Parental Interest in Genomic Sequencing of Healthy Newborns: Experiences from the BabySeq Project

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Boston Children's Hospital
Until every child is well™

BWH BRIGHAM AND WOMEN'S HOSPITAL

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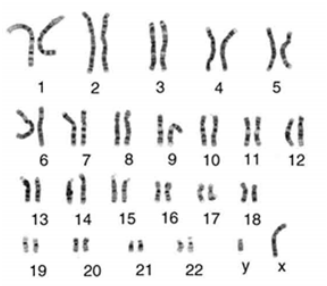
Baylor College of Medicine

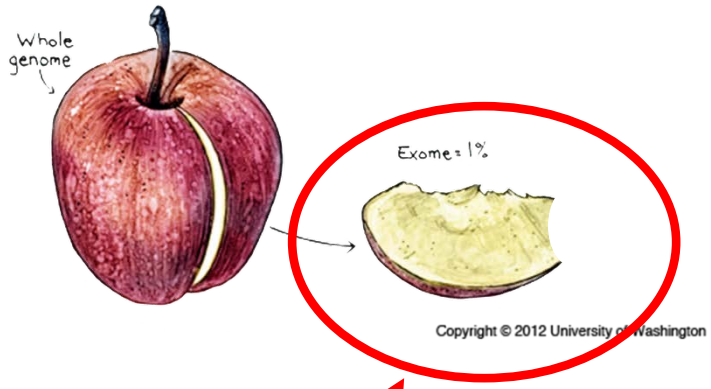
DISCLOSURE

Scientific Advisory Board

Parabase Genomics, Boston, MA

History of Genetic Diagnostics in Newborns





- Karyotype
- Single point mutations (SNPs)
- Mutation panels (multiplexed assays)
- Microarrays for microdeletions/insertions (CGH)
- Single gene exon sequencing (Sanger or NGS)
- Whole exome sequencing (WES) (NGS, Sanger)
- Whole genome sequencing (WGS) (NGS, Sanger)

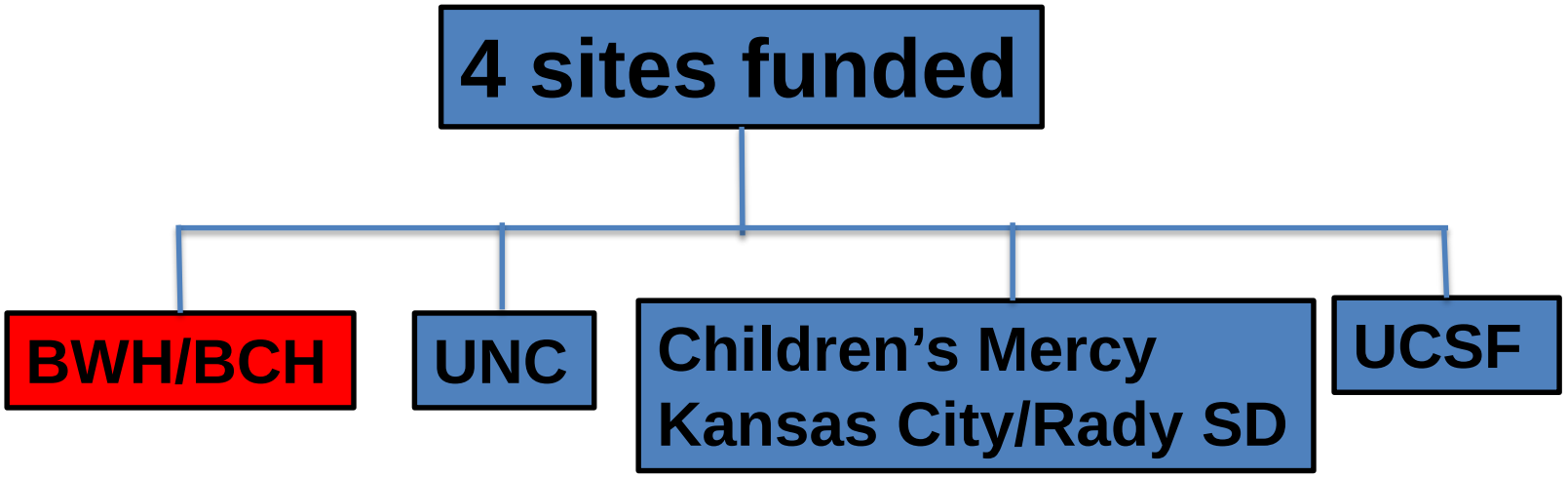
U19: NHGRI/NICHD Initiative

Should Newborns be Sequenced?

- Primary DNA-based newborn screening is now technically feasible
- Genomic technology advancing rapidly with lower cost and faster speed
- What are possible applications of new genomic concepts and technologies to newborn screening and child health?

What is BabySeq?

NIH funded U19 grant entitled:
"Genomic Sequencing for Childhood Risk and Newborn Illness"



Genomic Newborn Sequencing

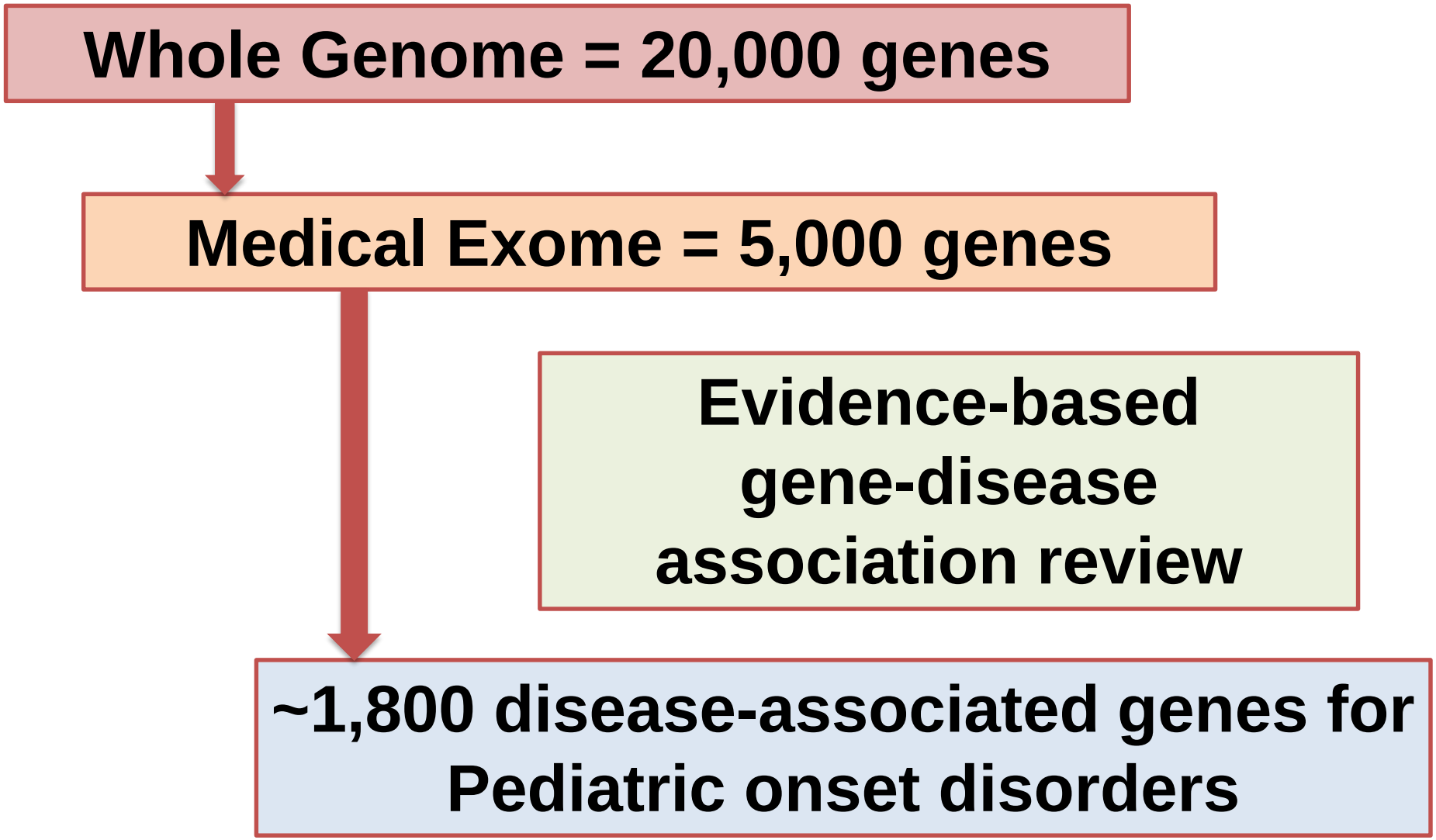
Benefits

- Diagnose affected infants, especially for actionable disorders not included in currently NBS
- Early warning for management of disease
- Optimal use of drugs for treatment
- Blood group and platelet antigen predictions
- Reproductive planning information for families
- Discovery for treatable pediatric disease

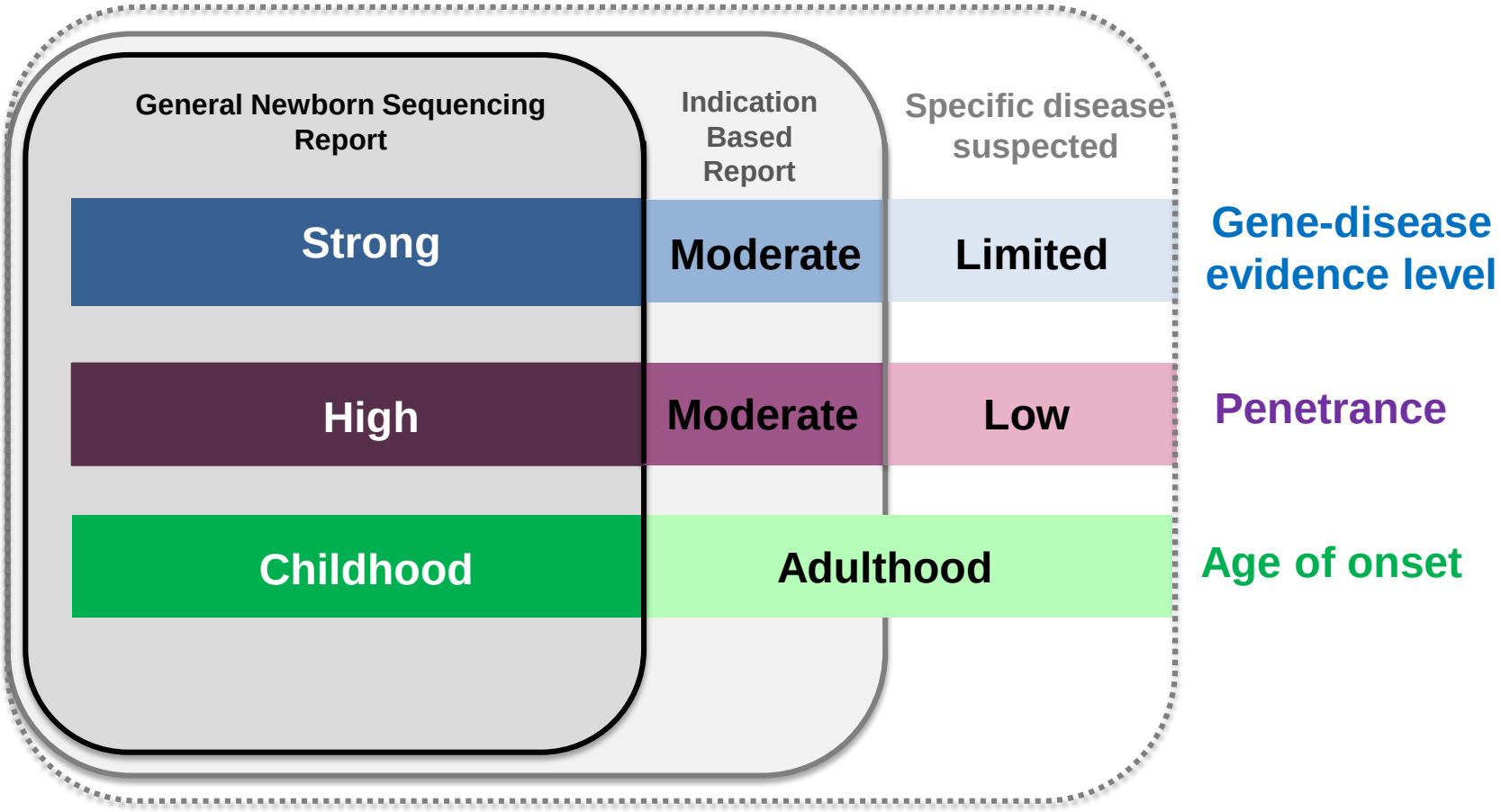
Risks

- Psychological distress due to unexpected disease risk
- Anxiety due to uncertain results
- Easy to misunderstand results
- Negative impact on parent-child relationship
- Children learn about later-onset disease risk
- Stigmatization/discrimination
- Discovery of non-paternity
- Costs high with resources limited

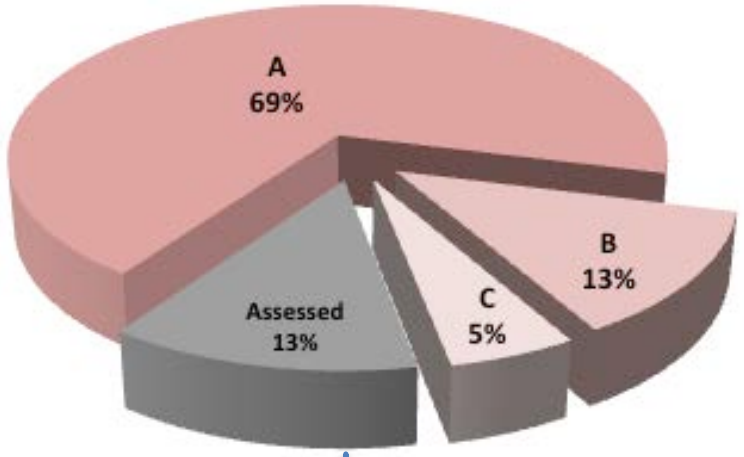
Identifying Genes to Report



Genes Identified to Report: Criteria



Criteria for Reporting a Variant



Pathogenic	Likely pathogenic	Uncertain significance	Likely benign	Benign

Genomic Newborn Screening Report

Indication-Based Analysis

BRIEF REPORT | Genetics inMedicine

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

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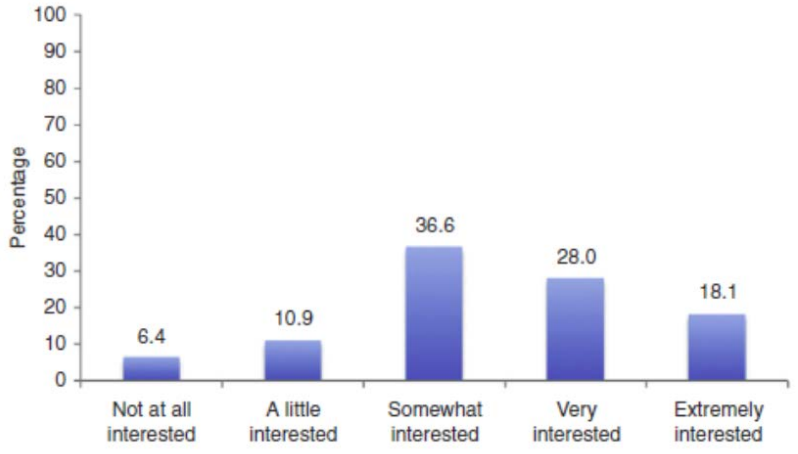
Variable	In-patient cohort (n = 514)	OR (95% CI)	P value
Mean age ± SD (range)	32.7 ± 6.4 (15–65)	1.05 (1.00–1.10)	0.066
Female, n (%)	335 (65.2)	1.03 (0.61–1.72)	0.917
White, n (%)	314 (61.2)	1.53 (0.89–2.62)	0.123
Hispanic or Latino, n (%)	64 (12.5)	0.94 (0.43–2.05)	0.882
Married, n (%)	407 (79.3)	0.36 (0.16–0.80)	0.012
Some graduate school or higher, n (%)	248 (48.3)	0.87 (0.51–1.48)	0.611
First biological child, n (%)	270 (52.7)	1.44 (0.89–2.33)	0.142
Family history of genetic disease, n (%)	70 (13.7)	0.85 (0.42–1.73)	0.655
Infant health concerns, n (%)	29 (5.7)	0.39 (0.16–0.91)	0.030

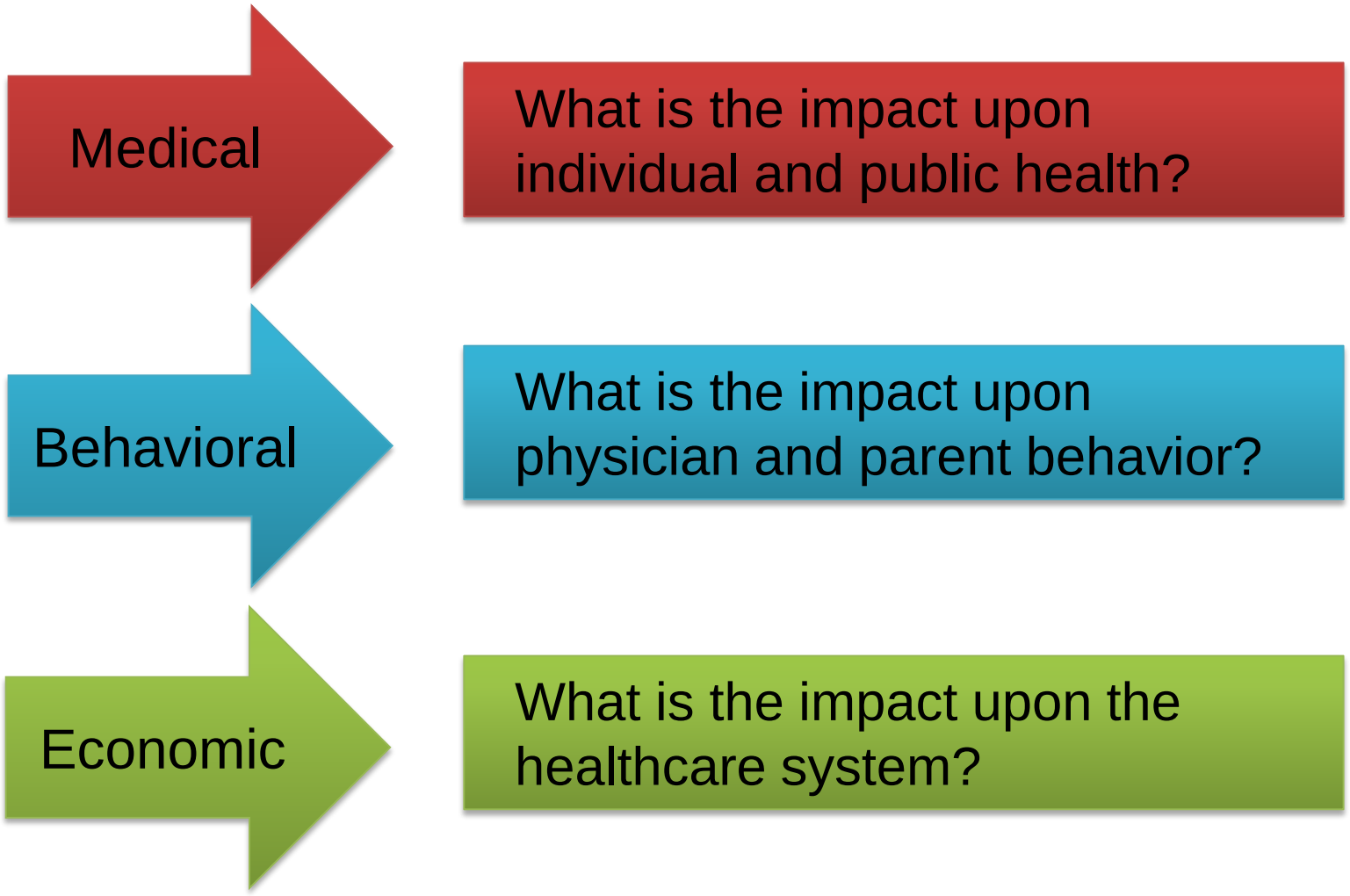


BabySeq ™ Project

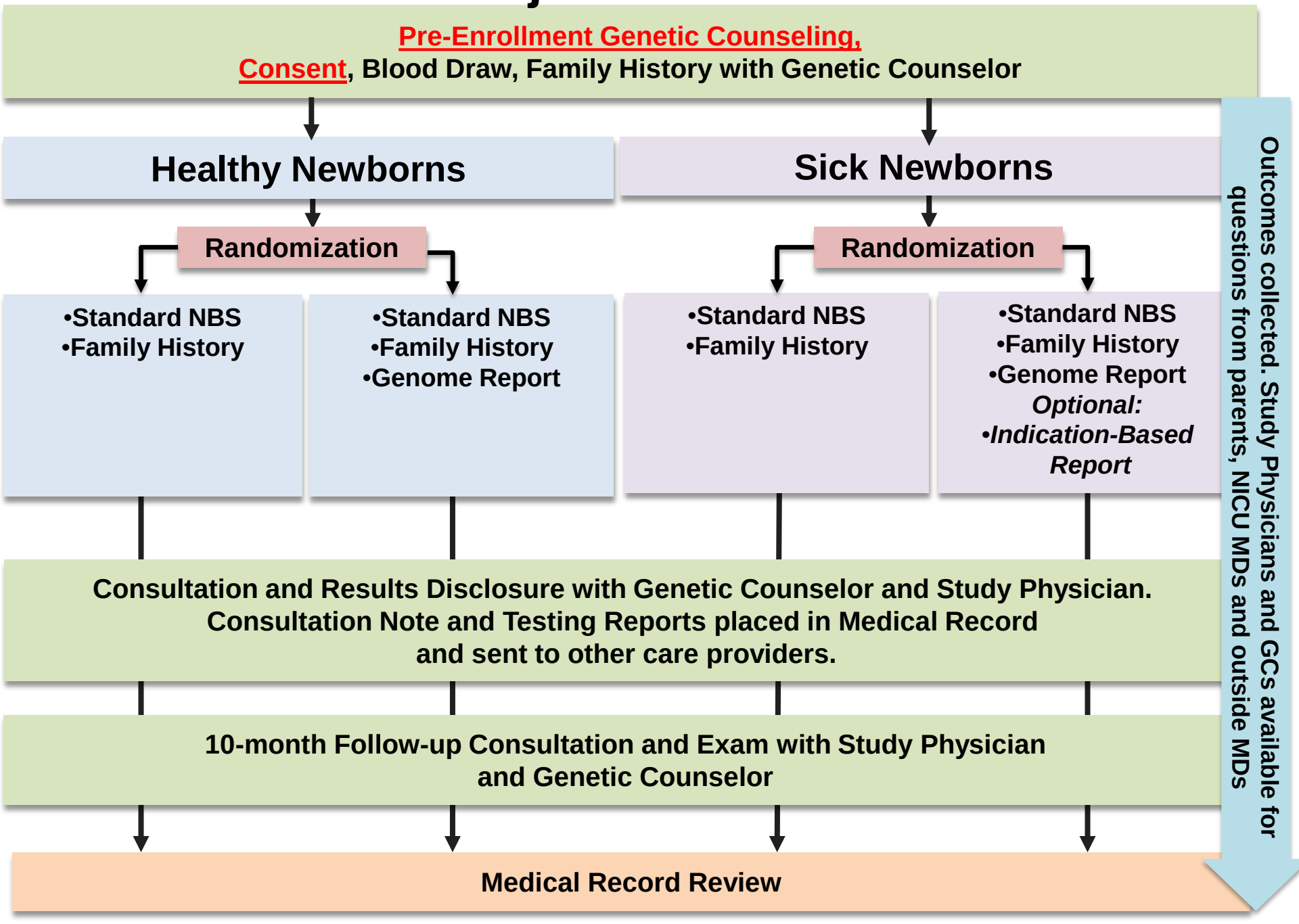
- Explores impact of genomic sequencing (GS) on the healthcare of newborns and well-being of their families.
- Well newborns randomized to receive either standard of care (SOC) (state mandated newborn screening) or SOC plus GS that will evaluate genes with strong evidence for causing childhood disorders.
- Detection of both disease and carrier status is reported.
- Families and their Pediatricians are monitored over time.

STUDY GOALS

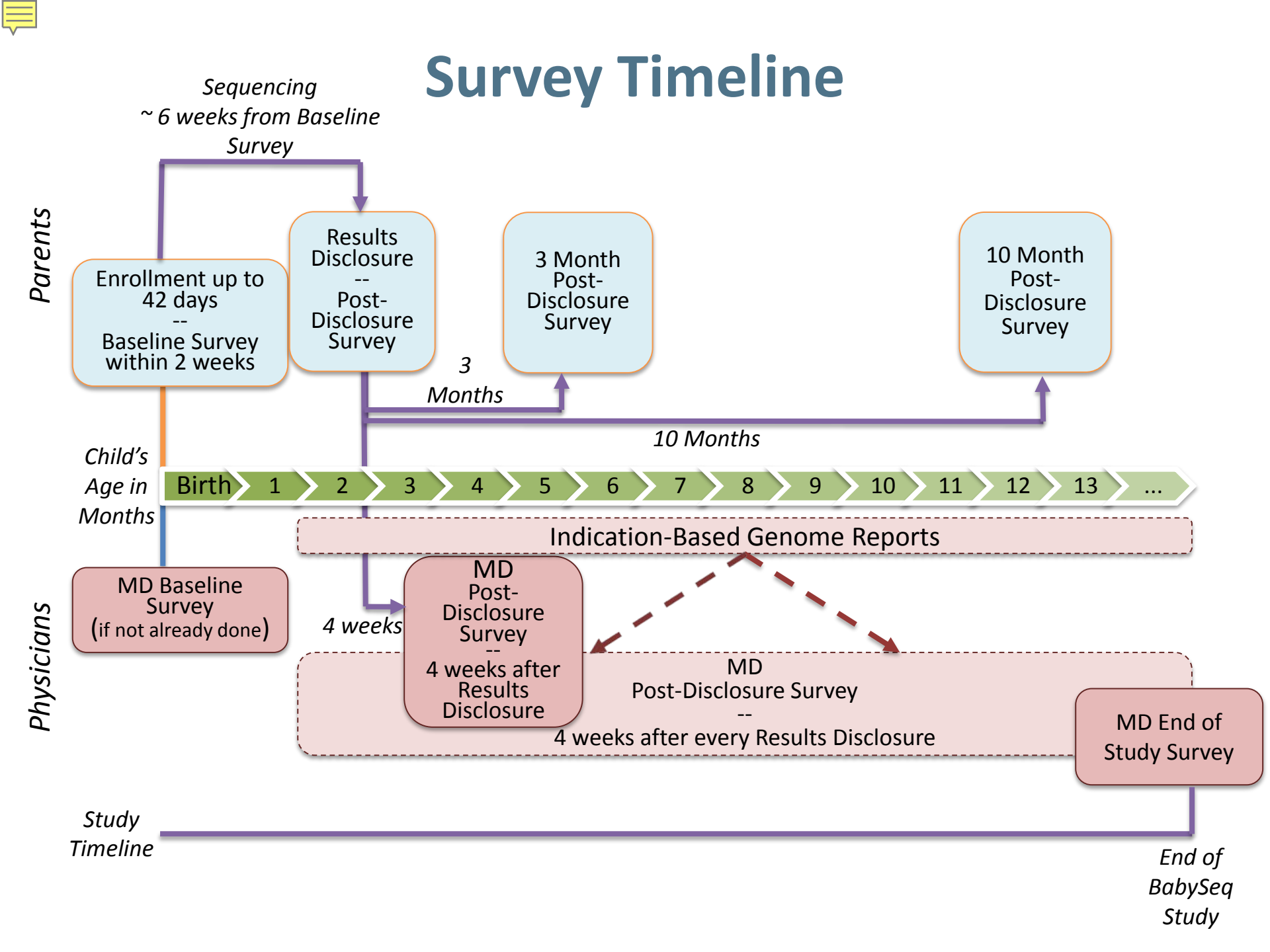
Explore potential impact of newborn genomic sequencing on families and providers



Project Overview



Survey Timeline



Two reporting strategies

Well newborn nursery

NICU

Genomic Newborn Sequencing Report (GNSR)

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

Indication-Based Sequencing Report (IBGR)

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

Sample Genomic Newborn Sequencing Report

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65 Landsdowne St, Cambridge, MA02139
Phone: (617) 768-8500 / Fax: (617) 768-8513
http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

Name: **DOE, JOHN**
DOB: **10/10/2014**
Sex: **Male**

Accession ID: **PM14-12345**
Specimen: **DNA from peripheral blood**
Received: **10/11/2014**

MRN: **123456**
Family #: **F00123**
Referring physician: **Dr. Robert Smith**
Referring facility: **BCH**

GENOMIC NEWBORN SEQUENCING REPORT

RESULT: VARIANT OF CLINICAL SIGNIFICANCE IDENTIFIED

RESULT SUMMARY

Sequencing of this individual's exome identified 1 variant that may be responsible for existing disease or may cause disease during childhood. All results are summarized on page 1 with further details provided on subsequent pages.

These results should be interpreted in the context of the patient's medical evaluation, family history, and racial/ethnic background. It should be noted that the disease risk section of this report is limited only to variants with evidence for causing highly penetrant childhood-onset diseases. Please note that certain types of variants such as triplet repeat expansions, translocations and large copy number events are currently not reliably detected by exome sequencing. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. Moreover, not all disease-associated genes have been identified and the clinical significance of variation in many genes is not well understood. Variant interpretation may change over time if more information becomes available.

INTERPRETATION SUMMARY

A. MONOGENIC DISEASE RISK VARIANTS

This test identified 1 genetic variant that may cause disease or be responsible for existing disease in this individual. Please see page 2 for more detailed variant information.

Disease, Inheritance	Gene Transcript	Zygosity Variant	Classification	Penetrance
Wilson disease, Autosomal recessive	ATP7B NM_000053.3	Homozygous c.2333G>T p.Arg778Leu	Pathogenic	High

B. CARRIER STATUS VARIANTS

This test identified carrier status for 1 recessive disorder.

This individual likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant. Please note that the possibility of a second variant in this gene that was not detected by this test cannot be excluded.

Disease, Inheritance	Gene Transcript	Zygosity Variant	Classification	Penetrance
Hearing loss, Autosomal recessive	GJB2 NM_004004.5	Heterozygous c.35delG p.Gly12fs	Pathogenic	High

Pathogenic variants in both copies of GJB2 gene are necessary to cause hearing loss, therefore the presence of one pathogenic variant in GJB2 suggests that this individual will not be affected but represents a carrier. However, it should be noted that a second variant is not identified in a large percentage (10-50%) of individuals with nonsyndromic hearing loss and a GJB2 variant (del Castillo 2003). Therefore, evaluation of hearing is recommended to ensure that the individual is not at risk for disease due to the presence of a second variant, which was not detected in this test.

Genetic counseling is recommended for this individual and their relatives. Familial variant testing is available for other relatives if desired. For assistance in locating genetic counseling services or disease specialists, and for questions about this report, please contact the Genome Resource Center at GRC@partners.org.

DETAILED VARIANT INFORMATION

A. MONOGENIC DISEASE RISK VARIANTS

Disease, Inheritance	Gene Transcript	Chromosome Genomic coordinate Reference genome	Zygosity Variant	Classification	Penetrance	References (PMID)
Wilson disease, Autosomal recessive	ATP7B NM_000053.3	Chr 13 g.52,532,465 GRCh37 (hg19)	Heterozygous c.35delG p.Gly12fs	Pathogenic	High	7626145 9837819 11405812 19937698 23235335 23843956

VARIANT INTERPRETATION: The Arg778Leu variant has previously been identified in trans with another pathogenic variant in >20 individuals with Wilson disease, who presented with childhood-onset liver degeneration or neurologic impairment, segregated with disease in 4 affected relatives, and was not identified in > 500 ethnically-matched control chromosomes (Thomas 1995, Wu 2001, Li 2013, Gu 2013). This variant was not identified in large population studies. Studies have shown that the Arg778Leu variant impacts protein function (Forbes 1998, van der Berghe 2009), although these in vitro assays may not accurately represent biological function. In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM) based upon its segregation in individuals with disease and absence from controls.

DISEASE INFORMATION: Wilson disease is characterized by dramatic accumulation of intracellular hepatic copper with subsequent hepatic and neurologic disturbances, including recurrent jaundice, chronic liver disease, movement disorders, dystonia, and intellectual deterioration. Age of onset can vary from 3 to over 60 years. Individuals are asymptomatic at birth and treatment with copper chelating agents initiated as soon as possible can effectively prevent or reduce the majority of the hepatic and neurologic symptoms. Wilson disease currently cannot be detected by traditional newborn screening due to the lack of available biochemical testing methods to reliably differentiate affected individuals. Adapted from GeneReviews and OMIM: http://www.ncbi.nlm.nih.gov/books/NBK1512/; http://www.omim.org/entry/277900

FAMILIAL RISK: Wilson disease is inherited in an autosomal recessive manner. A carrier of Wilson disease has a 50% (or 1 in 2) chance of passing on an ATP7B variant to any children. This patient likely inherited the ATP7B variants from each of the parents. Other biologically related family members may also be carriers of this variant.

B. CARRIER STATUS VARIANTS

Disease, Inheritance	Gene Transcript	Chromosome Genomic coordinate Reference genome	Zygosity Variant	Classification	Penetrance	References (PMID)
Hearing loss, Autosomal recessive	GJB2 NM_004004.5	Chr 13 g.20,763,686 GRCh37 (hg19)	Heterozygous c.35delG p.Gly12fs	Pathogenic	High	9285800 12833397 15070423 19925344 20073550 20739944

VARIANT INTERPRETATION: The 35delG (Gly12fs) variant in GJB2 is known to be pathogenic for hearing loss with many supporting publications (Zelante 1997, Maheshwari 2003, Roux 2004, Mahdieh 2009, Kokotas 2010, Dzhemileva 2010).

DISEASE INFORMATION: Hereditary sensorineural hearing loss due to GJB2 variants is typically nonsyndromic and presents prelingual (before language develops). Early auditory intervention through amplification, otologic surgery, or cochlear implantation is essential for optimal cognitive development in children with prelingual deafness. Adapted from GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1434/

FAMILIAL RISK: GJB2-related hearing loss is inherited in an autosomal recessive manner. A carrier of hearing loss has a 50% (or 1 in 2) chance of passing on a GJB2 variant to any children. This patient likely inherited the GJB2 variant from a parent. Other biologically related family members may also be carriers of this variant. Please note that the presence of a second variant in this gene that was not detected by this test cannot be excluded.

COVERAGE SUMMARY

Sequencing of this individual's exome was performed and covered 95% of all positions at 20X coverage or higher, resulting in over 45,000 variants compared to a human reference genome. Please note that the presence of pathogenic variation in genes not analyzed or with incomplete coverage cannot be fully excluded.

METHODOLOGY AND LIMITATIONS

Exome sequence is generated from extracted DNA that is fragmented, adapted, barcoded, and subjected to a solution phase hybridization with the Agilent SureSelect Human All Exon V2 probe set. Next generation sequencing is performed on the Illumina HiSeq platform. Exomes are sequenced to at least 150X mean coverage and a minimum of 95% of bases are sequenced to at least 20X coverage. Paired-end reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). Variants are subsequently filtered to identify: (1) variants with a minor allele frequency <5% and (2) variants classified as disease causing mutations in public databases and (3) predicted loss-of-

What is asked of families?

Enrollment session with genetic counselor

Provide blood (neonate) and saliva (neonate and parents)

Four surveys and two hospital visits between enrollment and 1 year of age

Families will be compensated for each survey that they complete

There is no cost for the families to participate

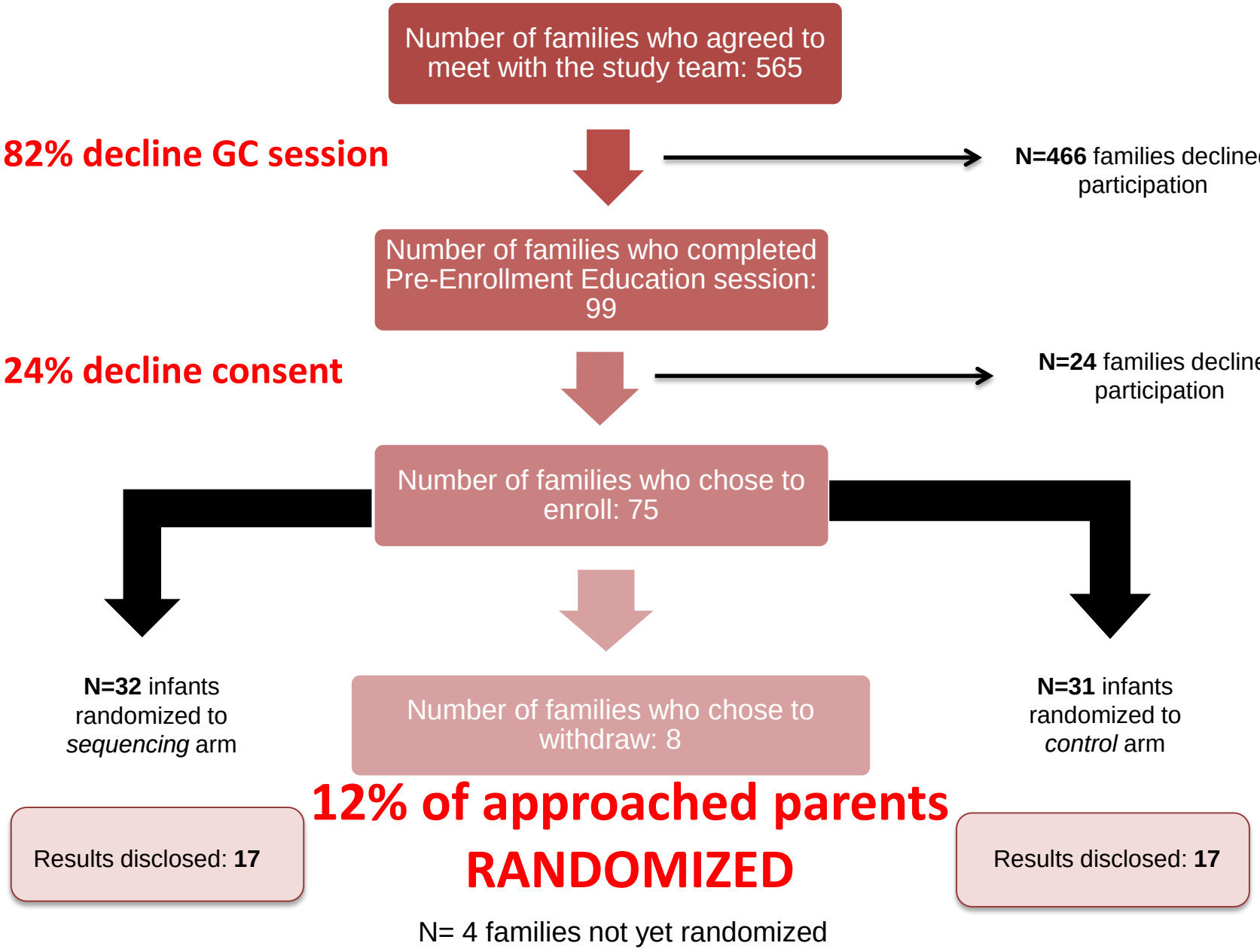
Consent Process

- Our protocol requires that we obtain parental consent and a newborn blood sample in the short time between 24 hours of life and discharge (generally 48 hours of life) from the birth hospital.
- We assessed how often and why parents who expressed an initial interest in the BabySeq project chose to decline consent or participation.

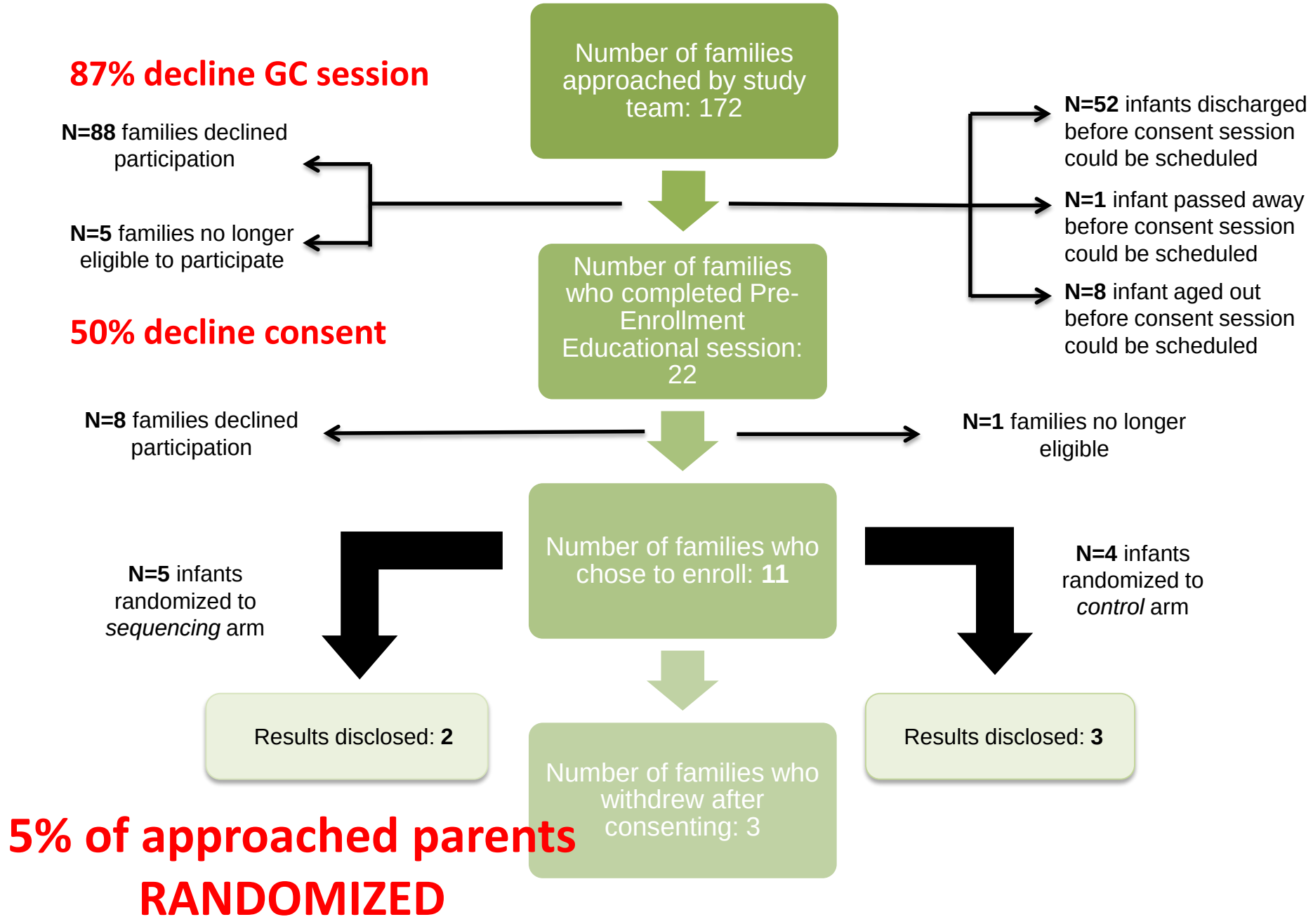
Approach

- >24 hours after birth and prior to discharge
- Research assistant screens for eligibility and provides parents with research menu
- If interested in learning about BabySeq, study coordinator schedules GC/education-consent session (1 hour)
- With consent, blood/saliva collected, trio
- Baseline survey may be returned within 2 weeks – when received, randomization proceeds.

Brigham and Women's Hospital Healthy Infant Cohort Recruitment Details



Sick Infant Cohort Recruitment Details



Constraints in Approaching and Counseling Families for Consent

- The protocol
  - tight time window
  - hard to meet for an hour
  - time of stress for parents
  - blood collection from the newborn
- The genetic information: perceived negative impacts
  - privacy (results becomepartof medical record)
  - insurability
  - anxiety about results

BabySeq

Participant Decline Form

Room Number: _____ Date: ____/____/____ Taken By: _____

Infant: Year of Birth: _____ **Gender:** _____ **Primary diagnosis (if NICU):** _____

Please briefly describe your reason(s) for decline: _____

_____

_____

Parent 1: Year of Birth: _____ **Gender:** _____ **First child?** _____

Race: (*Choose all that apply*)

- ○ White
- ○ Black/African American
- ○ American Indian/Native Alaskan
- ○ Asian
- ○ Pacific Islander/Native Hawaiian
- ○ Other, *please specify*: _____
- ○ Prefer not to answer

Of Hispanic, Latino, or Spanish origin?: (*Choose one*)

- ○ Yes
- ○ No
- ○ Prefer not to answer

Highest Education Level: (*Choose one*)

- ○ Grade school (grades 1-8)
- ○ Some high school (grades 9-12)
- ○ High school graduate or GED
- ○ Post high school training (i.e. vocational)
- ○ Some college or associate's degree
- ○ College graduate
- ○ Master's degree
- ○ Doctoral degree/professional degree (MD, JD)
- ○ Prefer not to answer

Political Orientation: (*Circle one*) 10 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 10 / Prefer not to answer
Liberal **Moderate** **Conservative**

Parent 2: Year of Birth: _____ **Gender:** _____ **First child?** _____

Race: (*Choose all that apply*)

- ○ White
- ○ Black/African American
- ○ American Indian/Native Alaskan
- ○ Asian
- ○ Pacific Islander/Native Hawaiian
- ○ Other, *please specify*: _____
- ○ Prefer not to answer

Of Hispanic, Latino, or Spanish origin?: (*Choose one*)

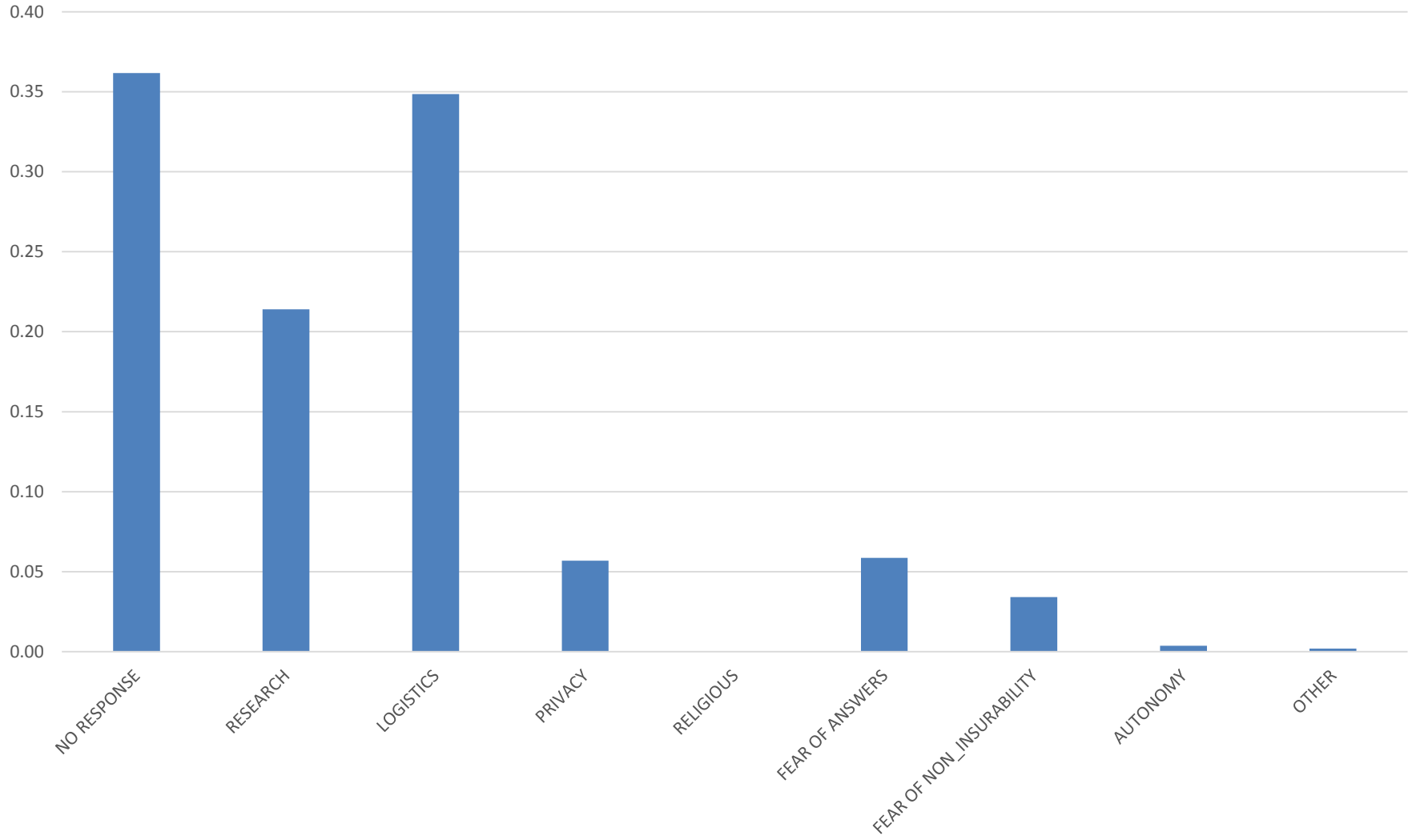
- ○ Yes
- ○ No
- ○ Prefer not to answer

Highest Education Level: (*Choose one*)

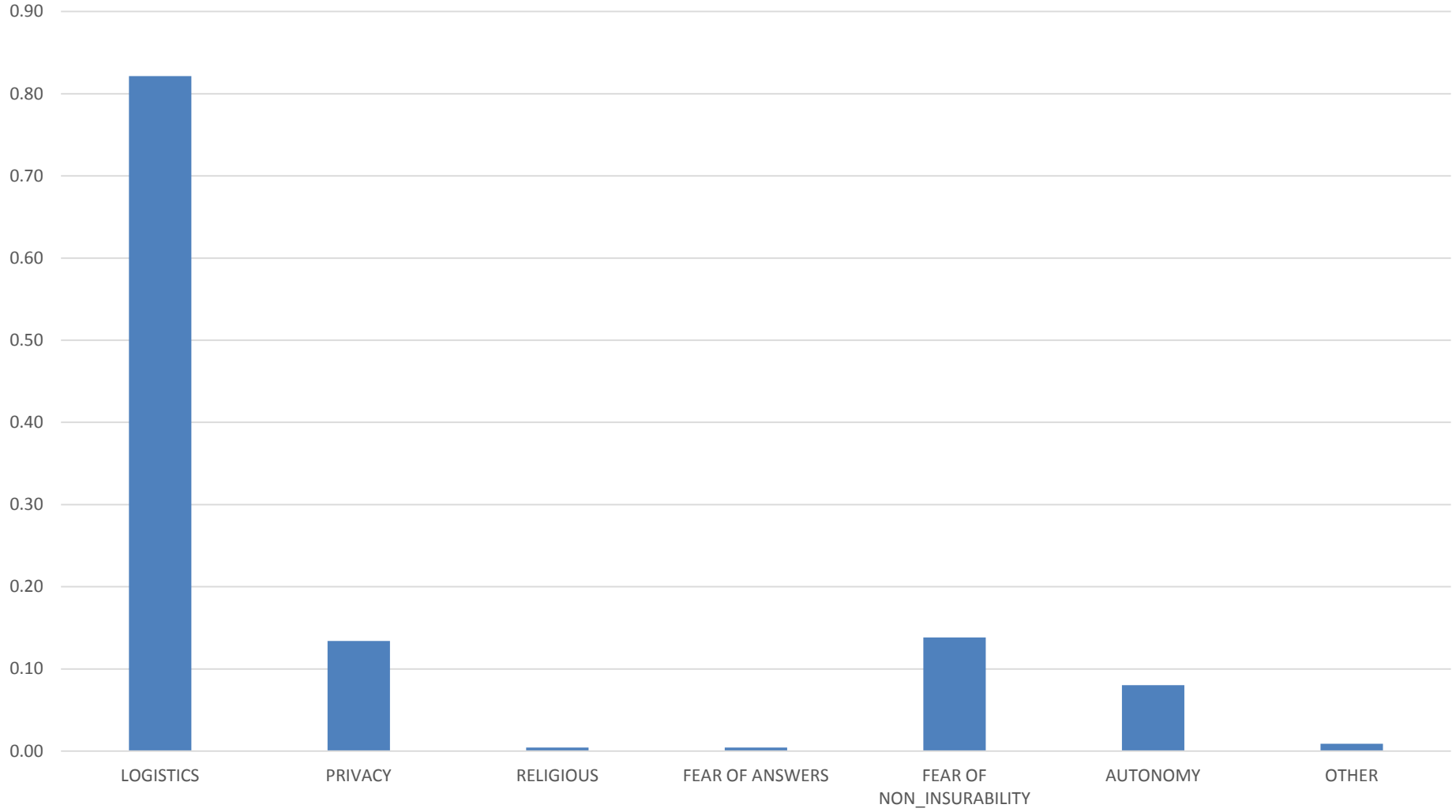
- ○ Grade school (grades 1-8)
- ○ Some high school (grades 9-12)
- ○ High school graduate or GED
- ○ Post high school training (i.e. vocational)
- ○ Some college or associate's degree
- ○ College graduate
- ○ Master's degree
- ○ Doctoral degree/professional degree (MD, JD)
- ○ Prefer not to answer

Political Orientation: (*Circle one*) 10 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 10 / Prefer not to answer
Liberal **Moderate** **Conservative**

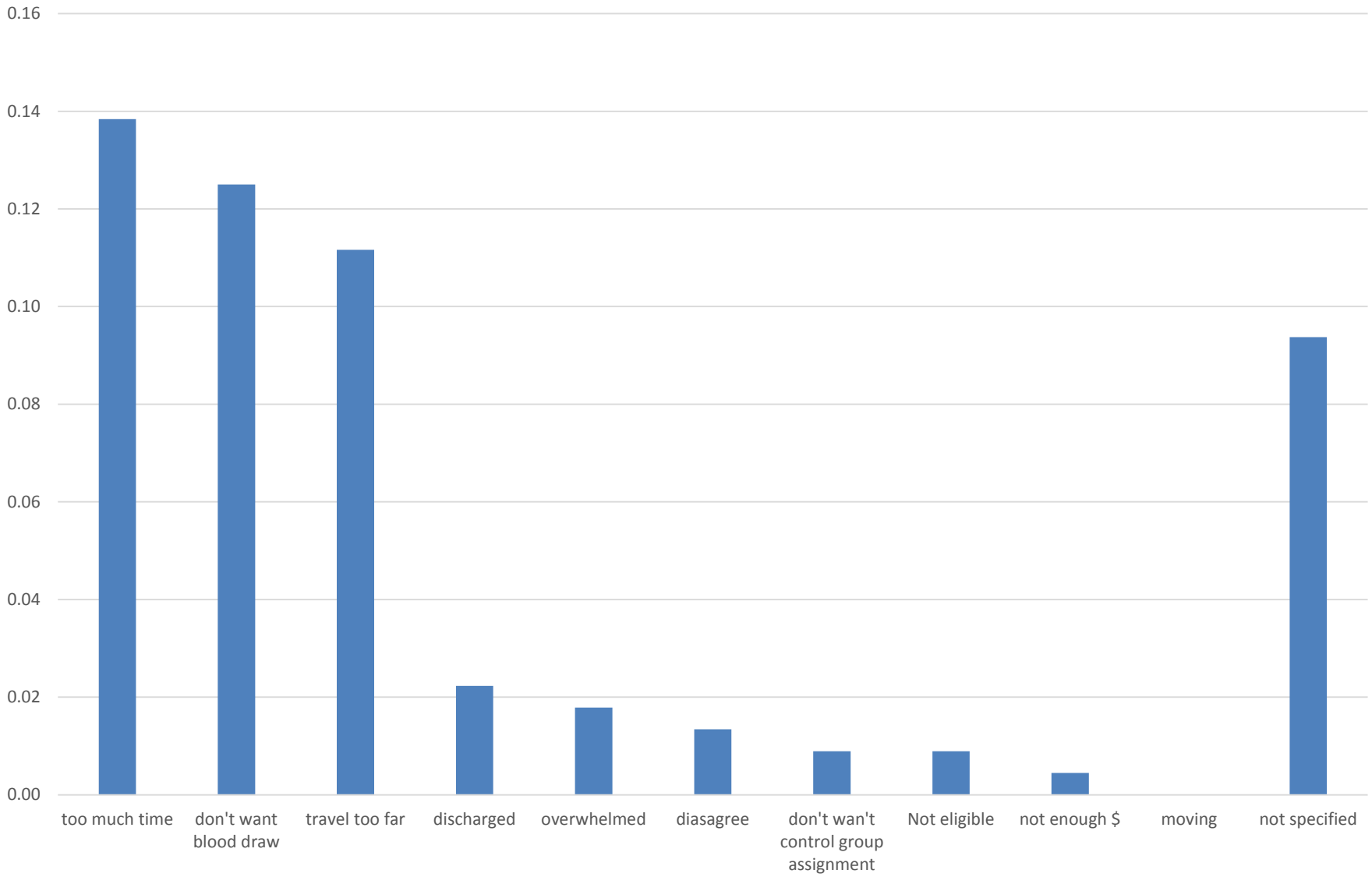
DECLINED BABYSEQ PARTICIPATION (N=405)



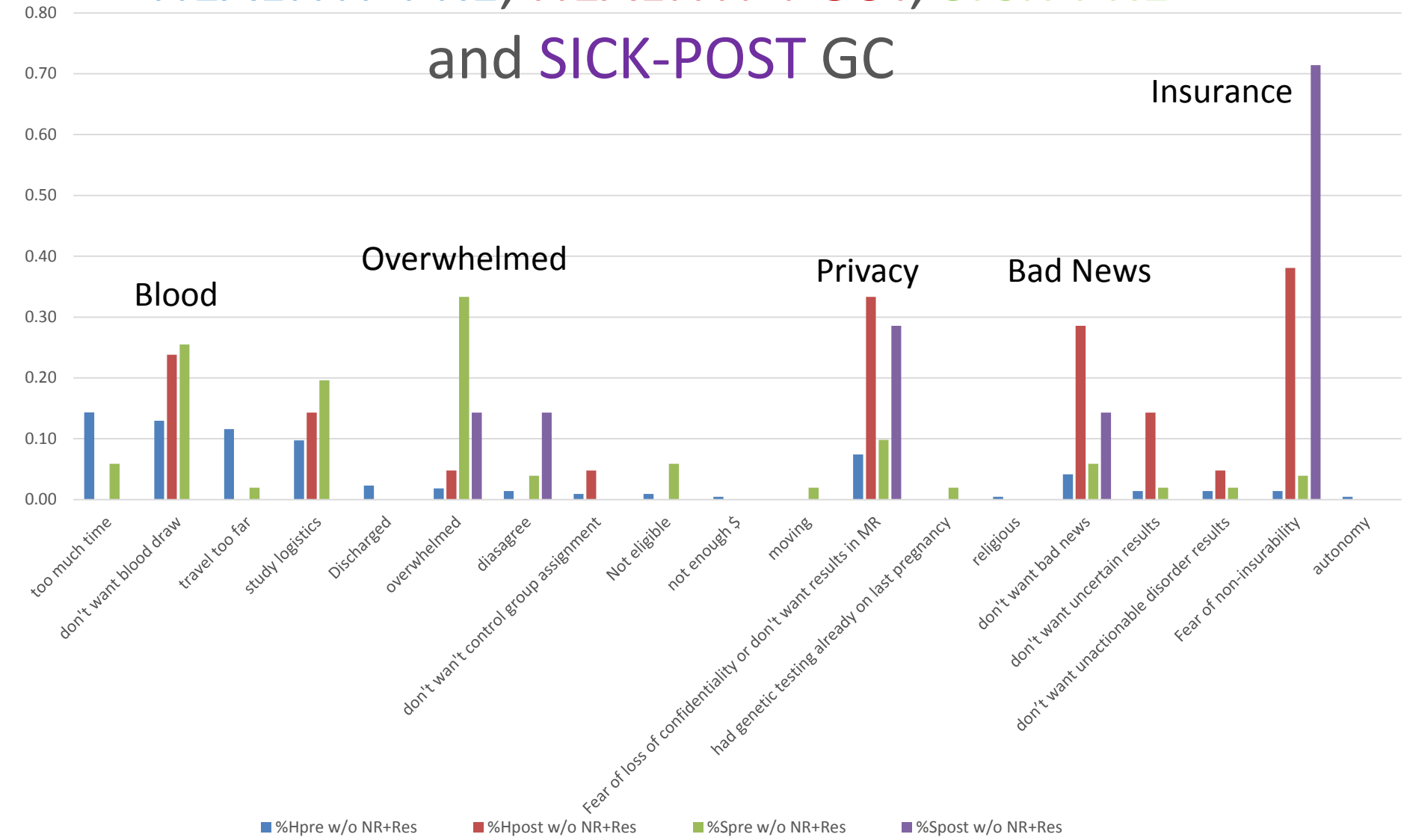
REASONS FOR DECLINING AFTER REMOVAL OF NO RESPONSE AND NO RESEARCH (N=224)



LOGISTICS: REASONS FOR DECLINE



REASON FOR DECLINE BY HEALTHY-PRE, HEALTHY-POST, SICK-PRE and SICK-POST GC



CONCLUSIONS

- Participation was only a fraction of that anticipated by the pre-BabySeq project survey.
- 50% of parental reasoning was influenced by protocol constraints
- ~15% of interested parents expressed enough concern about privacy and insurability that they steered away from consideration of potential newborn GS benefits.
- These initial findings provide valuable insights into parental thoughts and feelings regarding GS as well as feasibility of newborn GS implementation on a population-based level.

The BabySeq Project Team

Project Leadership

Alan Beggs, PhD (Joint PI)
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