Heartland Genetics and Newborn Screening Collaborative Conference

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BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 8 SPECIALTIES 2013-14

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Objectives

- Background on genetic screening in children and newborns
- CMH experience with NGS
  - STAT-seq
- NSIGHT overview
  - Overall project components and group goals
  - Summary of four sites and their projects
- Development of NSIGHT project at CMH
  - Background
  - Project goals

The Hard Facts

- There are 7,482 genetic (inherited) diseases which:
  - affect 1 child in 30 in the United States
  - cause 1 in 6 children's hospital admissions
  - cause 1 in 5 infant deaths
- The locations in the genome of the mutations that cause 4,983 genetic diseases are known
  - Diagnosis often takes years
  - Getting a diagnosis is an emergency for a family
  - Delayed diagnosis delays treatment, allows a disease to worsen, hurts a family and costs money

Center for Pediatric Genomic Medicine (CPGM)

The Children's Mercy Hospitals and Clinics

- Established January, 2011

  Directed by Dr. Stephen Kingsmore

- Directors: Laboratory, Operations, Medical, Bioinformatics, Physician Scientist
- Research Coordinators
- Highly specialized IT support and lab personnel
- 21 physicians representing specialties throughout the hospital
- Essential collaborations with CMH Center for Bioethics and Clinical Genetics Program

CPGM Goals

Clinical

- Diagnose patients
- Target treatment
- Avoid unnecessary treatments/tests
- Educate patients and offer genetic counseling

Research

- Discover genes/phenotypes
- Develop drugs /treatments
- Innovate – test new methods and technologies
- Illuminate disease state pathophysiology

Pediatric Genetic Disease Diagnostic Complexity

- Early in disease progression = incomplete symptoms
- Early in development
  - Stereotyped adaptation to challenges to homeostasis
- Genocopies/genetic heterogeneity
  - Several genes cause same “disease”
- Poorly defined clinical heterogeneity
- Phenocopies
- Early diagnosis = optimal outcome, prevention of unplanned recurrence

Genetic Testing of Children

For children at risk of childhood-onset conditions, testing is permitted with parental consent, and when feasible, the child's assent. Testing for adult-onset conditions is discouraged, but exceptions can be made with appropriate counseling and the consent of the parent and child. ~AAP

Special considerations for genetic testing in pediatrics

- "Incidental" findings
  - What are they?
  - Actionability
- Insurability
- Employment status
- Minor status and the right to choose
- Costs to the medical system

Secondary Findings

- Also called incidental or unanticipated findings
- Highly likely, if not inevitable, whenever WGS/WES is performed
- Examples include:
  - finding of a previously unsuspected high risk of future disease
  - discovery of a disorder in an asymptomatic individual
  - detection of carrier status

Genetic testing in children

- Mandate to avoid violating a child's *right to an open future*
  - The problem of secondary findings
- Impacts:
  - Test design
  - Consent
  - Communication of results
- CPGM current research pipeline not designed for return of these findings and analysis focused to phenotypically related genes

STAT-Seq
Rapid whole exome analysis

RESEARCH ARTICLE

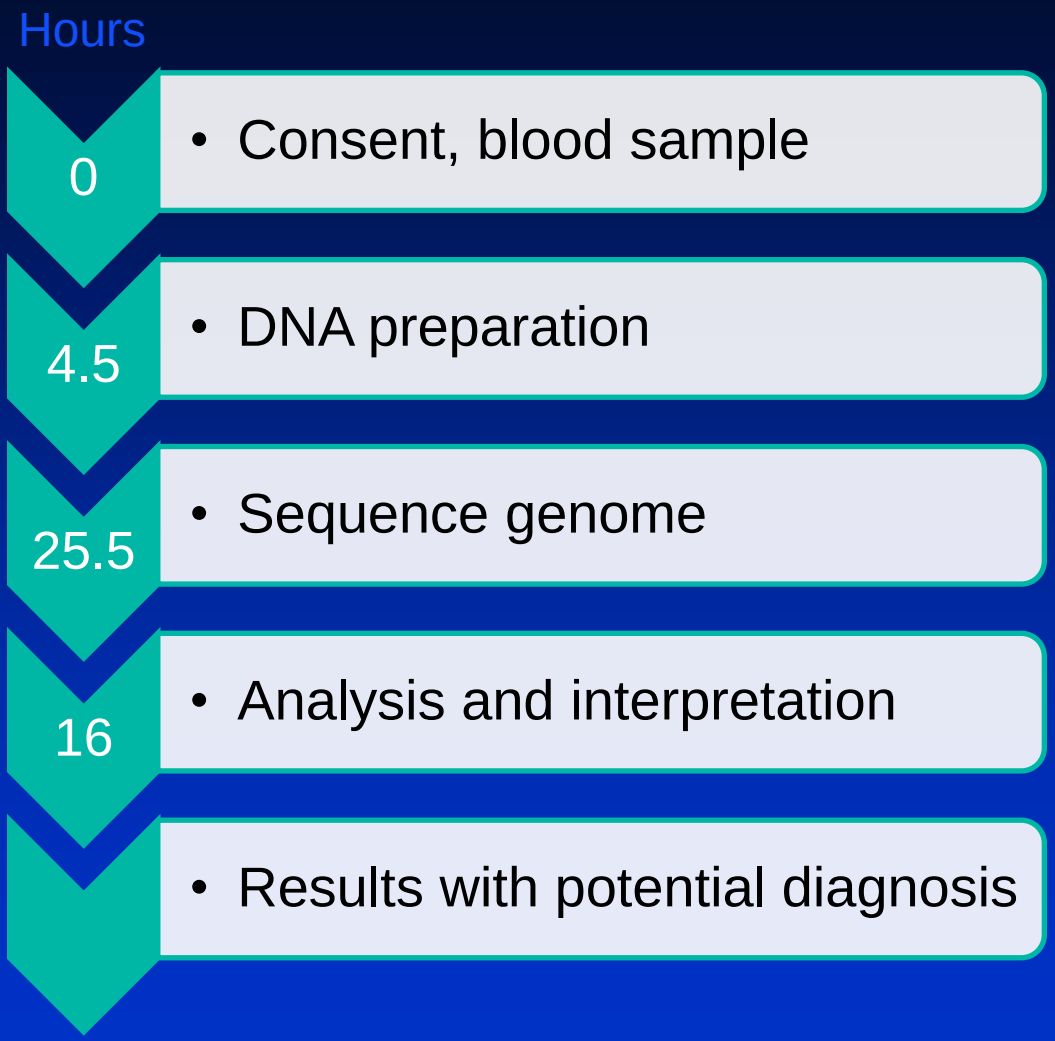
DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5*] Neil Andrew Miller,[1,2,4*] Sarah Elizabeth Soden,[1,2,4*] Darrell Lee Dinwiddie,[1,2,3,4,5*] Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4] Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5†]

- 50 hour whole genome sequencing plus analysis and interpretation
- Collaboration with Illumina, Inc. research lab, Essex, U.K.
- Available to Level IV CMH NICU patients under research protocol

Current Rapid WGS: "STAT-seq"



Statseq Experience

- 36 affected individuals, 32 families
- 13 families with confirmed diagnoses (Diagnosis rate of 40%)
- 3 families with partial diagnoses (ie: only part of the phenotype explained)
- 7 families with candidate genes being investigated further
- 10 families with no diagnosis or candidate gene
- 5 diagnoses changed clinical management

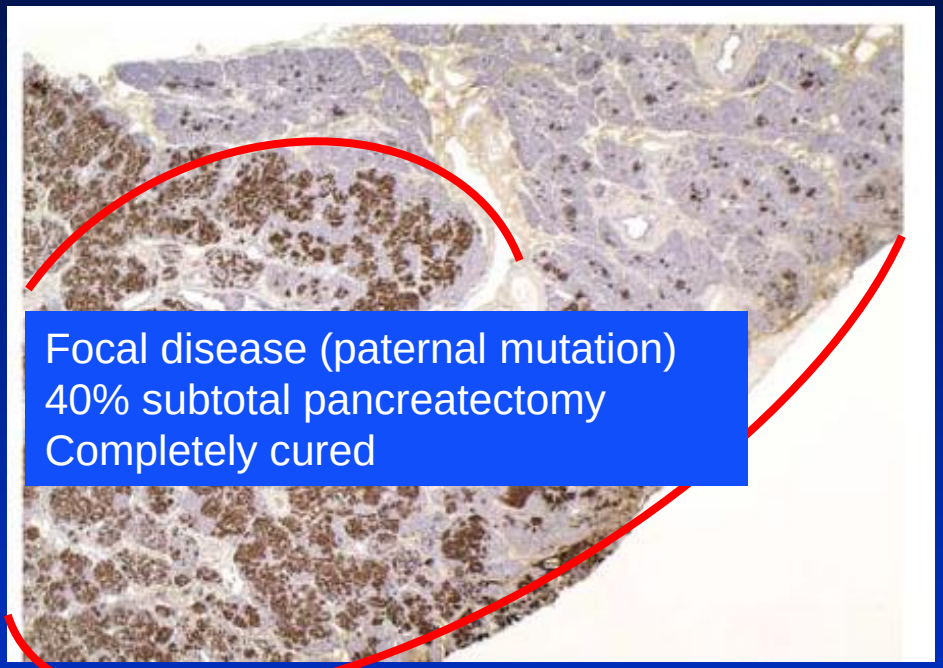
Case: CMH569

- History of hypoglycemia since birth: glucose level 18
- Transferred to CMH at 4 weeks:
  - Glucose of 29; repeat, 18
  - Fed for 30 min: glucose 19, insulin 22
- 4th child born to 27 year old parents; no one with similar concerns
- Normal MO NBS
- Dangerously unstable glucose levels despite aggressive management: diet change, max diazoxide; very high glucose infusion with still breakthrough hypoglycmia.
- Considering total pancreatectomy.

Results

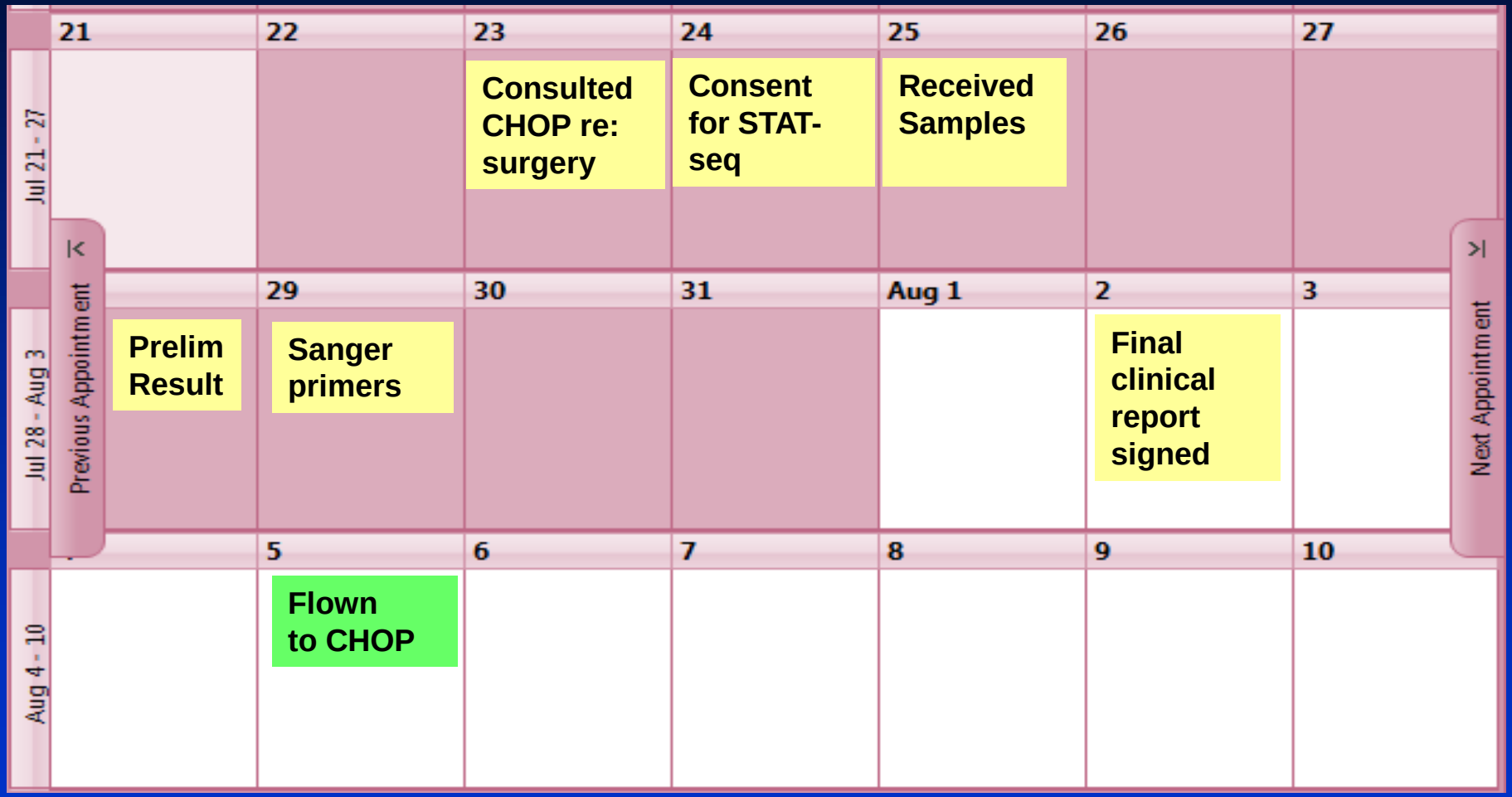
- Heterozygous known pathogenic *ABCC8* variant, p.Arg1215Trp inherited from dad; no second variant.
- *ABCC8*-related congenital hyperinsulinism is an autosomal recessive disease
- Except when it's not!
  - 2nd "hit": somatic event leads to loss of maternal allele in subset of βcells.
  - Paternal inheritance is highly suspicious for focal disease.

Drastically different treatment and outcome:



Sohnet al. 2006

Timeline



Context of NSIGHT Study

- **Can genomic sequencing of newborns provide useful medical information beyond current newborn screening?**

NSIGHT Research Questions

Must address one or more of the following:

A.

For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results?

B.

What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?

C.

What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

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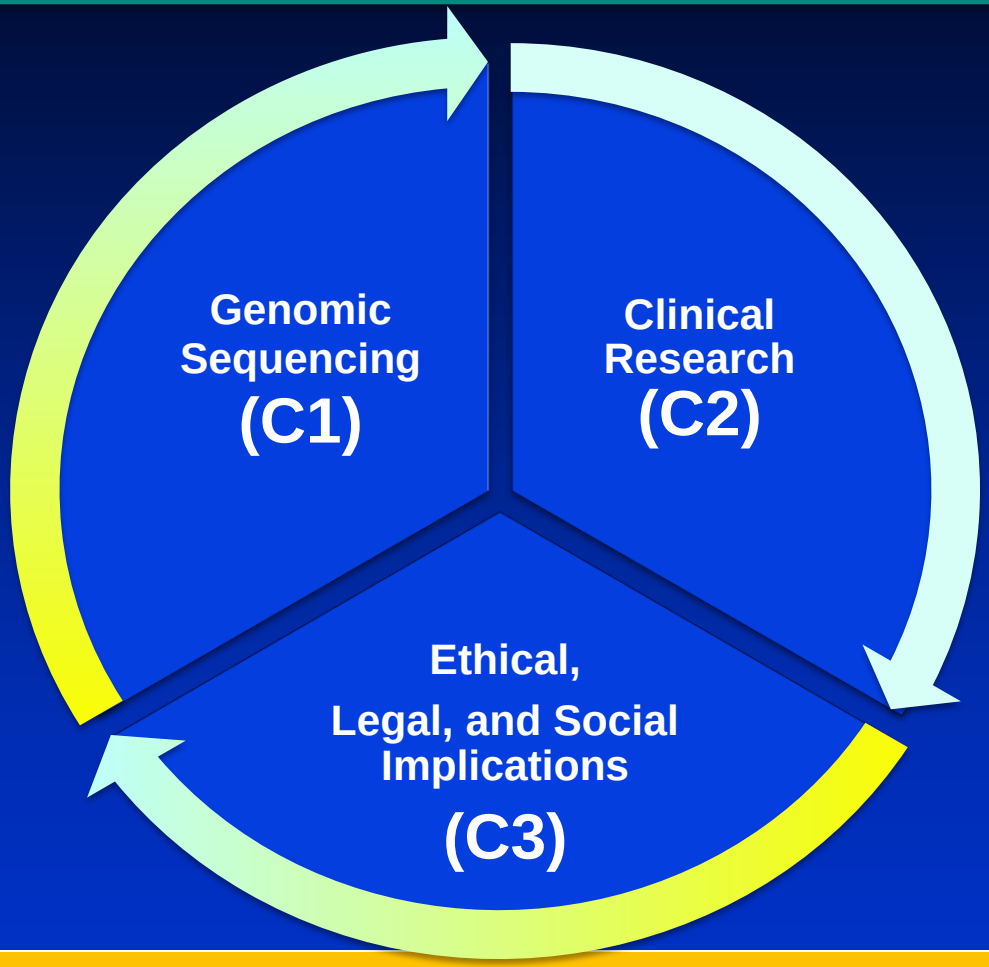
Required 3 Components



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Components

- **Component 1: Data Acquisition and Analysis**
- **Component 2: Clinical research to advance understanding of specific disorders identifiable in the newborn period using DNA technology**
- **Component 3: Ethical, legal and social implications of genomic sequencing in newborns**

Important themes of the projects as a whole

- Defining the actionable set of diseases identifiable via newborn sequencing
- Defining the “incidentalome” for a newborn
- Best practices for return of results for this population
- Exploring parental attitudes in regards to return of results
- Exploring clinician and parental attitudes in regards to newborn genomic testing

Members of the NSIGHT Program

- **Robert Green, M.D., and Alan Beggs, Ph.D.**
  Brigham and Women's Hospital, Boston
  NICU and healthy newborns, 240 exomes, data sharing, return of results
- **Stephen Kingsmore, M.D.**
  Children's Mercy Hospital, Kansas City, Mo.
  NICU, 1000 genomes, data sharing optional, return of results
- **Robert Nussbaum, M.D.**
  University of California, San Francisco
  NBS, 1620 exomes, limited data sharing, return of results
- **Cynthia Powell, M.D., M.S., and Jonathan Berg, M.D., Ph.D.**
  University of North Carolina at Chapel Hill
  NBS, 400 exomes, data sharing optional, return of result options

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CMH Overview
Component 1: Technology Study Aims

- Efforts performed in the Genome Center
- Improve diagnostic sensitivity
- Improve time to diagnosis

CMH Overview
Component 2: Clinical Study Aims

- Examine risks and benefits of rapid genomic sequencing in the NICU population.
- Does STAT-Seq change the clinical care of newborns in the NICU?
  - 28-day definitive diagnostic yield of Stat-Seq vs. standard testing
  - Time to definitive diagnosis of WGS vs. conventional tests
  - Physician perception of change in clinical management in WGS-Dx vs. standard tests
  - Surrogate measures of objective change in clinical management in WGS-Dx vs. standard tests

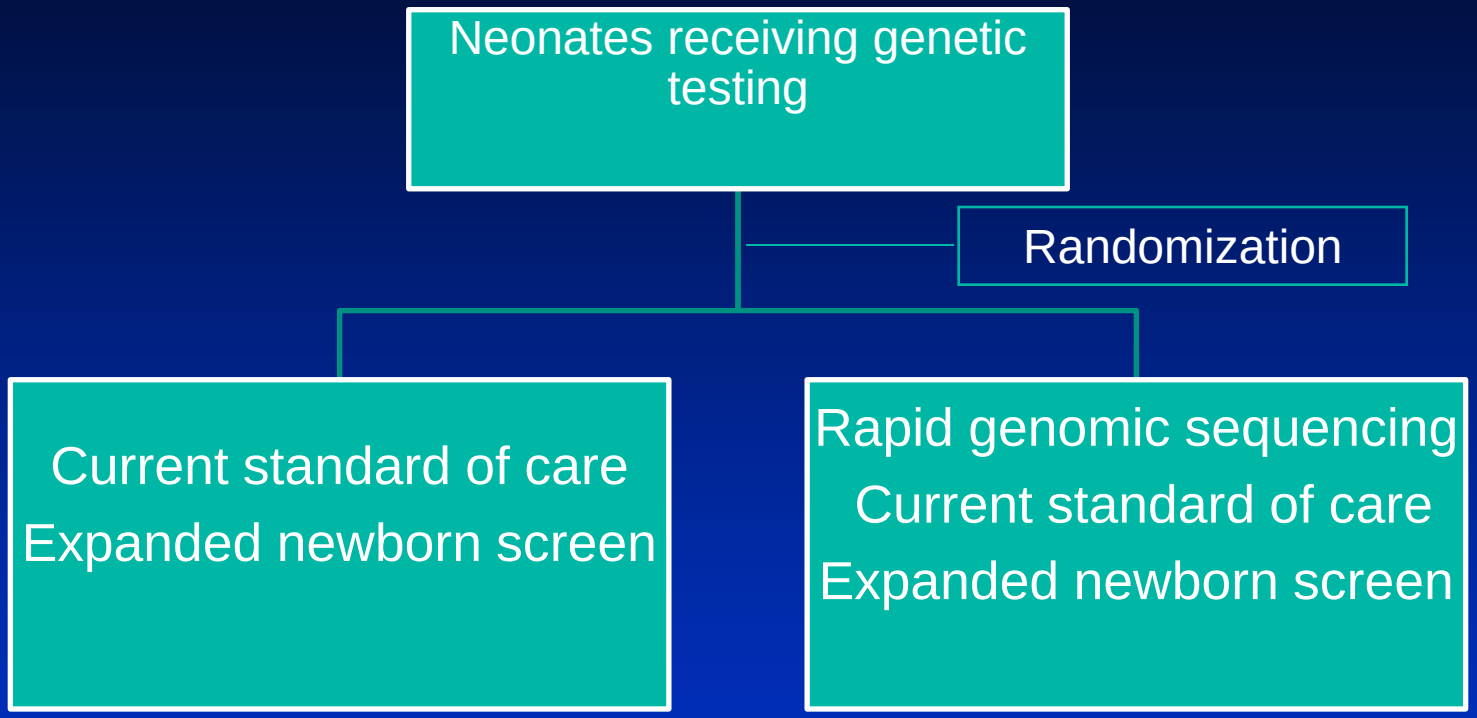
CMH Overview
Component 3: Social and Ethical Study Aims

- Describe:
  - clinicians' and parents' perceptions of value of STAT-seq in ill neonates
  - the quality of communication of STAT-seq results
  - expectations for STAT-seq in the context of clinical outcome data collected under Component 2
- Is STAT-Seq viewed as beneficial, harmful, or immaterial
  - What factors influence these perceptions
- How do these perceptions change pretest to post-test and at 12 months follow up
- Investigate the ethical and legal issues in WGS for screening in the NICU

NSIGHT Study: CMH Overview

- 5 year initially blinded randomized control trial of acutely ill neonates
- Enrollment of ~1000 babies
  - 500 rapid whole genome testing+EBS+SOC
  - 500 expanded newborn screening+ SOC
- Includes psychosocial assessment and 1 year follow up

Initial Study Design



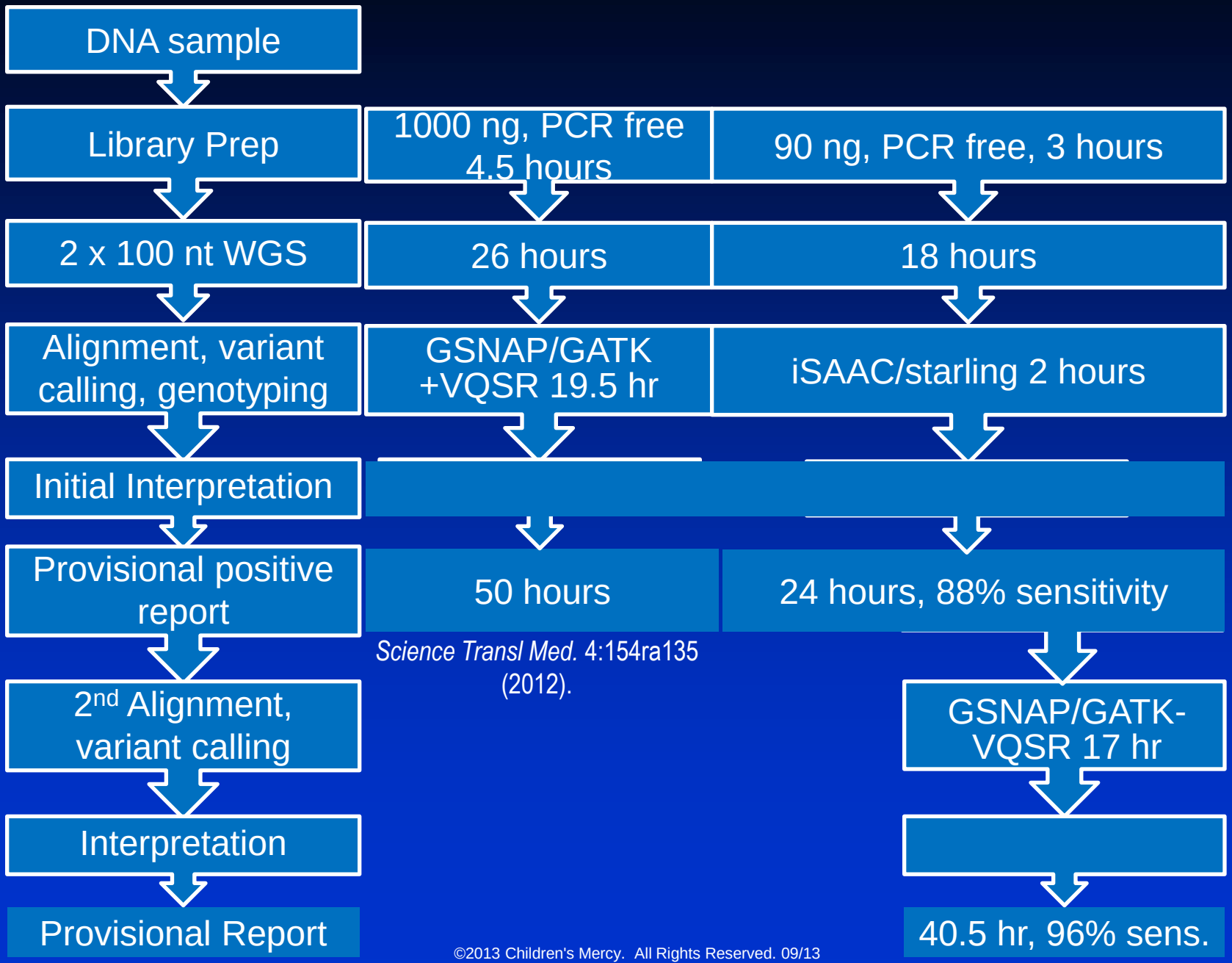
In rare instances where the clinical team/genome center team feels that randomization to the standard of care group would severely compromise care, crossover to the STAT-Seq group will be allowed and data analyzed with an Intention to Treat protocol.

Initial Study Visit Plan

Consent/Initial Visit	Pretest Questionnaires	Return of Results to Clinician	Return of Results to Family	72 hours Post test results	12 months post results
Genome Consult/Consent Blinded randomization Blood draw	Parent questionnaires	Phone conference or care conference with neonatal attending to discuss results/treatment decisions	Patient care team to return findings to families. Genome care team present if requested.	Parent Questionnaires	Patient questionnaires and medical follow up
Refusal Assessment	Clinician questionnaires			Clinician questionnaires	

Unblinding
Day 10 post enrollment

Current Methods Development has led to a ~24 hour preliminary result



Science Transl Med. 4:154ra135 (2012).

Return of results

ACMG Cat1-3

Category	Description	Criteria
1	Previously reported, recognized cause of the disorder	HGMD variant type of 'Disease Mutant' dbSNP Snp Clinical Significance of 'pathogenic'
2	Novel, of a type expected to cause the disorder	loss of initiation premature stop codon disruption of stop codon whole transcript deletion frameshifting in/del disruption of splicing through deletion causing CDS/intron fusion overlap with splice donor or acceptor sites.
3	Novel, may or may not be causative	non-synonymous substitution in-frame in/del disruption of polypyrimidine tract overlap with 5' exonic, 5 ' flank or 3' exonic splice contexts
4	Novel, probably not causative of disease	all variants not in categories 1 – 3 synonymous AA changes overlap with 5' intronic or 3' flank splice contexts pyrimidine substitutions in polypyrimidine tract, other intronic variants dbSNP GMAF of greater than 0.02
5	Known neutral variant	not used
6	Not known or expected to be causative of disease but found to be associated with a clinical presentation	not used

Return of results

- More evidence/discussion required when considering category 3 variants
- Examining our current reporting practice on incidental findings (working with NSIGHT groups)

Genome Care Team

- Goals:
  - Function in coordination with current clinical care team
  - Focus on genomic diagnosis and explore possible treatments related to said diagnosis
  - Provide thorough documentation and set of recommendations to clinical care team
  - Provide consultation to families with clinical care team if requested
  - Provide educational conferences for clinicians on regular basis

Breakdown of Genome Care Team

- Genome Center Personnel:
  - Geneticist
  - Genomic Neonatologist
  - Primary Genome Analyst
  - Pharm D/Personal Therapeutics if indicated
  - Genetic counselor
- Clinical Care Team:
  - Neonatologist of record
  - Subspecialists as indicated by patient condition
  - Medical Genetics

Timeline

- IRB submission: April 2014
- Begin enrolling June 2014
- Enroll 200 patients per year (~1/4 of admissions to the NICU)
- Study design may change from Year to year depending on what is learned
- Comments/Questions
- Contact information:
  - Laurel Willig, MD, MS lkwillig@cmh.edu

The End

- Questions?