolled
n=21
Randomized to receive WES, family history & standard of care
n=11
Randomized to receive family history & standard of care
n=10
Deceased/withdrew n=1
LTFU n=1
Completed results disclosure visit
n=6
Completed results disclosure visit
n=6


Enrollment:
Healthy cohort
Spoke with study team member
n=1848
Attended pre-enrollment session n=188
Declined n=57
Thinking n=4
Overall Enrollment Rate: 6.4%
Signed consent form
n=125
Passive withdrawal n=10
Active withdrawal n=1
Not yet randomized n=3
Completed baseline survey; fully enrolled
n=110
Randomized to receive WES, family history & standard of care
n=54
Randomized to receive family history & standard of care
n=56
Withdrew n=1
LTFU n=1
LTFU n=4
Completed results disclosure visit
n=41
Completed results disclosure visit
n=37

Reasons Parents Declined to Participate



BabySeq Findings Returned

- Results (both arms) disclosed for 12 ICU and 78 well babies
  - Time from DNA extraction to report– average 50 days
  - Faster time available if clinically indicated

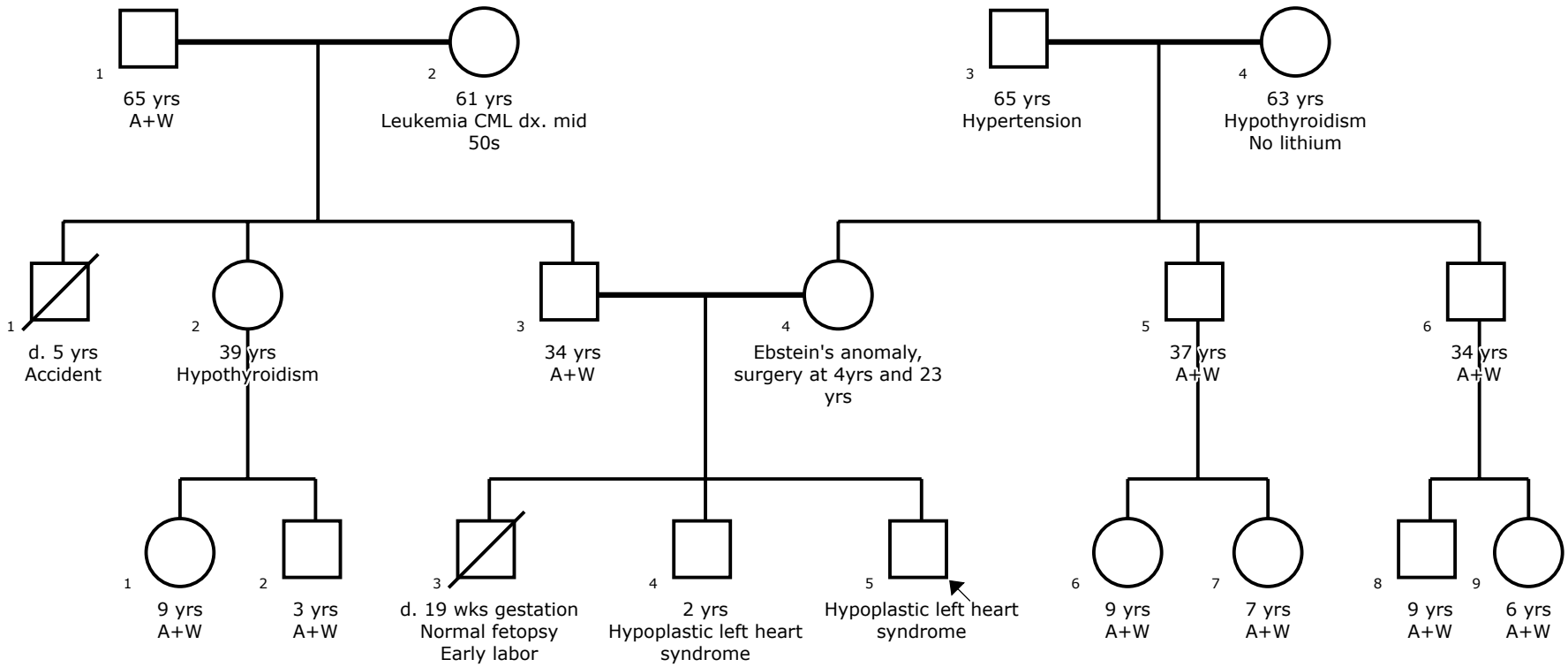
- 43/47 sequenced infants heterozygous for one or more recessive alleles

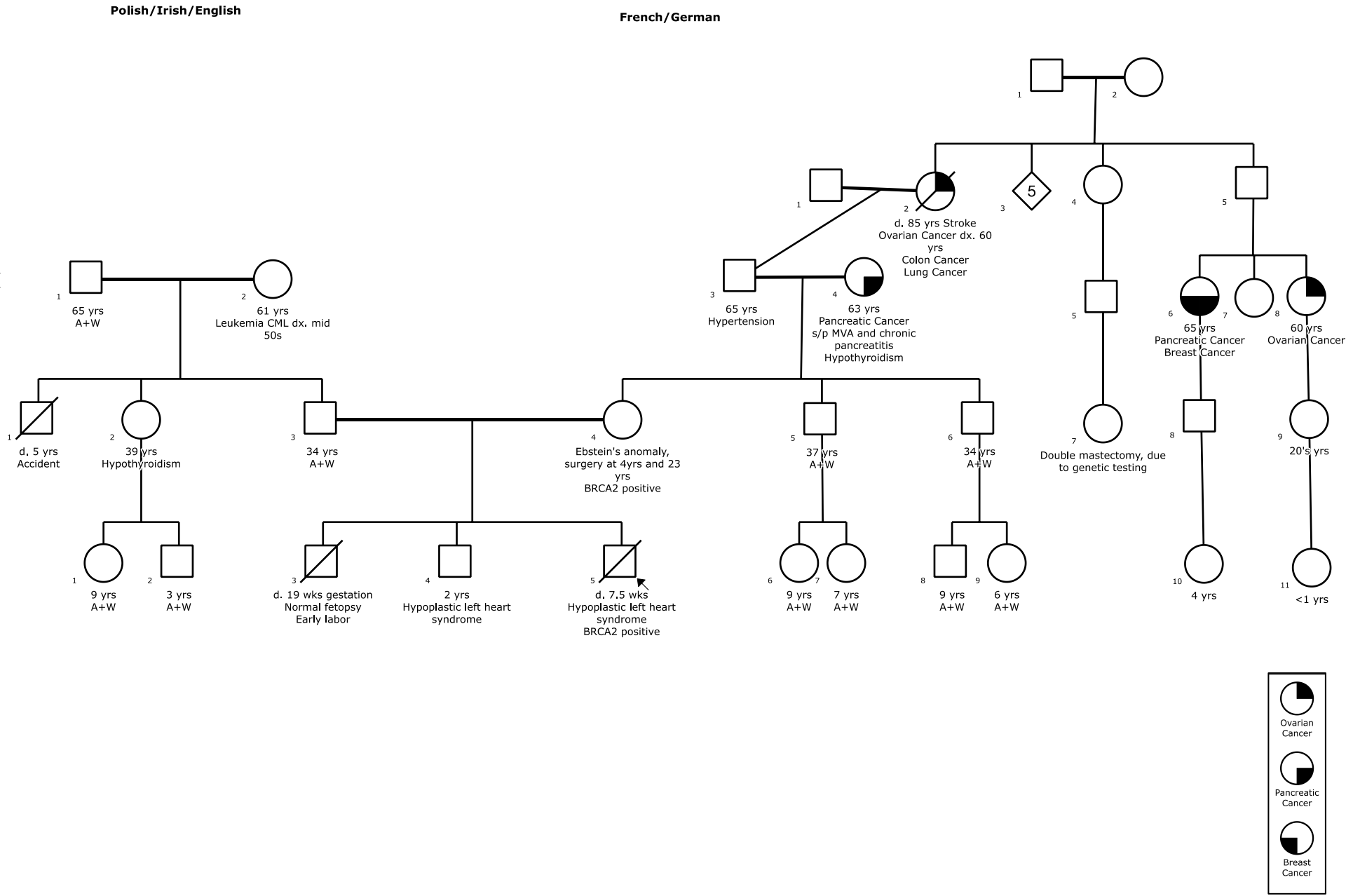
- 2/47 sequenced infants have reportable PGx variants

- 3/47 unanticipated dominant monogenic variants

Dominant Monogenic Variants

Disease	Gene	Variant	Classification	Parent of Origin
Supravalvular aortic stenosis	*ELN*	c. 1957G>T p. Gly653X	Pathogenic	Maternal
Dilated cardiomyopathy	*VCL*	c. 1713delA p. Ala573HisfsX8	Likely Pathogenic	Paternal


Polish/Irish/English
French/German
1
65 yrs
A+W
2
61 yrs
Leukemia CML dx. mid
50s
3
65 yrs
Hypertension
4
63 yrs
Hypothyroidism
No lithium
1
d. 5 yrs
Accident
2
39 yrs
Hypothyroidism
3
34 yrs
A+W
4
Ebstein's anomaly,
surgery at 4yrs and 23
yrs
5
37 yrs
A+W
6
34 yrs
A+W
1
9 yrs
A+W
2
3 yrs
A+W
3
d. 19 wks gestation
Normal fetopsy
Early labor
4
2 yrs
Hypoplastic left heart
syndrome
5
Hypoplastic left heart
syndrome
6
9 yrs
A+W
7
7 yrs
A+W
8
9 yrs
A+W
9
6 yrs
A+W


Polish/Irish/English
French/German
1
2
65 yrs
A+W
61 yrs
Leukemia CML dx. mid
50s
d. 5 yrs
Accident
39 yrs
Hypothyroidism
34 yrs
A+W
9 yrs
A+W
3 yrs
A+W
d. 19 wks gestation
Normal fetopsy
Early labor
2 yrs
Hypoplastic left heart
syndrome
d. 7.5 wks
Hypoplastic left heart
syndrome
BRCA2 positive
Ebstein's anomaly,
surgery at 4yrs and 23
yrs
BRCA2 positive
65 yrs
Hypertension
63 yrs
Pancreatic Cancer
s/p MVA and chronic
pancreatitis
Hypothyroidism
37 yrs
A+W
9 yrs
A+W
7 yrs
A+W
34 yrs
A+W
9 yrs
A+W
6 yrs
A+W
d. 85 yrs Stroke
Ovarian Cancer dx. 60
yrs
Colon Cancer
Lung Cancer
5
Double mastectomy, due
to genetic testing
65 yrs
Pancreatic Cancer
Breast Cancer
60 yrs
Ovarian Cancer
4 yrs
20's yrs
<1 yrs
Ovarian
Cancer
Pancreatic
Cancer
Breast
Cancer

The BabySeq Project Team

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