South Carolina Newborn Screening

Emily Black, MD
Biochemical Geneticist
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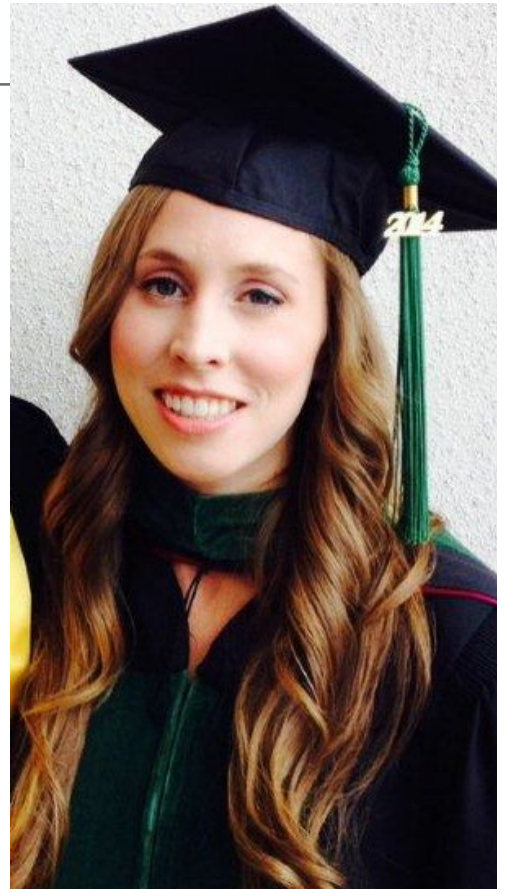
Greenwood Genetic Center

Agenda

- The Basics of Newborn Screening
- Current Diseases and Upcoming Additions
- Processes for Follow Up and Areas for Improvement
- Future Directions for Newborn Screening

Personal Background

- Medical School: University of South Carolina SOM Columbia
- Pediatrics Residency: University of Virginia
- Genetics Residency: Emory → Biochemical Fellowship: Emory
- Attending at Emory: 2 years → Greenwood Genetic Center (GGC) July of 2022
- General genetics and metabolic clinics
- 4 clinical biochemical geneticists in the state



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Basics of Newborn Screening

Past to Present

Basics of Newborn Screening

- **State-run healthcare initiative**
    - Parental education
    - Infant screening
    - Appropriate follow-up
    - Diagnostic testing
    - Disease management
- **Goal**: Identify clinically occult but potentially serious disorders that require expedient intervention
- **4 million infants** screened annually in the US → approximately **3400** receiving diagnosis and early intervention

- **Recommended Uniform Screening Panel (RUSP)**
    - Updated by Health & Human Services with input from the ~~Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)~~
- State to state variability

SC Advisory Committee

In South Carolina, we meet quarterly and are comprised of Department of Public Health (DPH) members, GGC and MUSC physicians and advanced practice providers and other specialists from across the state

Newborn Screening Advisory Committee Structure

NBS Program	Existing Advisory Committee	Advisory Committee Voluntary	Meeting Frequency	Committee Structure
South Carolina	Yes	Mandatory	As needed	Specialty care providers, primary care providers, program leadership and staff convened as needed by specialty and required by SC law.
South Dakota	Yes	Voluntary	Ad hoc	Ad hoc meetings through DOH
Tennessee	Yes	Voluntary	Every quarter	Members include geneticists, hematologists, pulmonologists, immunologists, neonatologists, and lawyer. The committee is chaired by the Assistant Commissioner of Family Health and Wellness and a Division Director from the Division of Laboratory Services.
Texas	Yes	Mandatory	Required 3x per year; at least one time in person	Data not provided
US Virgin Islands	No	Data not provided	Data not provided	Data not provided
Utah	Yes	Mandatory	Every quarter	In rules to have a committee; chair must have MD or PhD in genetic/metabolic or other relevant field; minimum of 7 people; Utah Hospital Associoation representative; community pediatrician; o family advocate; others as recommended

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Origins and Timeline

1934

Dr. Ivar Asbjørn Følling

PKU dx

PKU diet

1953

Dr. Horst Bickel

1962

Dr. Robert Guthrie

PKU test

More Dx

1970s – 1980s

Congenital hypothyroidism

Congenital adrenal hyperplasia

Hemoglobinopathies

Galactosemia

2000s

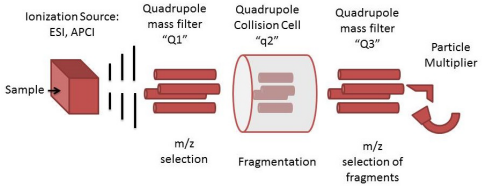
Tandem MS

2010

Severe combined immunodeficiency, Critical congenital heart defects

Expanded

58 conditions on SC NBS currently



Criteria for Screening

- The Wilson and Jungner criteria, published in 1968 by the World Health Organization, provide a **framework for evaluating potential population-based screening programs**

- Refined in 2008 in light of genomic testing advances with focus on rare disease

Important considerations for population-based screening programs synthesized from 40 years of use of the original Wilson and Jungner criteria

- The screening program should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening program effectiveness.
- The program should integrate education, testing, clinical services and program management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The program should ensure informed choice, confidentiality and respect for autonomy.
- The program should promote equity and access to screening for the entire target population.
- Program evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Source: Andermann et al. (2008).

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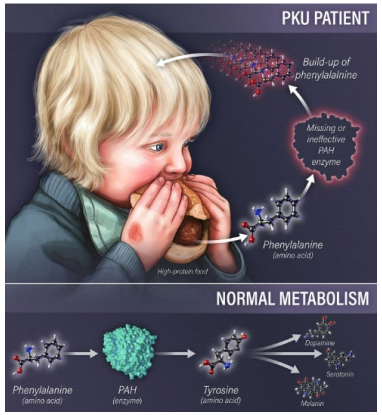
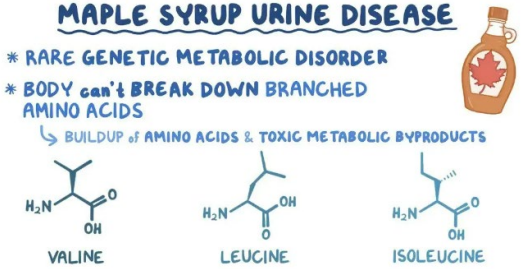
Current List of Conditions and Soon to be Added

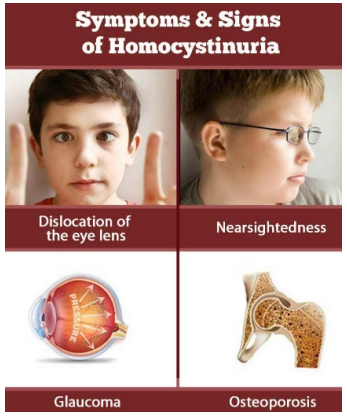
Where we are and where we are going...

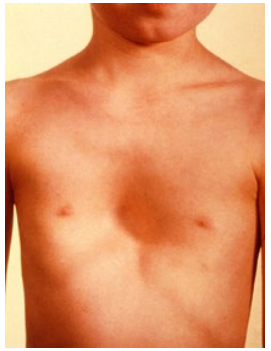
Amino Acid Metabolism Disorders

- **Elevated PHE and elevated PHE/TYR**
  - Classic PKU, Hyperphenylalaninemia, Defect of biopterin cofactor synthesis/regeneration
- **Elevated VAL and/or Elevated LEU+ILE**
  - Maple Syrup Urine Disease
- **Elevated MET**
  - Homocystinuria, Hypermethioninemia
- **Elevated CIT**
  - Citrullinemia type I and II, Argininosuccinic aciduria
- **Elevated TYR +/- SUAC**
  - Tyrosinemia type I, II or III









Carbohydrate Metabolism Disorders

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- **Low GALT, elevated GAO**
  - Classic Galactosemia, Duarte Variant, Carrier
- **Normal GALT, elevated GAO**
  - Galactokinase deficiency, Galactose epimerase deficiency, Galactose mutatrotase deficiency

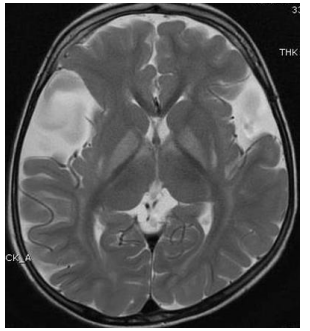
Organic Acidemias

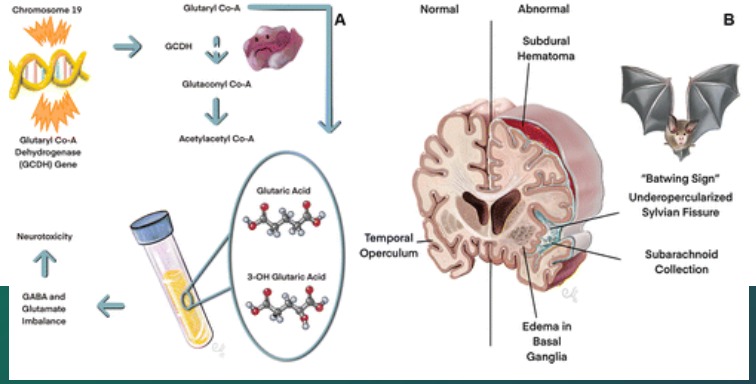
- **Elevated C3**
  - Propionic Acidemia, Methylmalonic Acidemia, Intracellular Cobalamin metabolism disorder, B12 deficiency
- **Elevated C3-DC**
  - Malonic acidemia
- **Elevated C5**
  - Isovaleric acidemia, 2-methylbutyryl CoA dehydrogenase deficiency

Elevated C5-OH

- 3-methylcrotonyl coA carboxylase deficiency, B-ketothiolase deficiency, 3-methyl-3-OH-glutaryl CoA lyase deficiency, 3-methyl-glutaconyl coA hydratase deficiency, 2-methyl-3-OH butyric aciduria

- **Elevated C5-DC**
  - Glutaric Aciduria type I





Fatty Acid Metabolism Disorders

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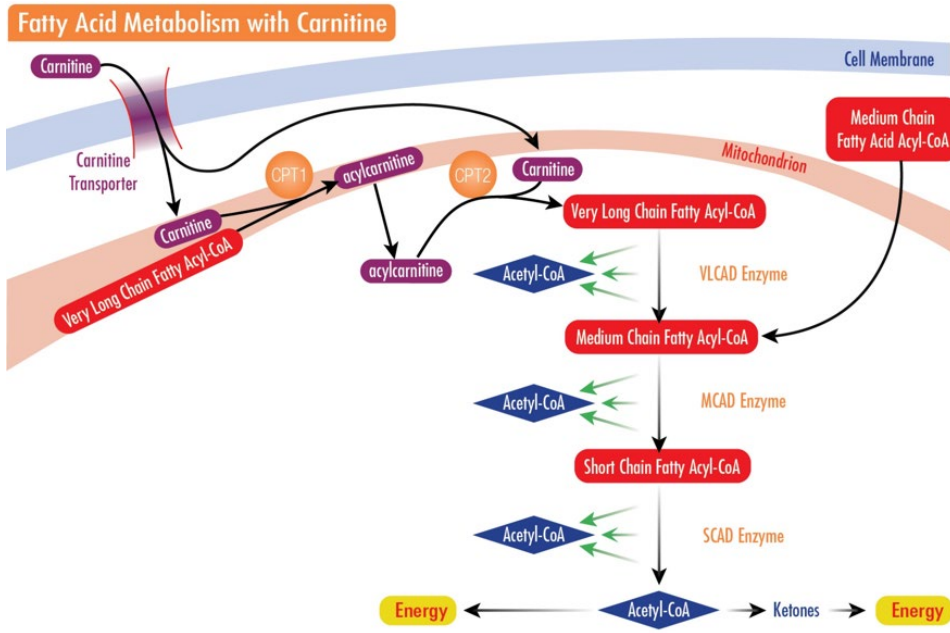
- **Elevated C8**
  - Medium Chain Acyl CoA Dehydrogenase deficiency (MCADD), Medium chain ketoacyl coA Thiolase deficiency
- **Elevated C10:2**
  - Dienoyl coA Reductase Deficiency
- **Elevated C16 OH**
  - Long Chain 3-OH coA dehydrogenase deficiency (LCHADD), Trifunctional Protein Deficiency

Elevated C14:1

- Very long Chain Acyl coA Dehydrogenase Deficiency (VLCADD)

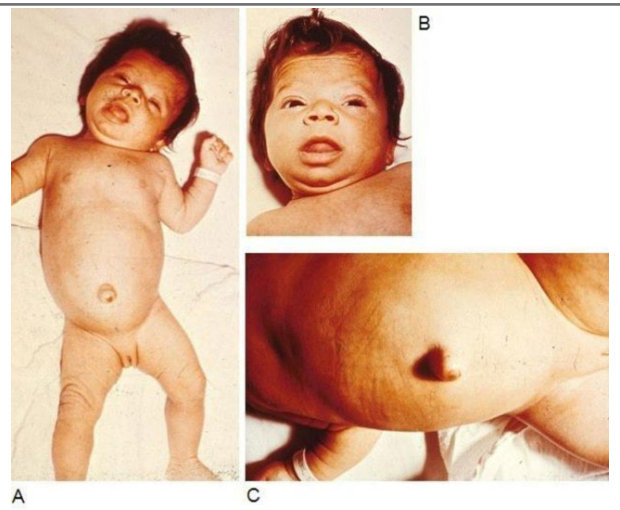
- **Elevated C4 and C5**
  - Multiple Acyl coA Dehydrogenase Deficiency (GA2)
- **Low Free Carnitine**
  - Carnitine Uptake/Transport Deficiency
- **Elevated C0; C0/C16+C18**
  - Carnitine Palmitoyl Transferase I deficiency (CPT I)
- **Elevated C16 and C18:1**
  - Carnitine Palmitoyl Transferase II Deficiency, Carnitine/Acylcarnitine Translocase Deficiency (CPT II/CACT)

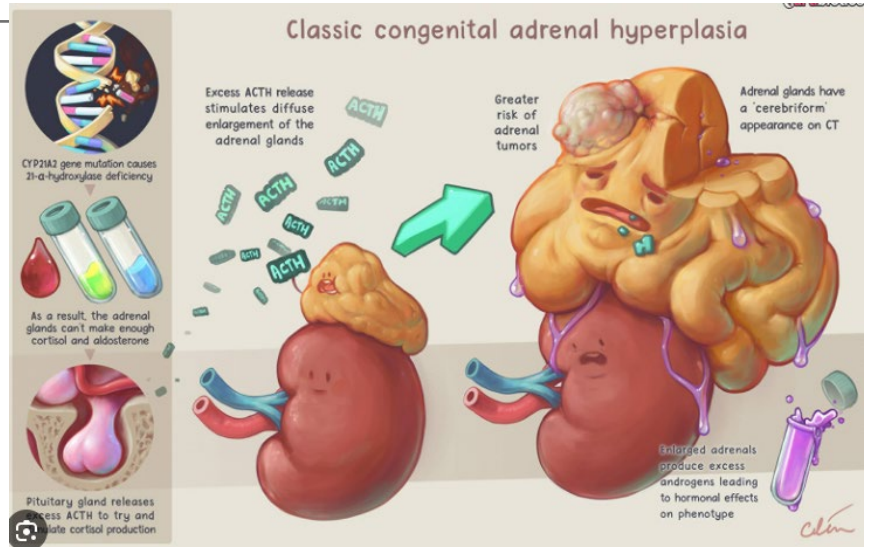


Hypoketotic Hypoglycemia

Hormone and Enzyme Disorders

- **Elevated TSH**
  - Congenital Hypothyroidism
- **Elevated 17-OH Progesterone**
  - Congenital Adrenal Hyperplasia
- **Low Biotinidase activity**
  - Biotinidase deficiency





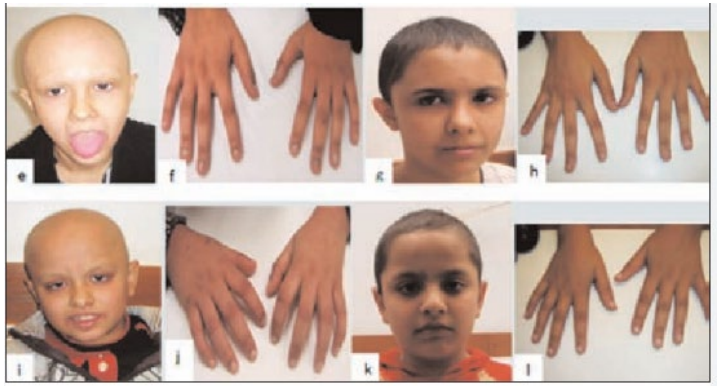
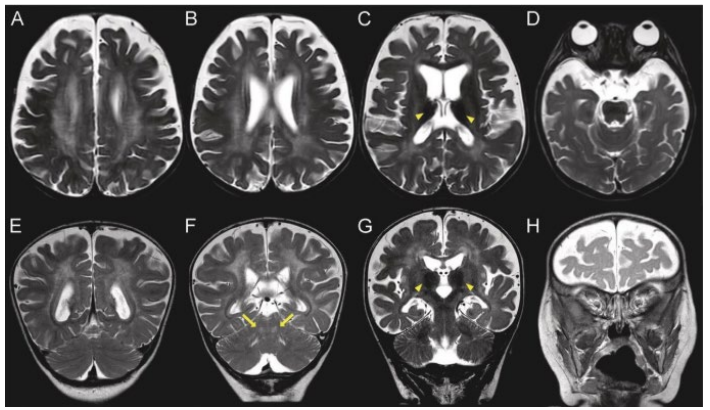
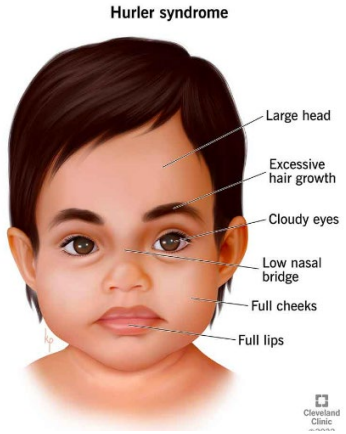


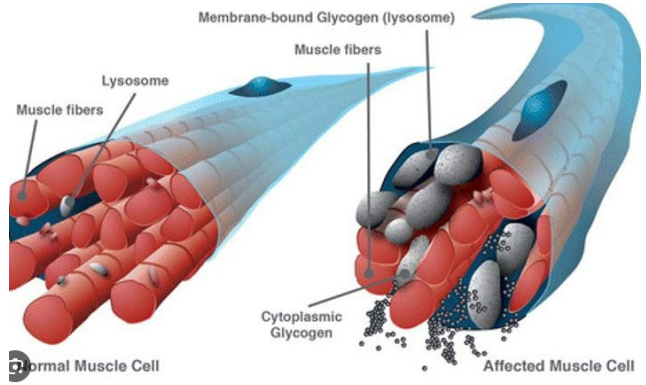
Figure 1: (a-d) Patient 1. **(e-h)** Patient 3. **(i-l)** Paitent 4. **(a,e,i)** Alopecia, perioral and periorbital rashes before treatment. **(b,f,j)** Peri-ungual rashes before treatment. **(c,g,k)** Resolved perioral, periorbital rashes and growth of scalp hair after treatement. **(d,h,l)** Resolved periungual rashes after treatment

Lysosomal Storage Disease

- **Galactocerebrosidase enzyme (GALC)**
  - Krabbe disease
- **Acid alpha glucosidase (GAA)**
  - Pompe disease
- **IDUA (alpha-L-Iduronidase)**
  - MPS I

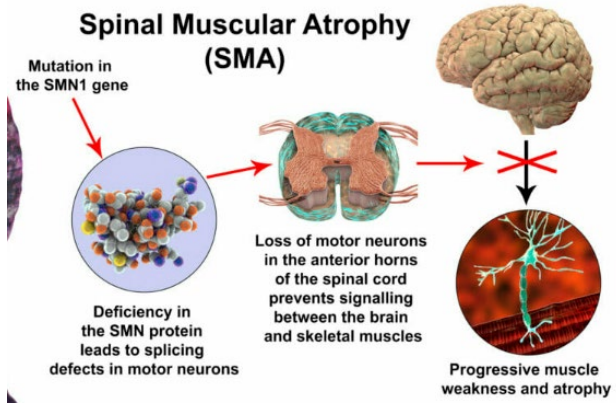


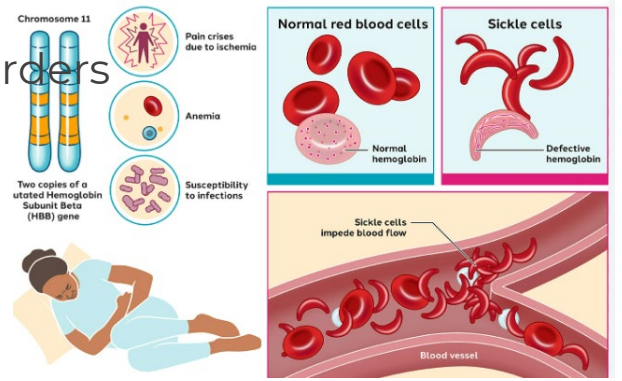


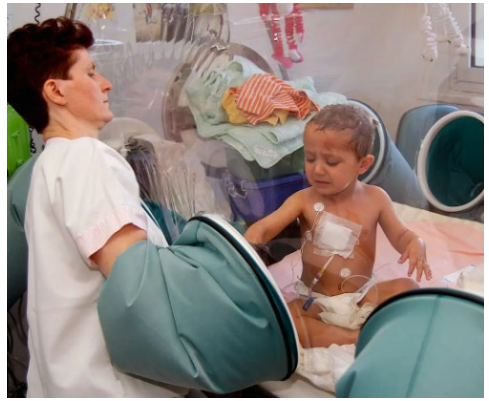


Other Genetic Disorders

- **Elevated Immunoreactive Trypsinogen (IRT)**
  - Cystic Fibrosis
- **Abnormal Hemoglobin**
  - Sickle Cell Disease, Sickle C disease, Sickle B Thalassemia, Variant Hemoglobinopathy Disorders and Traits (including Sickle Cell Trait)
- **Decreased (copies) of TRECs**
  - Severe Combined Immunodeficiency and Related Disorders
- **SMN1 absent**
  - Spinal Muscle Atrophy







South Carolina: Conditions to be Added Soon

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- **Expected in 2025:**
  - **MPS II**
    - Hunter syndrome; X-linked
  - **Fabry Disease**
    - X-linked Lysosomal Storage Disease

Will we get to a point of Whole Genome Sequencing (WGS)??

- **Later… ?**
  - MPS III (Sanfilippo syndrome)
  - Metachromatic Leukodystrophy
  - GAMT deficiency
  - Duchenne Muscular Dystrophy

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Processes for Follow Up and Areas for Improvement

State of the Union for SC

SC LAW Re: Newbo Screening

South Carolina Code of Laws Unannotated

Title 44 - Health

CHAPTER 37

Care of the Newly Born

SECTION 44-37-30. Neonatal testing of children; storage and availability of blood samples for future tests; confidentiality; religious exemption; violation and penalties; Newborn Screening Advisory Committee.

(A) A child born in this State, except a child born of a parent who objects on religious grounds and indicates this objection before testing on a form promulgated in regulation by the Department of Health and Environmental Control, shall have neonatal testing to detect inborn metabolic errors and hemoglobinopathies.

(B)(1) Information obtained as a result of the tests conducted pursuant to this section is confidential and may be released only to a parent or legal guardian of the child, the child's physician, and the child when eighteen years of age or older when requested on a form promulgated in regulation by the department.

(2) If the results of the neonatal testing are abnormal, the department may recommend additional testing and, in addition to the notification requirements established in Section 44-37-30(B)(1), notify one or more of the following to ensure timely provision of follow-up services:

(a) the physician or health care provider attending the child's birth or his designee;

(b) the physician or health care provider responsible for newborn care in the hospital; or

(c) the physician or health care provider identified for follow-up care after the newborn's discharge from the hospital.

(3) If the results of the neonatal testing are abnormal, time-sensitive, or time-critical, the department may, in addition to notification requirements established in Section 44-37-30(B)(1) and (2), notify and provide information about the abnormal, time-sensitive, or time-critical screening results to a qualified pediatric specialist in accordance with guidelines established by the department's Newborn Screening Advisory Committee for the timely provision of the follow-up services.

The Importance of Timeliness

Timely collection, shipping, and reporting of newborn screening results is necessary to achieve early identification of affected newborns. Delays in the process can hinder timely reporting and treatment, which may lead to poor outcomes.

Baby Born *(Hour 0)*

Specimen Collected *(24–48 hours of life)*

Specimen Drying *(3-4 hours needed to dry)*

Courier Pickup: *(Sunday-Friday after 9pm)*

Specimen Received by PHL *(within 24 hours after collection or same day)*

Which Packaging Is Acceptable?

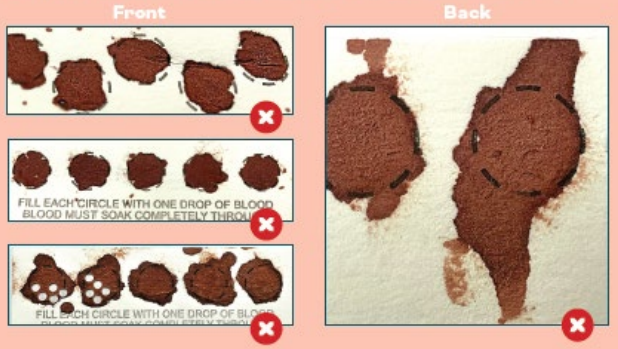
ACCEPTABLE
Paper and or cardboard envelopes and shipping boxes

UNACCEPTABLE
Plastic bags or polymer bags (including bubble-wrap)

SOUTH CAROLINA DEPARTMENT OF PUBLIC HEALTH

What does a Scratched or Abraded specimen look like?

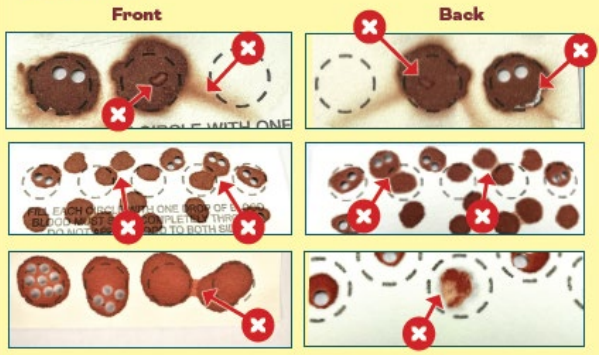
Rough, rippled blood drops and/or folded, torn, or bent filter paper.



What causes Contamination?

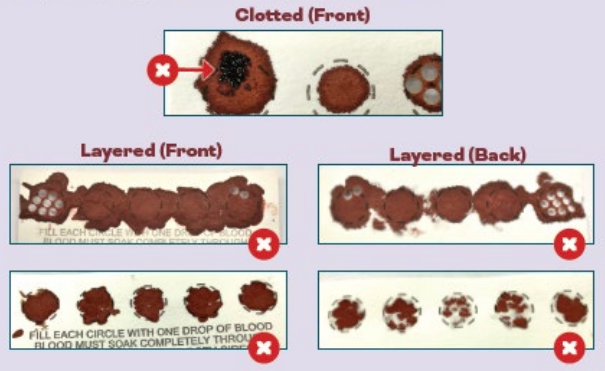
- Milking the heel
- Specimen touches a liquid substance
- Alcohol has not dried

What does a Contaminated specimen look like?



What does a Layered or Clotted specimen look like?

Multiple drops applied to the same pre-printed circle.



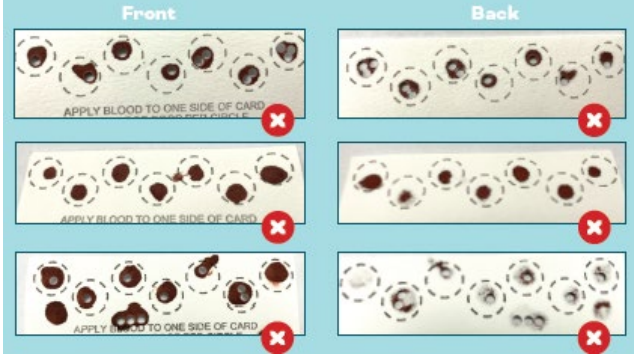
Examples of Satisfactory Specimens

What causes QNS?

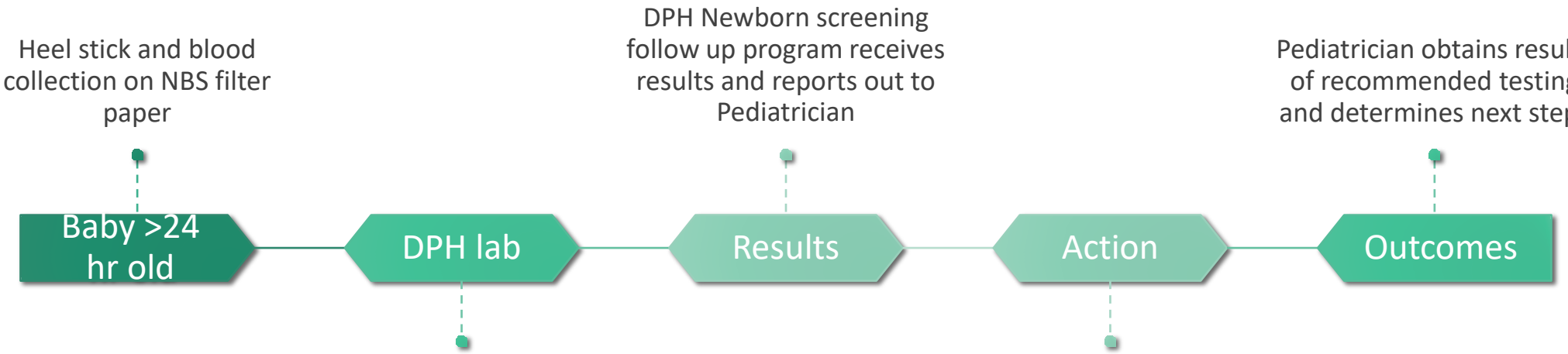
- Prematurely applying blood drop before a large drop has formed.
- Drop is less than 75% of pre-printed circle.
- Blood did not absorb fully or soak through the back.

What does a QNS specimen look like?

This is **NOT** enough blood to complete the testing.



SC Newborn Screening Process



Structures for clinical follow-up: Newborn screening

R. Rodney Howell · Gilian Engelson ·

J Inherit Metab Dis (2007) 30:600–605
DOI 10.1007/s10545-007-0674-z

NEWBORN SCREENING

The excellent recent review by James and Levy explored follow-up in detail, and stated clearly that the biggest challenge in newborn screening is clinical follow-up (James and Levy 2006) and that the majority of missed cases in newborn screening have been the result of lack of follow-up or inappropriate follow-up testing.

(Hoff et al 2006). The importance of a follow-up system was noted by the 1999 American Academy of Pediatrics newborn screening task force, which endorsed the advice of the United Kingdom's David Hall who stated that 'if it is important enough to screen for, it is important enough to follow-up' (Academy of Pediatrics 2000). The follow-up component of our newborn screening systems within the United States has, however, lagged behind the actual screening component in both organization and support.

and in general is satisfactorily handled. It is widely felt that short-term follow-up should remain under the purview of each state's Department of Health in the United States where newborn screening is clearly considered a public health programme. One of the

In short-term follow-up, it is also common to need consultation and expertise of a medical specialist to develop a confirmatory diagnosis. Since most state programmes lack this expertise and lack funding to provide it, this responsibility often falls on the academic and other specialty centres (Hoff and Hoyt 2006) who commonly have no funding to provide these services. In addition, it has been noted that there is

Structures for clinical follow-up: Newborn screening

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NEWBORN SCREENING

While the ACT sheets provide some standard guidelines, short-term follow-up could still benefit if a national bioinformatics system were in place; such a bioinformatics system would track newborn infants from the time a sample is taken through the time the newborn infant is in a medical home to the long-term monitoring of these individuals, thus ensuring continuity in care and providing an added measure of security so that there is no loss to follow-up of these fragile newborns.

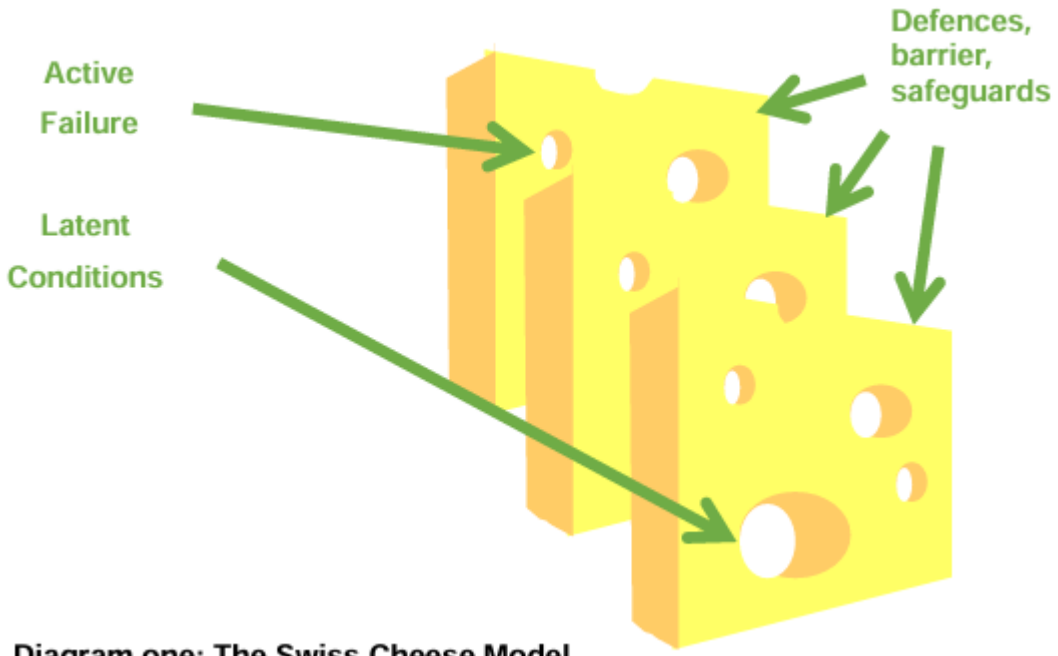

Diagram one: The Swiss Cheese Model

SC Newborn Screening Process

- Ultimately in SC, the responsibility for newborn screen results and outcomes **falls on the pediatrician**
  - **You cannot rely on DPH NBS Follow up program to closely track abnormal results in South Carolina**
- DPH reports out the abnormal screens, but **does not currently follow all screens to CLOSE**
  - **Your office/unit needs to have a system in place for timely NBS follow up**
- If a patient has abnormal screening and they are referred to a metabolic specialist, then we (biochemical geneticists) are able to be **involved once they are established and take over the case**
- However, every abnormal screen **does not NEED an evaluation by a specialist NOR do we have the capacity** to see every abnormal newborn screen in clinic

Why this is of Concern:

- **Liability falls on Pediatrician** ultimately for follow up and outcome of an abnormal screen
  - Pediatric offices:
    - Staff members lacking experience with conditions on NBS
    - Overbooked physicians relying on support staff to take calls, upload results, etc
    - High turn over of support staff with risk for errors in office outlined work flows

- **Deficiency in NBS tracking and follow up**
  - DPH NBS Follow up program also working with high turnover and understaffing; Not a clinical team
  - Currently lacking in software program that supports detailed tracking of cases to close (plans for working on this underway)

- **Significant delays and missed follow up cases** do occur in South Carolina due to **unresolved system issues**

- Lack of single EMR use by all offices and hospitals makes tracking and follow up much more difficult

Additional Concerns

- **Deficiency of Clinical Biochemical Geneticists**
  - South Carolina currently has 4 biochemical geneticists to cover the entire state
  - Positions for Genetics and Biochemical fellowships go unfilled every year
  - More conditions added to screening, increased calls and consults for biochemical geneticists lacking the resources and support needed
  - Necessary for pediatricians to initiate work up with send out labs

› Mol Genet Metab. 2021 Dec;134(4):285-286. doi: 10.1016/j.ymgme.2021.11.007. Epub 2021 Nov 16.

Metabolic providers in crisis – Burning out on the road to burnout?

Georgianne L Arnold [1], Shibani Kanungo [2], Lynn Bush [3];
Wellness Committee of the Society for Inherited Metabolic Disorders

Goals to Improve?

- **Clinical Nurse Team** embedded in DPH NBS Follow up Program
  - Would allow for clinical recommendations and use of a protocol to triage next steps for follow up and/or confirmatory testing
  - **This may require legislative change**

- Software Program that is built for **tracking and follow up of abnormal screens** that reduces human error
  - **Will require more staff members** to be able to contact provider offices and obtain updates and outcomes of abnormal screens

- Conditions continue to be added despite the weak areas in follow up…

Case Examples

- The following slides are some patient cases that highlight the challenges of Newborn Screening in SC

Case Examples in SC

- 1/7/25 - Full term baby, NBS drawn at 24 hours of life
- GAA (acid-a-glucosidase): 3.6% with normal >20% of daily median

- 1/15/25 - Metabolic on call GGC provider received notification
- Advised to PCP office baby needs to be seen ASAP and obtain CK, urine Glc4, CKMB, CMP and CXR; DBS sent to GGC from DPH lab for *GAA* sequencing to run concurrently

- 1/16/25 – Metabolic on call provider called PCP office 4 times and still had not heard back

- 1/17/2025 – Still no returned call from PCP office; *GAA* sequencing resulted consistent with Infantile Pompe disease
- Baby is now 10 days old; optimal outcomes requires treatment to be started within 14 days of life
- 1/17/2025 PM – made contact with PCP however concern that family actually resides in NC

Case Continued

- 1/20/25 – Metabolic team spoke with PCP nurse, unsure if patient knew about results yet; nurse agreed to contact family immediately and express need for urgent medical evaluation
- Nurse made contact, family reported that they did understand the results of screen but had not received the genetic test results and had not had any evaluation yet; they were advised to present to the ED at Duke

- 1/22 – ERT initiated at 16 days of life

Infantile Pompe Disease

- Glycogen Storage Disease type II
- Infantile onset Pompe disease is characterized by disease onset before age 12 months with cardiomyopathy
- Median age of clinical onset of symptoms: 4 months
  - hypotonia, generalized weakness, feeding difficulties, failure to thrive, respiratory distress and hypertrophic cardiomyopathy
- Without treatment → IOPD commonly results in death before age 2 years
- Signs of **IOPD cardiac disease are usually present within the first few weeks of life**

- **Enzyme replacement therapy (ERT)**
  - Dependent on CRIM status – If no residual enzyme, patients develop high titer anti-rhGAA antibodies and require modified immune tolerance induction protocols prior to first infusion
- Myozyme/Lumizyme/Nexviazyme – IV infusion every 2 weeks for life

Infantile Pompe Disease

- **Initiation of ERT before age 14 days is associated with significantly improved gross motor function at age 12 months (Yang et al. 2016)**
  - **This is the goal with newborn screening**

- Those in whom ERT was initiated before age 6 months and before the need for ventilatory assistance, a majority had improved survival, improved ventilator-independent survival, reduced cardiac mass and significantly improved acquisition of motor skills compared to untreated cohort.

- Longer-term survivors who underwent early ERT may show sustained improvement in cardiac and motor function (Prater et al 2012)

Another time critical to intervention

- **Krabbe Disease** (Galactocerebrosidase Deficiency)
  - Neurodegenerative disease
    - Infantile → early normal development followed by extreme irritability, spasticity, feeding difficulties, developmental delay during the first year of life with rapid progression and loss of acquired skills; death before 2 years
  - Brain MRI shows demyelination, with T2-weighted images showing involvement of periventricular white matter, deep gray matter, and centrum semiovale as well as enhancement of cranial nerves.
  - Newborn screen
    - Enzyme activity → Psychosine 2nd tier → Molecular testing 3rd tier
      - Pseudodeficiency
  - **Goal is to have stem cell transplant completed before 30 days of life for best outcomes (PMID:40074005)**

Case Examples in SC

- Full term baby with initial abnormal NBS with elevated phe 150 umol/L and phe/tyr ratio of 3.4
- Repeat screen resulted unsat (no contact made with a metabolic provider)

- Metabolic on call physician received a call from PCP on day of life 36 – almost 6 weeks old – no repeat or confirmatory labs completed yet

- Plasma amino acids completed with Phe of 233 umol/L (HIGH)

- Seen in metabolic clinic and diagnosis confirmed of PKU – hyperphenylalaninemia

Phenylketonuria

- Deficiency of phenylalanine hydroxylase; can't convert Phenylalanine to Tyrosine
- Phenylalanine accumulates and crosses the blood brain barrier → irreversible neurologic damage
- Classic PKU is more severe with very high phe levels → Hyperphenylalaninemia is milder

- Early on, phe levels are lower but as protein intake increases → **Phe can increase**

- **The goal with newborn screening is to initiate treatment within 7-10 days of life in PKU to limit brain damage from high Phe levels**

Case Examples in SC

- Abnormal NBS for Biotinidase deficiency – resulted on 8/26/2022
- 2nd tier testing resulted with *BTD* c.454A>G heterozygous VUS and c.1330G>C heterozygous pathogenic variant

- Metabolic on call provider received a call 10/17/2022
- Baby was 2 months old, family did not know of the abnormal newborn screen result and had not been started on treatment

- **Diagnosis confirmed of partial biotinidase deficiency**

Biotinidase Deficiency

- Enzyme deficiency that results in deficient recycling of biotin, which is a critically important cofactor for multiple carboxylase enzymes
- Treatment with biotin prevents ANY symptom development
- If treatment is delayed, individuals can experience seizures, developmental delay, skin rash, alopecia, optic atrophy, hearing loss and respiratory problems. Acute metabolic acidosis can also occur. **Neurologic impact, optic atrophy, hearing loss are not reversible with biotin.**

- **Symptom onset can be as early as days of life, or delayed to months or years later. It has resulted in death in untreated cases (PMID: 31594257).**

A Biochemical Geneticist's Goals for SC

Greenwood Genetic Center

- Newborn Screen Follow up Program that has Clinical staff able to follow and track all cases to close.
  - This requires a program or method that prompts follow up in set intervals for any pending case
  - Follow up program team members call pediatrician offices, request the outcomes of labs, confirm those who need treatment (such as carnitine or biotin) have been started on it, etc
- More team members and more funding needed

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Future Directions for Newborn Screening

Whole Genome Sequencing??

Whole Genome as a Newborn Screening tool?

Greenwood Genetic Center

- Current use of clinical whole genome:
  - Symptomatic patients
  - Driven by phenotype
  - Patients opt in or opt out of secondary findings
- Genomes can be reanalyzed over time

ACMG secondary findings

Phenotype	MIM disorder	PMID Gene Reviews entry	Typical age of onset	Gene	MIM gene
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	*BRCA1* *BRCA2*	113705 600185
Li-Fraumeni syndrome	151623	20301488	Child/adult	*TP53*	191170
Peutz-Jeghers syndrome	175200	20301443	Child/adult	*STK11*	602216
Lynch syndrome	120435	20301390	Adult	*MLH1* *MSH2* *MSH6* *PMS2*	120436 609309 600678 600259
Familial adenomatous polyposis	175100	20301519	Child/adult	*APC*	611731
MYH-associated polyposis; adenomas, multiple colorectal, *FAP* type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456 132600	23035301	Adult	*MUTYH*	604933
Juvenile polyposis	174900	20301642	Child/adult	*BMPR1A* *SMAD4*	601299 600993
Von Hippel–Lindau syndrome	193300	20301636	Child/adult	*VHL*	608537
Multiple endocrine neoplasia type 1	131100	20301710	Child/adult	*MEN1*	613733
Multiple endocrine neoplasia type 2	171400 162300	20301434	Child/adult	*RET*	164761
Familial medullary thyroid cancer[d]	1552401	20301434	Child/adult	*RET*	164761
PTEN hamartoma tumor syndrome	153480	20301661	Child/adult	*PTEN*	601728
Retinoblastoma	180200	20301625	Child	*RB1*	614041
Hereditary paraganglioma-pheochromocytoma syndrome	168000 (PGL1) 601650 (PGL2) 605373 (PGL3) 115310 (PGL4)	20301715	Child/adult	*SDHD* *SDHAF2* *SDHC* *SDHB*	602690 613019 602413 185470
Tuberous sclerosis complex	191100 613254	20301399	Child	*TSC1* *TSC2*	605284 191092
WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379
Ehlers-Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180

Whole Genome as a Newborn Screening tool?

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- Asymptomatic babies
  - How do you determine what should be reported?
- WGS doesn't align with the principles that have been outlined for NBS since screening programs started to emerge in the 1960's

- Revision of criteria for NBS published in 2008 taking genetic testing into account
  - Among these criteria, no mention of treatment but the concepts of informed choice and equity of access
- CDC in 2011 published the ACCE tool, a framework through which to evaluate the use of genetic tests in a healthy population
  - 4 key domains of analytical validity, clinical validity, clinical utility, and ethical, legal and social implications

Whole Genome as a Newborn Screening tool?

Greenwood Genetic Center

- **Anticipated Challenges:**
  - Education and Consent
    - Time consuming, who will complete it?
  - Risks of loss of autonomy of the child
  - Genetic discrimination
  - Decreased uptake of traditional NBS (tNBS) program
  - Burden of variants of uncertain significance
    - Can’t interpret them in an asymptomatic child
  - Diseases with decreased penetrance or wide clinical variability
  - Cost
  - Storage of genetic material and privacy of data

- Benefits include ability to screen for more disease, preventative health care measures, impact on family planning

Factors for Consideration in Designing a gNBS program

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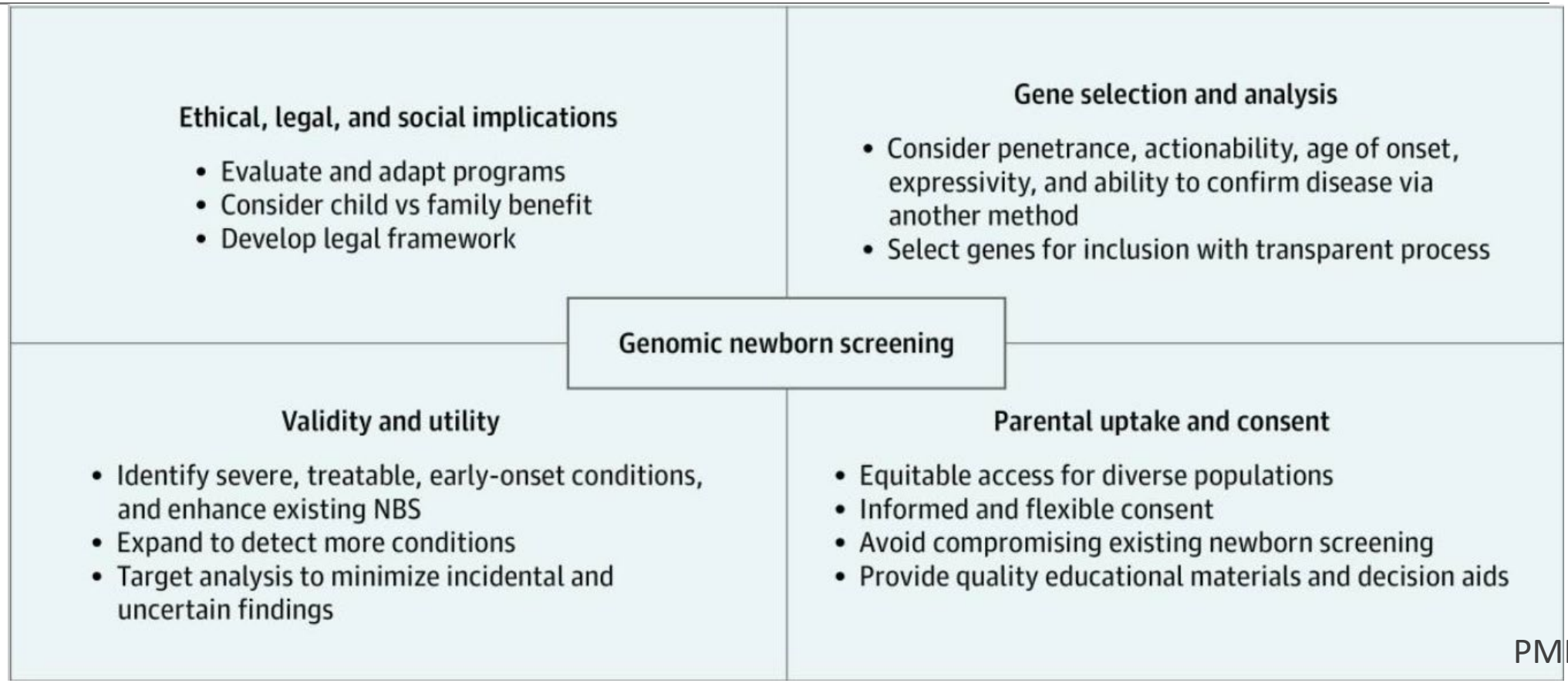


PMID: 34283230

BABYSEQ™

Greenwood Genetic Center

Phase I randomized clinical trial measuring utility of genomic sequencing in routine newborn care; 500 healthy infants; ½ randomized to WGS

Preliminary Data

- The BabySeq project revealed unanticipated monogenic disease risks in 11% of newborn babies.
  - Some infants already had signs or symptoms of the associated conditions, allowing for personalized management. You can hear one family's story here.
  - Other participants had a family history of related health problems, and this information helped their parents and relatives be more proactive about their health.
  - 88% of newborns had at least one recessive carrier variant that could be relevant to their parents' future reproductive planning, and 5% of babies had an atypical pharmacogenomic variant related to how they might process medications used in childhood.

Further expansion with BabySeq2 Project

Sensitivity of WGS for NBS

- Sensitivity in one study of NBSeq estimated **80.3% sensitivity** for Inherited Metabolic diseases (PMID 393559880)
  - Lower detection of variants in African American individuals and infants with public health insurance
  - Sensitivity of screening is increased when both biochemical analytes and genomic data are analyzed

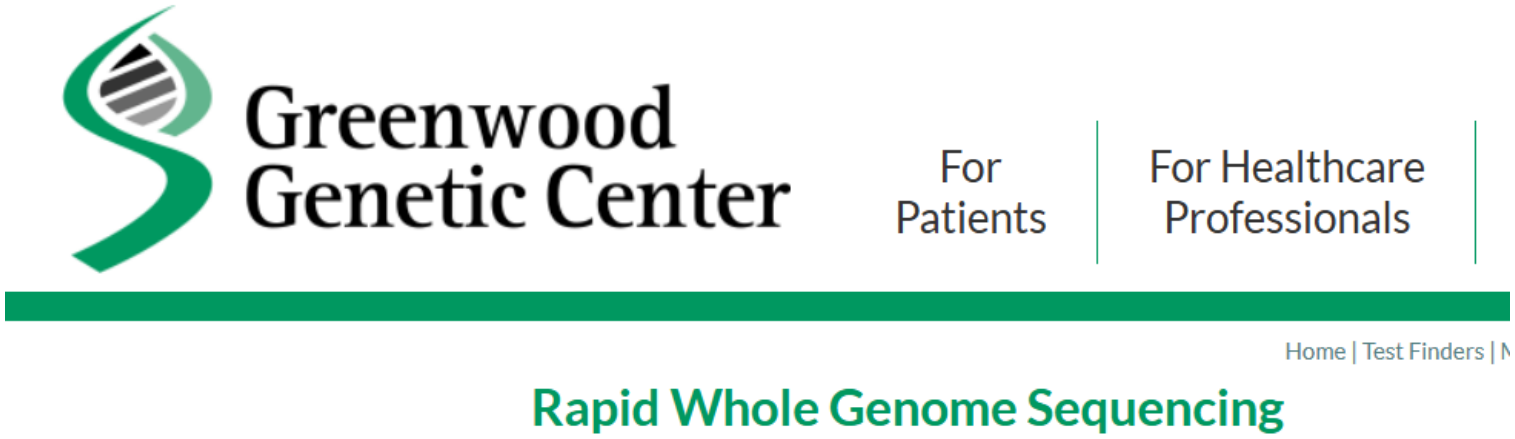
- Among 1728 DBS from infants with IMDs in California**, traditional NBS (tNBS) had a sensitivity of 99.0%,** whereas exome sequencing had **a sensitivity of only 88%.3**
  - Advantage of sequencing comes with the ability to expand and include many more disorders

- Concerns with completely eliminating tNBS

Whole Genome Sequencing

- Currently in SC we have many conditions that have second tier molecular testing through the Greenwood Genetic Center
- No established plans for genome based NBS in the near future

- GGC is doing Rapid Genome Sequencing for critical NICU/PICU cases → TAT approximately 5 days



Concluding Statements

- **Newborn Screening will continue to expand in South Carolina**
  - This will result in increased abnormal results (true and false positives) and work load for everyone involved

- **With the current infrastructure**, local pediatricians are ultimately liable for the timely follow up and outcome of abnormal newborn screens

- **There is room for improvement** of newborn screening in South Carolina if more resources were available
  - Goals would include a clinical newborn screen follow up program as well as methodology for timely tracking of all open cases to close

Metabolic On-Call

- 1 (866) 262-3070
- Save this number!

More Helpful Info

To gain access to NBS results, email request to:
nbslab@dph.sc.gov

To access eReports
eReports by Revvity

If you cannot access eReports and need results urgently contact:
Toshiro Washington
(803) 896-0795
washints@dph.sc.gov
OR
nbslab@dph.sc.gov

For questions regarding follow up recommendations:
NBSFollowup@dph.sc.gov

For questions regarding NBS lab results
NBSLab@dph.sc.gov

Request for Diagnosis

SOUTH CAROLINA DEPARTMENT OF PUBLIC HEALTH

REQUEST FOR DIAGNOSIS

Attention healthcare facilities and physicians: *South Carolina Laws 44-37-30 and 44-37-35 and Regulation 61-80 mandate the reporting of inborn metabolic errors and hemoglobinopathies to the SC Department of Public Health.*

Note: *Federal HIPAA legislation allows disclosure of protected health information, without consent of the individual, to public health authorities for the purpose of preventing or controlling disease. (HIPAA 45 CFR §164.512).*

Email *completed form to* nbsfollowup@dph.sc.gov *or* ***Fax*** *to* 803-898-0337

Patient's Name:	**DOB:**
Mother's Name:	

PCP Name/Practice:
Referred to (Specialist Name/Practice):
Status: ☐ Cleared ☐ Diagnosed ☐ Expired

Fill out this form and return to DPH when you close out a newborn screen

There are ongoing plans for creating a live link to fill out and supply this form

Thank you

Emily Black, MD

eblack@ggc.org

Please reach out, I would be happy to connect!