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

Richard Parad, MD, MPH, Pankaj Agrawal, MBBS MMSc, Ingrid Holm, MD, MPH, Caroline Weipert, CGC, Meghan Towne, CGC, Cassie Genetti, CGC, Stacey Pereira, PhD, Jill Robinson, MA, Amy McGuire, JD, PhD, Alan Beggs, PhD and Robert Green, MD, MPH

Funded by NICHD/NHGRI Grant# U19HD077671
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)
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”

4 sites funded

BWH/BCH  UNC  Children’s Mercy Kansas City/Rady SD  UCSF
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

Whole Genome = 20,000 genes

Medical Exome = 5,000 genes

Evidence-based gene-disease association review

~1,800 disease-associated genes for Pediatric onset disorders
Genes Identified to Report: Criteria

- **Strong**
  - General Newborn Sequencing Report
  - Indication Based Report
  - Specific disease suspected
  - Gene-disease evidence level
- **High**
  - Childhood
  - Age of onset
- **Limited**
  - Adulthood
  - Penetrance
Criteria for Reporting a Variant

Pathogenic | Likely pathogenic | Uncertain significance | Likely benign | Benign

Genomic Newborn Screening Report

Indication-Based Analysis
Parents are interested in newborn genomic testing during the early postpartum period

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

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

- **Medical**: What is the impact upon individual and public health?
- **Behavioral**: What is the impact upon physician and parent behavior?
- **Economic**: What is the impact upon the healthcare system?
Project Overview

**Pre-Enrollment Genetic Counseling, Consent, Blood Draw, Family History with Genetic Counselor**

**Healthy Newborns**
- Standard NBS
- Family History

**Sick Newborns**
- Standard NBS
- Family History
- Genome Report
- Optional: Indication-Based Report

Randomization

Consultation and Results Disclosure with Genetic Counselor and Study Physician. Consultation Note and Testing Reports placed in Medical Record and sent to other care providers.

10-month Follow-up Consultation and Exam with Study Physician and Genetic Counselor

Outcomes collected. Study Physicians and GCs available for questions from parents, NICU MDs and outside MDs

Medical Record Review
Survey Timeline

- Enrollment up to 42 days -- Baseline Survey within 2 weeks
- Results Disclosure -- Post-Disclosure Survey
- 3 Month Post-Disclosure Survey
- 10 Month Post-Disclosure Survey
- Sequencing ~ 6 weeks from Baseline Survey
- Indication-Based Genome Reports
- MD Baseline Survey (if not already done)
- MD Post-Disclosure Survey -- 4 weeks after Results Disclosure
- MD End of Study Survey
- End of BabySeq Study

Child’s Age in Months
- Birth
- 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, ...

Study Timeline
Two reporting strategies

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

Well newborn nursery

NICU
Sample Genomic Newborn Sequencing Report

GENOMIC NEWBORN SEQUENCING REPORT

RESULT: VARIANT OF CLINICAL SIGNIFICANCE IDENTIFIED

RESULT SUMMARY
Sequenceing of this individual's exome identified a 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 disease in pedigrees with a high likelihood of autosomal recessive inheritance. Please note that the list of variants is not complete.

INTERPRETATION SUMMARY
A. MONOGENIC DISEASE RISK VARIANTS
This test identified a variant that may cause disease or be responsible for existing disease in this individual. Please see page 2 for more detailed variant information.

<table>
<thead>
<tr>
<th>Disease, Inheritance</th>
<th>Gene Transcript</th>
<th>Zygosity Variant</th>
<th>Classification</th>
<th>Penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson disease, Autosomal recessive</td>
<td>AIP1/B NM_000083.3</td>
<td>Homozygous c.352G&gt;C, p.Ala118Pro</td>
<td>Pathogenic</td>
<td>High</td>
</tr>
</tbody>
</table>

B. CARRIER STATUS VARIANTS
This test identified carrier status for 1 recessed disorder.

<table>
<thead>
<tr>
<th>Disease, Inheritance</th>
<th>Gene Transcript</th>
<th>Zygosity Variant</th>
<th>Classification</th>
<th>Penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss, Autosomal recessive</td>
<td>UQG2 NM_0000404.5</td>
<td>Homozygous c.616G&gt;A, p.Glu206Lys</td>
<td>Pathogenic</td>
<td>High</td>
</tr>
</tbody>
</table>

COVERAGE SUMMARY
Sequencing of this individual's exome was performed and covered 99% of all positions at 20X coverage or higher, resulting in over 45,000 variants compared to a 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 sequencing is generated from extracted DNA that is fragmented, adapted, barcoded, and subjected to a solution phase hybridization with the Agilent SureSelect Human All Exon 50M 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 the Genome Analysis ToolKit (GATK). Variants are then filtered to identify: (1) variants with a minor allele frequency < 5% and (2) variants classified as disease causing mutations in public databases (1) and (3) predicted loss-of-function.
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

Number of families who agreed to meet with the study team: 565

82% decline GC session

Number of families who completed Pre-Enrollment Education session: 99

24% decline consent

Number of families who chose to enroll: 75

N=466 families declined participation

N=32 infants randomized to sequencing arm

Number of families who chose to withdraw: 8

N=31 infants randomized to control arm

12% of approached parents RANDOMIZED

Results disclosed: 17

N= 4 families not yet randomized

Results disclosed: 17
Sick Infant Cohort Recruitment Details

87% decline GC session

N=88 families declined participation
N=5 families no longer eligible to participate

50% decline consent

N=8 families declined participation

N=5 infants randomized to sequencing arm

N=5 infants randomized to control arm

Results disclosed: 2
Results disclosed: 3
Results disclosed: 3

5% of approached parents RANDOMIZED
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 become part of medical record)
  – insurability
  – anxiety about results
Participant Decline Form

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

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

Of Hispanic, Latino, or Spanish origin?: (Choose one)
- Yes
- No
- 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

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

Of Hispanic, Latino, or Spanish origin?: (Choose one)
- Yes
- No
- 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 FORDECLINE

- too much time
- don't want blood draw
- travel too far
- discharged
- overwhelmed
- disagree
- don't want control group assignment
- Not eligible
- not enough $
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)
- Robert Green, MD, MPH (Joint PI)
- Pankaj Agrawal, MD
- Ingrid Holm, MD, MPH
- Amy McGuire, JD, PhD
- Richard Parad, MD, MPH
- Peter Park, PhD
- Heidi Rehm, PhD
- Tim Yu, MD PhD

**Project Managers**
- Maggie Helm, MS, CGC
- Meghan Towne, MS, CGC
- Cassie Genetti, MS CGC

**Partners**
- Patrice Milos, Claritas Genomics
- Stacey Gabriel, Broad Institute

**Project Personnel**
- Ozge Ceyhan-Birsoy, PhD
- Kurt Christensen, MPH, PhD
- Dmitry Dukhovny, MD
- Joel Krier, MD
- Harvey Levy, MD
- David Margulies, MD
- David Miller, MD, PhD
- Stacey Pereira, PhD
- Annapurna Poduri, MD
- Amy Roberts, MD
- Jason Vassy, MD, MPH, SM
- Susan Waisbren, PhD
- Louise Wilkins-Haug, MD, PhD

**External Advisory Board**
- Bruce Korf, MD, PhD (Chair)
- Les Biesecker, MD
- Stephen Cederbaum, MD
- Alex Kemper, MD, MPH, MS
- Zak Kohane, MD, PhD
- Louis Kunkel, PhD
- Jim Lupski, MD, PhD
- Sharon Terry, MA
- Christopher Walsh, MD, PhD

**Consultants**
- George Church, PhD
- Lisa Diller, MD
- Steve Joffe, MD
- Peter Kraft, PhD
- Michelle Lewis, MD, JD
- Inderneel Sahai, MD