

Knowledge Burst |

Patient Selection Criteria for NICU Genomic Testing

Learning Objectives

1. Recognize neonatal medical presentations which indicate genomic testing including encephalopathy without inciting event, multiple congenital anomalies, metabolic crises, seizures and other clinical presentations.
2. Identify patient selection criteria resources.
3. Describe the evolving nature of NICU patient selection models for genomic sequencing from restrictive to universal models (e.g., inclusion, exclusion and universal)



BBN Patient Selection criteria

Want:

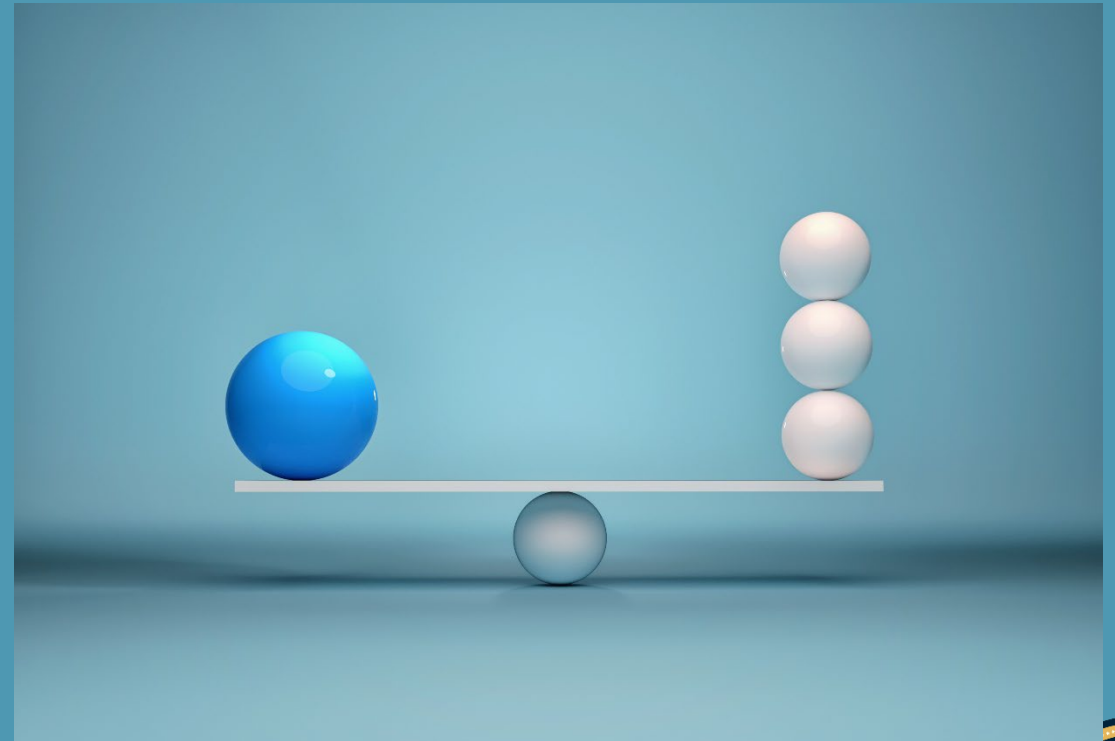
- Good diagnostic yield
- Good clinical utility

The Balance:

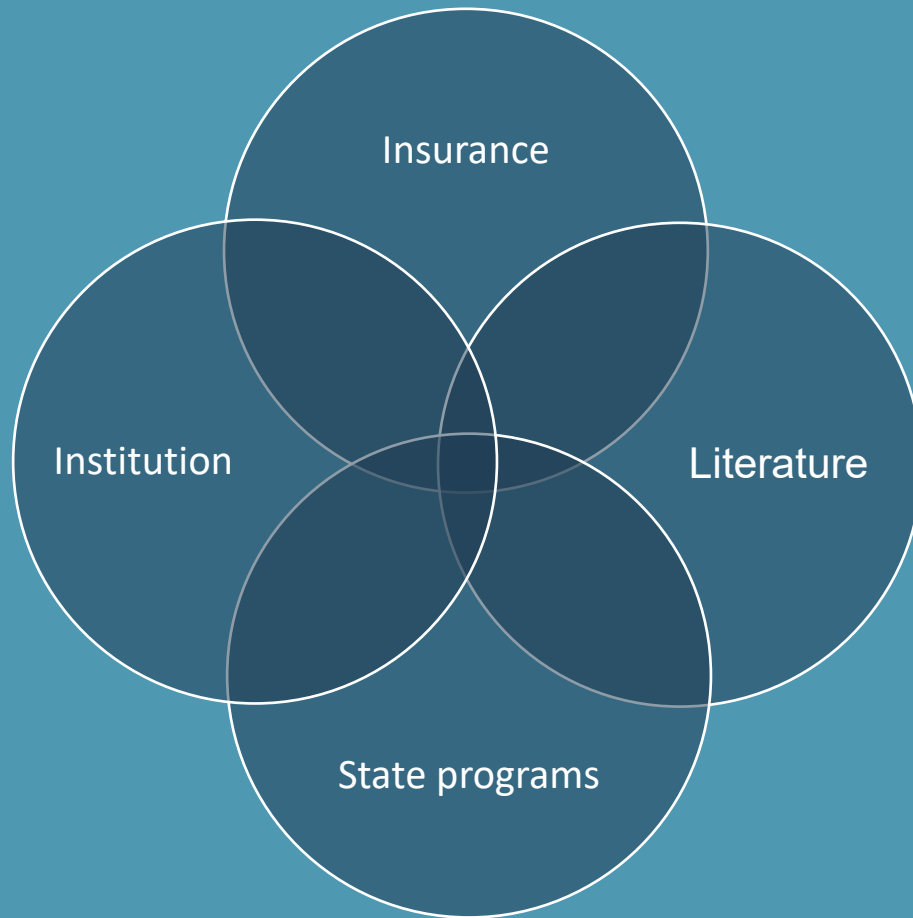
- If the patient criteria is too strict, will miss neonates that can benefit from a genetic diagnosis
- If the patient criteria is too loose, overuse (and expense of testing)

Other factors

- Evolving phenotype



Patient Selection criteria



Literature

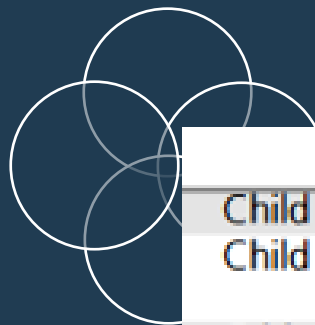
- Phenotype selection
- Broad phenotype
- Exclusion criteria

State programs

Institutions

Insurance





Child <4 months, acute illness with suspected genetic cause
Child <100 days, referred for exome sequencing on clinical basis

Critically ill children <1 year old in NICU or PICU with MCA or neurological symptoms

Table 2 Rapid c

Pa

Level IV NICU and PICU infants aged <4 months with suspected genetic disease defined as genetic test or consult ordered, one major or three minor congenital anomalies, abnormal lab test suggesting genetic disease, or abnormal response to therapy

Diagnostic yield

Willig et al.⁸
Meng et al.⁷

Ch
Ch

Acutely ill infants <1 year old, nominated by clinical provider

5 (57%)
278 (36.7%); rapid
ES: 32/63 (50.8%)

van Diemen
et al.⁹

Cr

PICU and CICU patients

(30%)

Petrilkin
et al.¹¹

Le
or
res

3 (32%)

Farnaes
et al.¹⁰

Ac

NICU and PICU patients with possible single-gene disorder with congenital anomalies, neurological symptoms, suspected metabolic disease, surgical necrotizing enterocolitis, extreme IUGR or failure to thrive, unexplained critical illness, or at clinician's request

2 (43%)

Mestek-
Boukhibar
et al.¹³

PIC

NICU neonates with unexplained seizures, metabolic disturbances, neurological abnormalities or depressed level of consciousness, MCA or significant physiological disturbance in keeping with genetic disorder for which diagnosis would likely change clinical management of genetic counseling

4 (42%)

French et al.⁵

NICU
su:
illness, or at clinician's request

95 (21%)

Elliott et al.¹²

NICU neonates with unexplained seizures, metabolic disturbances, neurological abnormalities or depressed level of consciousness, MCA or significant physiological disturbance in keeping with genetic disorder for which diagnosis would likely change clinical management of genetic counseling

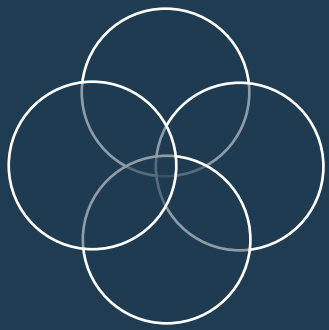
Geneticist and
research team

Trio rapid ES

15/25 (60%)

CICU cardiac intensive care unit, ES exome sequencing, GS genome sequencing, IUGR intrauterine growth restriction, MCA multiple congenital anomalies, NICU neonatal intensive care unit, PICU pediatric intensive care unit.





Patient selection criteria: Literature

- Phenotypically driven patient selection is effective
 - Infant (<6 months of age) in ICU with unexplained symptoms
 - New onset
 - Hypotonia
 - seizures
 - multiple congenital anomalies (MCA) - excluding VATER/VATERAL, OIES
 - Complex metabolic phenotype
 - Not likely trisomy or non-genetic cause
- Table shows hypotonia, seizures and multiple congenital anomalies are higher yield criteria

Table 1 Characteristics of sequenced patients and diagnostic yield

	Number of patients	Number of diagnoses	Diagnostic yield (%)
Overall	50	29	58
Age at enrollment			
<7 days	18	11	61
>7 days	32	18	53
Sex			
Male (XY)	25	14	56
Female (XX)	25	15	60
Location			
NICU	43	24	56
Other ICUs	7	5	71
Clinical criteria			
Hypotonia	20	16	80 ^a $p = 0.01$
Seizures	10	9	90 ^a $p = 0.02$
MCA	36	23	64

Clinical criteria

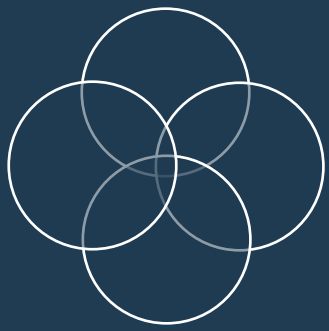
Hypotonia	20	16	80 ^a	$p = 0.01$
Seizures	10	9	90 ^a	$p = 0.02$
MCA	36	23	64	
Metabolic	16	8	50	
DSD	3	1	33	
Immunodeficiency	1	1	100	

DSD disorders of sex development, ICU intensive care unit, MCA multiple congenital anomalies, NICU neonatal intensive care unit.

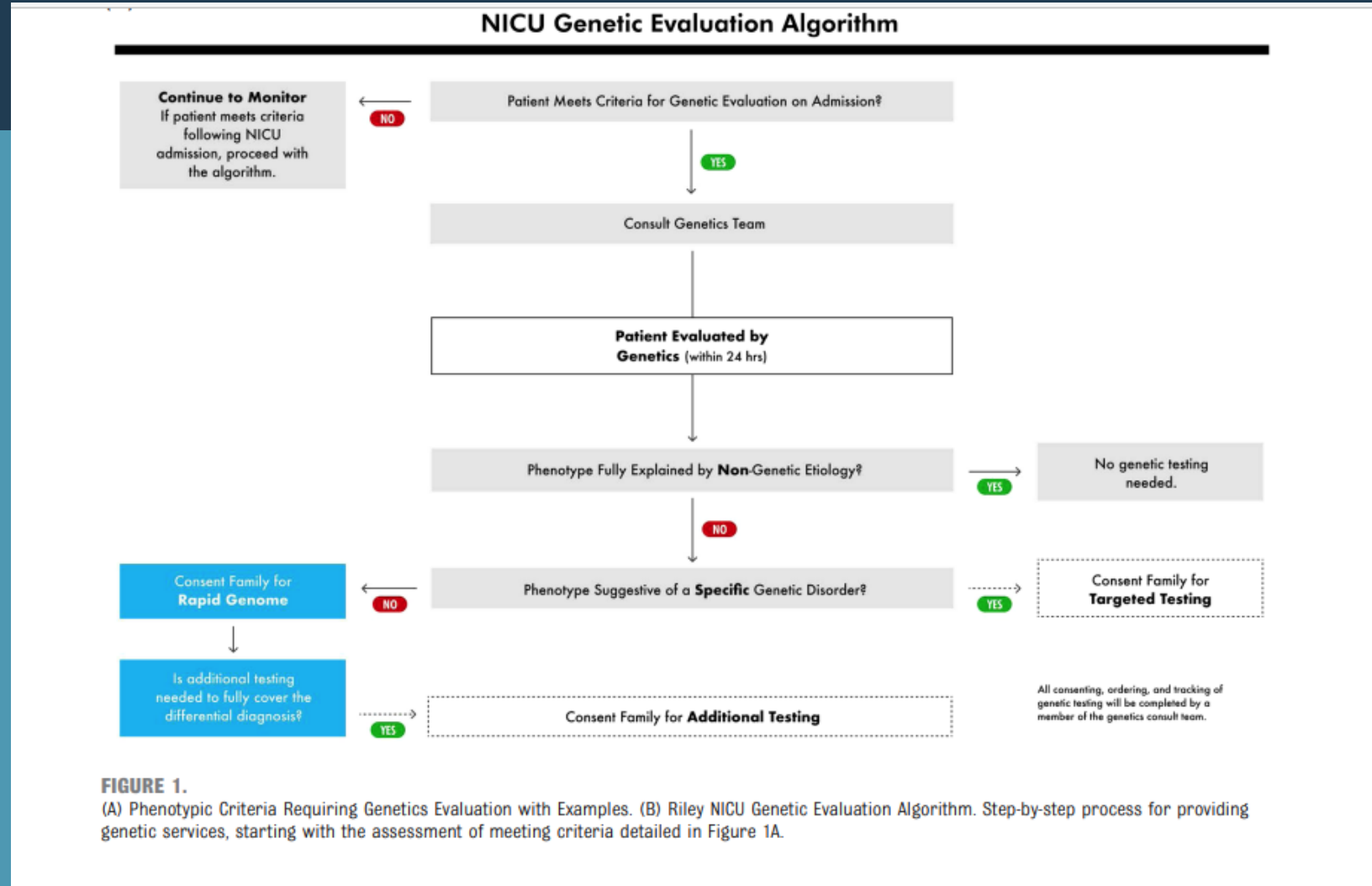
^aStatistically significant difference between patients with and those without characteristic on Pearson chi-square. $p < 0.05$ was considered significant.

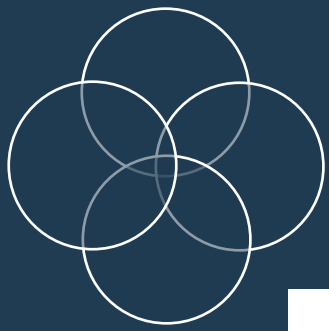
doi: 10.1038/s41436-019-0708-6





Patient selection criteria: Literature



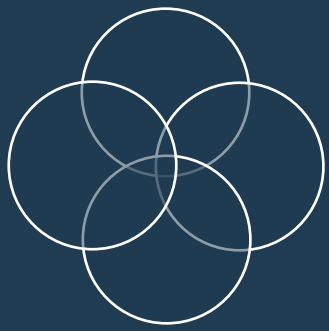


Patient selection criteria: Literature

(A)

CRITERIA	EXAMPLES
Congenital Anomalies, Dysmorphic Features, and/or Hydrops Fetalis	congenital heart disease, brain anomalies, cleft palate
Unexplained Metabolic Abnormalities	hyperammonemia, unexplained acidosis and/or electrolyte abnormalities
Cardiac Dysfunction	cardiomyopathy, heart failure, abnormal cardiac valves
Unexplained Respiratory Symptoms	respiratory failure, needing oxygen or positive pressure at term gestation not consistent with infection, delayed surfactant production
Unexplained Neurological Symptoms	hypotonia, hypertonia, seizures, arthrogryposis, abnormal muscle mass
Unexplained Hematological Findings	bleeding, clotting without a central line in place, indirect hyperbilirubinemia secondary to non-immune hemolysis, unexplained anemia, thrombocytopenia
Evidence of Malignancy	solid tumor or hematological malignancy
Evidence of Immune Dysfunction	infections not congenital or explained by prematurity, chorioamnionitis, or foreign body (i.e. central line or foley catheter); infection with unusual organisms
GI Abnormalities and/or Dysfunction	cholestasis, abnormal stooling, liver failure, hepatitis, pancreatic insufficiency
GU Abnormalities and/or Dysfunction	abnormal renal function, abnormal urine quality or quantity
Bone or Joint Abnormalities	unexplained fractures, missing or hypoplastic bones, abnormal bone structure
Abnormal Skin Findings (not related to a benign newborn condition)	abnormal pigmentation, unexplained blistering, nail abnormalities
Endocrine Dysfunction (not related to isolated hypothyroidism)	hyperinsulinemia, pituitary dysfunction, adrenal dysfunction
Evidence of Systemic Inflammation (with or without joint involvement)	unexplained fevers, evidence of inflammation without infection, joint swelling
Developmental or Constitutional Delay	unexplained feeding difficulties at term, failure to thrive, abnormal responsiveness





Patient selection criteria: Literature

Seattle Children's SeqFirst - Study using exclusion criteria

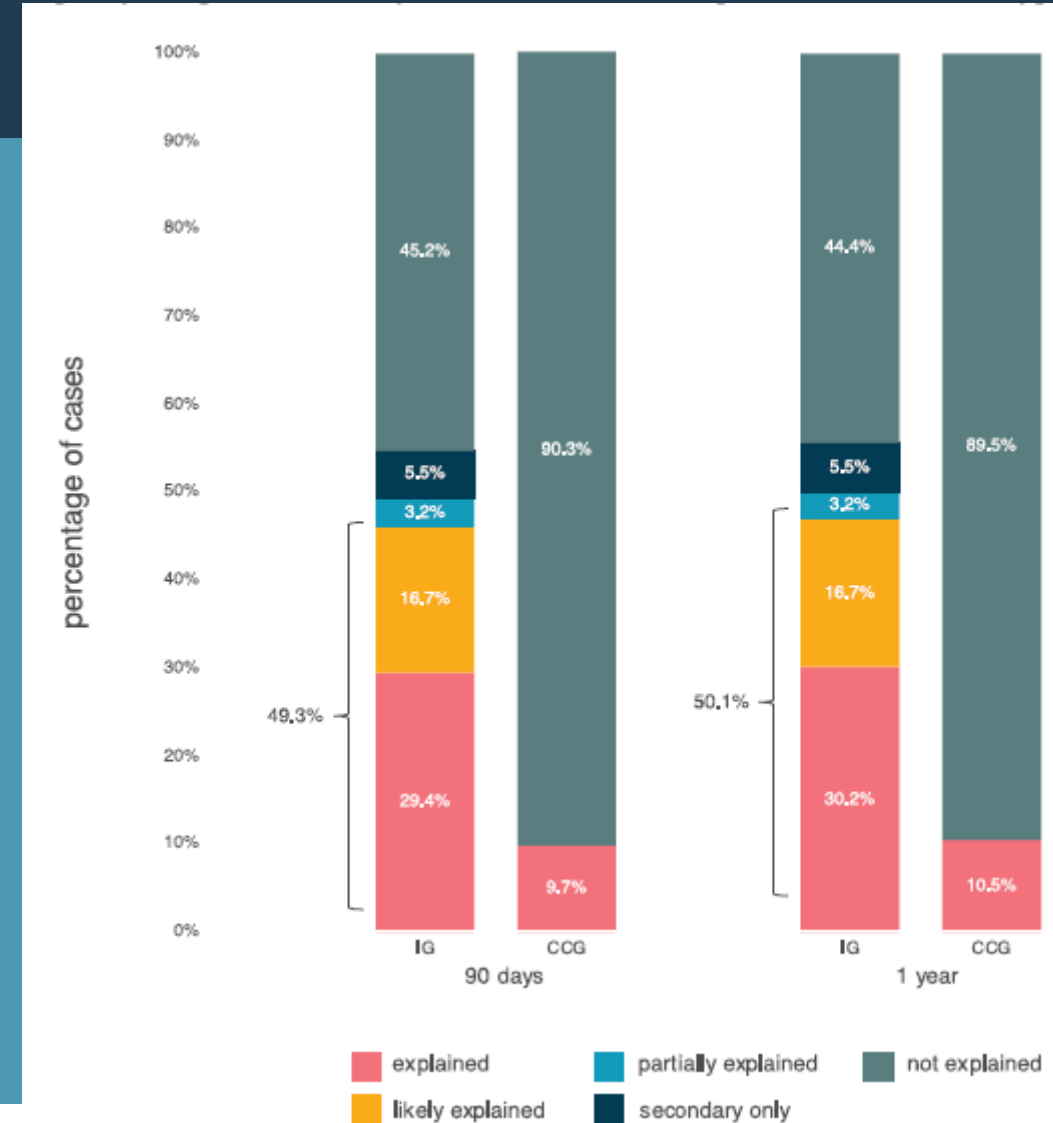
Exclusion criteria included:

- Corrected age >6 months
- Clinical findings fully explained by physical trauma, infection, or complications of prematurity.

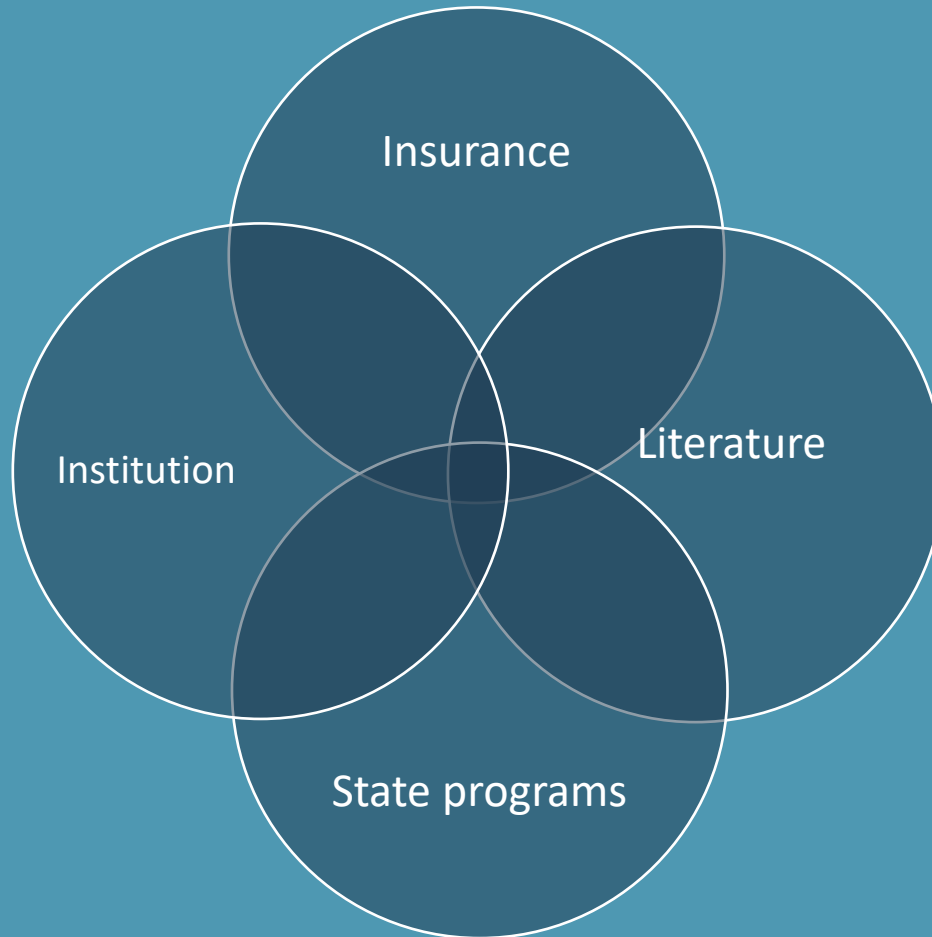
Infants with clinical findings initially considered fully explained by physical trauma, infection, or complications of prematurity who developed, as judged by a neonatologist, an atypical clinical course (e.g., excessive bleeding) during their hospitalization were offered enrollment.

Group with rGS (vs conventional treatment) were much more likely to have an explanation or likely explanation for their clinical course

Illustrates the conventional care is missing genetic diagnoses



Patient Selection criteria



Literature

- Pilot studies
- Phenotype selection
- Reviews

State programs

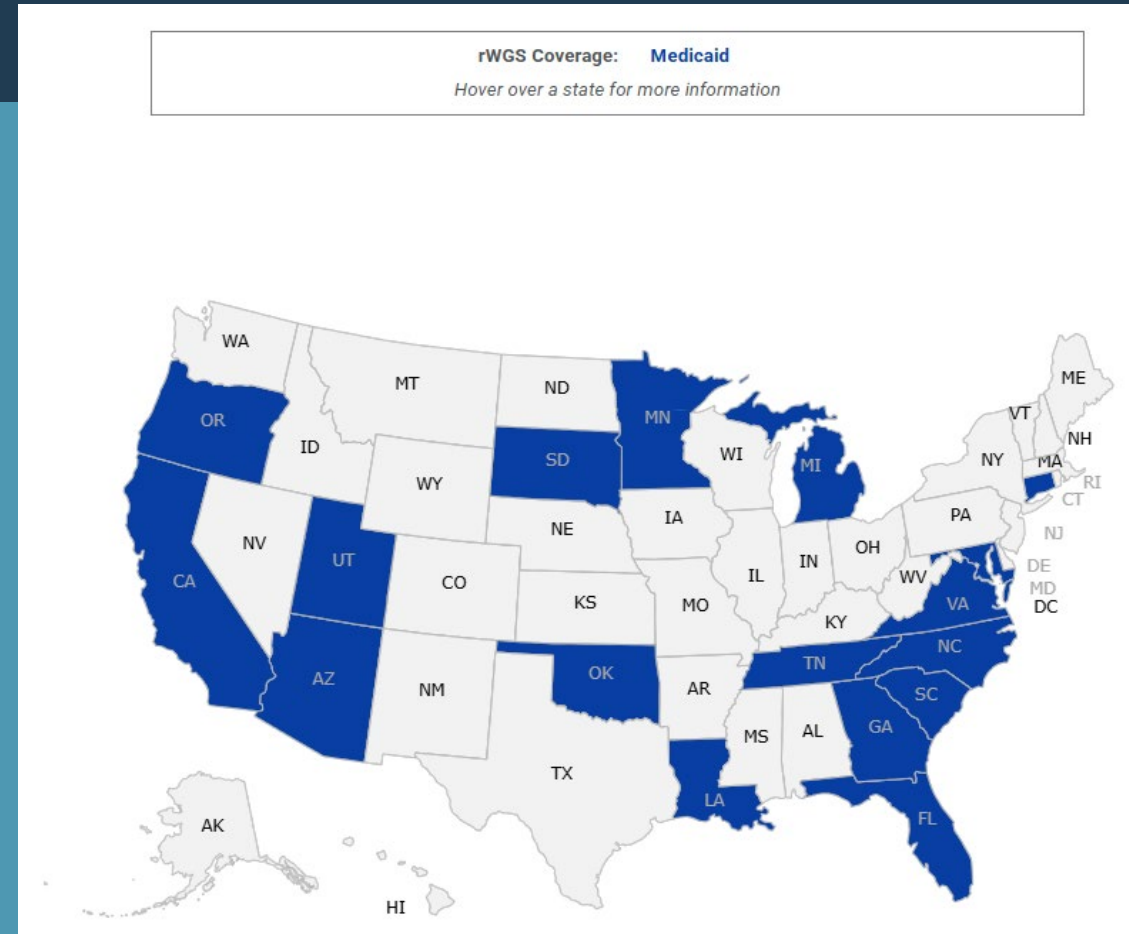
Institutions

Insurance



Patient selection criteria: State Programs

- Variable criteria often based on
 - Critical illness (location)
 - Age
- May be based on:
 - Policy
 - Legislation



Patient selection criteria: State Programs



Inclusion Criteria

Acutely ill inpatient, <1-year old Medi-Cal beneficiary:

- Admitted to a project site between November 2018 and May 2020
- within 1 week of hospitalization or
- within 1 week of development of abnormal response to standard therapy for underlying condition

Exclusion Criteria

Patients whose clinical course is entirely explained by:

- Isolated prematurity
- Isolated unconjugated hyperbilirubinemia
- Infection or sepsis with normal response to therapy
- Hypoxic ischemic encephalopathy with clear precipitating event
- Previously confirmed genetic diagnosis that explains the clinical condition (i.e. a positive genetic test)
- Isolated transient neonatal tachypnea
- Meconium aspiration
- Trauma



INCLUSION CRITERIA

FLORIDA

- > Inpatient at a MI project site
- > <18 years old
- > Meets one of the following criteria:
 - Admitted to a critical care unit OR
 - Admitted to another high-acuity in-patient unit and is suspected of having a genetic diagnosis
- > Meets one of the following criteria:
 - Within 1 week of admission OR
 - Within 1 week of development of an abnormal response to standard therapy for an underlying condition

EXCLUSION CRITERIA

Patients whose clinical course is entirely explained by:

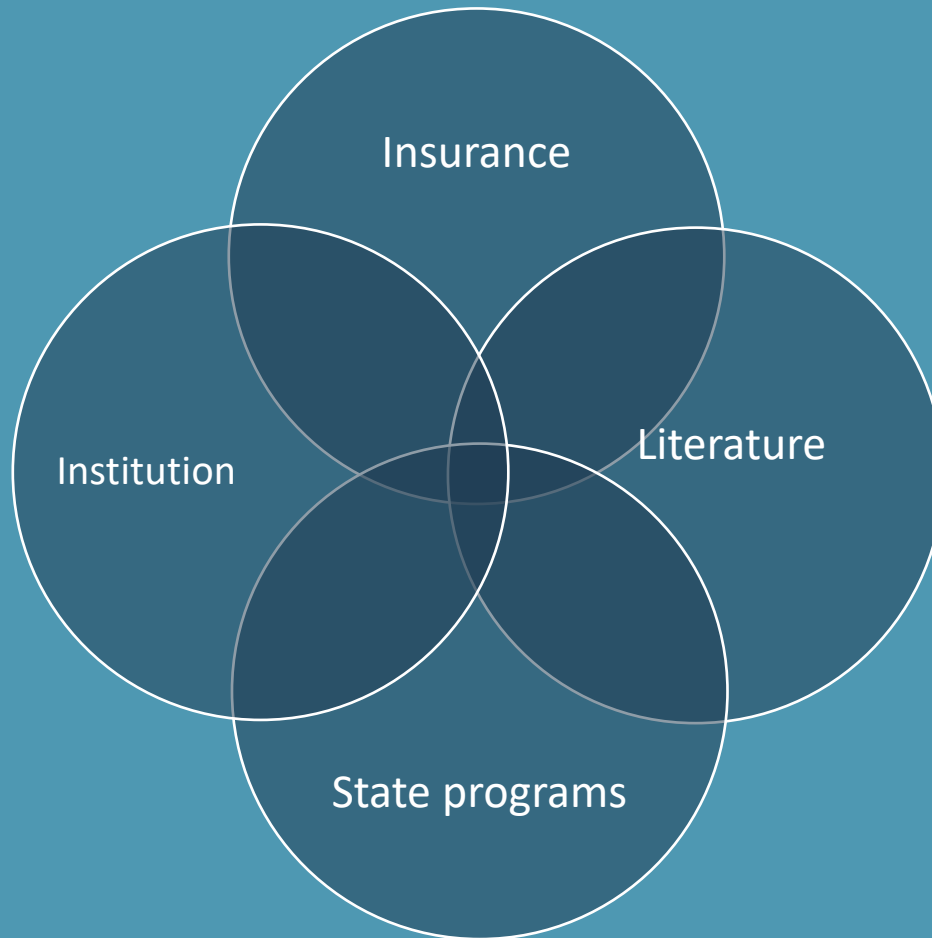
- > Infection or sepsis with normal response to therapy
- > Isolated prematurity
- > Isolated unconjugated hyperbilirubinemia
- > Hypoxic ischemic encephalopathy with clear precipitating event
- > Previously confirmed genetic diagnosis that explains the clinical condition (e.g. have a positive genetic test)
- > Isolated transient neonatal tachypnea
- > Trauma
- > Meconium aspiration



Inclusion: critically ill children from the NICU, PICU, CICU with poorly defined diseases of undetermined, possibly genetic causes.



Patient Selection criteria



Literature

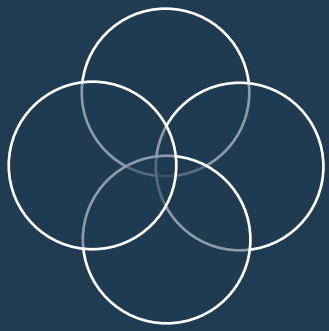
- Pilot studies
- Phenotype selection
- Reviews

State programs

Institutions

Insurance





Patient selection criteria: Institutions

**MAYO
CLINIC**



Expanded Genome Sequencing In NICU

Inclusion Criteria

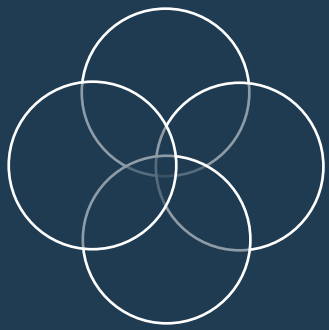
Any infant admitted to the Mary Brigh or Eisenberg NICU with:

- Major or minor congenital anomaly
 - Examples include but are not limited to congenital diaphragmatic hernia, omphalocele, tracheoesophageal fistula, structural malformation of a solid organ such as the heart, brain, kidneys, liver, bladder, eyes, or lungs, cleft lip and/or palate, malformation of a limb, or neural tube defects
- Dysmorphic features
- Gestational age at birth less than or equal to 27 weeks
- Seizures
- Hypotonia
- Neonatal encephalopathy (including but not limited to hypoxic ischemic encephalopathy)
- Concern for inborn error of metabolism
- Intrauterine growth restriction or SGA
- Respiratory failure of unknown etiology or unexpected course
- Hydrops fetalis with unknown etiology

Exclusion Criteria

- Previously confirmed genetic diagnosis that explains clinical condition
- Features consistent with an established genetic diagnosis for which there is an available test





Patient selection criteria: Insurance

Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS), with or without concurrent [Comparator Analysis](#), is proven and medically necessary when all of the following criteria are met:

- The affected individual displays signs or symptoms of an undiagnosed or unexplained disorder with a suspected genetic cause
- Test results are intended to directly impact the individual's medical management

or for which a specific test or a targeted gene or Targeted Panel should be used

by a genetic counselor, or developmental pediatrician

used by 18 years of age

Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)
UnitedHealthcare Commercial and Individual Exchange Medical Policy

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Effective 07/01/2026

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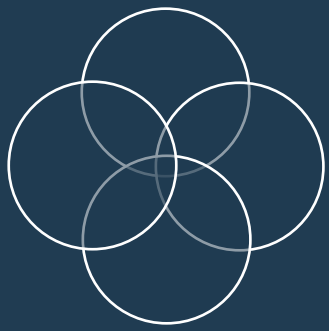


- Laboratory abnormalities suggestive of an inborn error of metabolism
- [Autism Spectrum Disorder](#)
- Neuropsychiatric condition (e.g., bipolar disorder, schizophrenia, obsessive-compulsive disorder)
- Hypotonia or hypertonia in infancy
- Dystonia, ataxia, hemiplegia, neuromuscular disorder, movement disorder, or other serious neurologic abnormality
- Unexplained developmental regression unrelated to Autism Spectrum Disorder or epilepsy
- Growth abnormality (e.g., failure to thrive, short stature, microcephaly, macrocephaly, or overgrowth)
- Persistent and severe immunologic or hematologic disorder
- Dysmorphic features
- [Consanguinity](#)
- Other first- or second-degree family member(s) with similar clinical diagnosis

Non-concurrent [Comparator Analysis](#) for WES or WGS is proven and medically necessary when both of the following criteria are met:

- The affected individual meets the above criteria for WES or WGS
- WES or WGS has been previously performed on the affected individual





Patient selection criteria: Insurance

Rapid Whole Genome Sequencing (rWGS)

The following criteria apply for individuals who are **inpatient** at the time of testing.

rWGS is considered medically necessary for the evaluation of acutely ill infants 12 months of age or younger when ALL of the following criteria are met:

- The member has not had previous exome sequencing performed, AND
- The member has not had previous genome sequencing performed, AND
- The member has had appropriate genetic and family history evaluation, AND
- The etiology of the infant's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on EITHER of the following:
 - Multiple congenital abnormalities affecting unrelated organ systems, or
 - TWO of the following criteria are met:
 - abnormality affecting at minimum a single organ system
 - encephalopathy
 - symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia)
 - family history strongly suggestive of a genetic etiology, including consanguinity
 - laboratory findings suggestive of an inborn error of metabolism
 - abnormal response to therapy, AND
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), AND
- Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available, AND
- A diagnosis cannot be made in a timely manner by standard clinical evaluation or laboratory testing, excluding invasive procedures such as muscle biopsy, AND
- Predicted impact on health outcomes, including immediate impact on medical management based on the molecular results, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and Other Considerations:

- Trio samples are preferred.

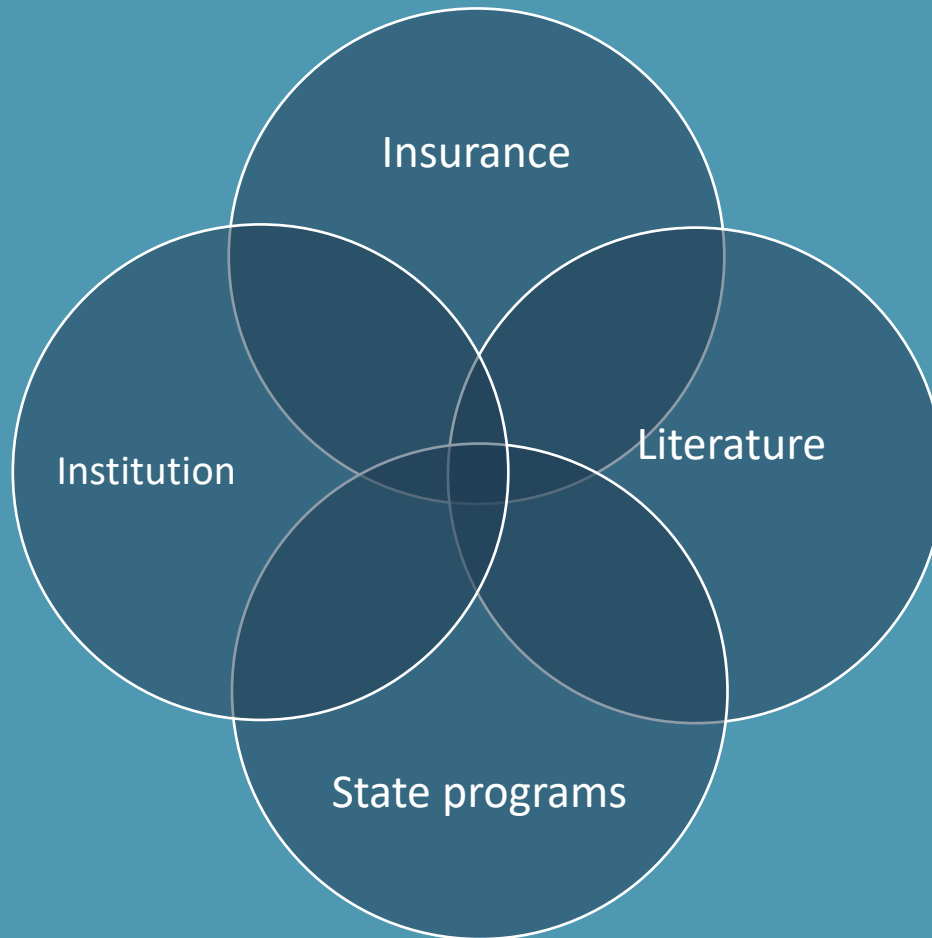
- rWGS is considered not medically necessary in individuals with the following diagnoses:
 - Isolated transient neonatal tachypnea
 - Isolated unconjugated hyperbilirubinemia
 - Isolated hypoxic ischemic encephalopathy with normal MRI
 - Isolated meconium aspiration
 - Isolated prematurity
 - Infection/sepsis with normal response to therapy
- GS or rWGS used for prenatal diagnosis is considered medically necessary
- GS on tissue from a pregnancy loss is considered medically necessary
- GS and rWGS are considered E/I/U for screening for asymptomatic or pre-symptomatic individuals.
- GS combined with Optical Genome Mapping (e.g., for research purposes, experimental, investigational, or unproven (E/I/U)).



eviCore Healthcare



Patient Selection criteria



Literature

- Pilot studies
- Phenotype selection
- Reviews

State programs

Institutions

Insurance

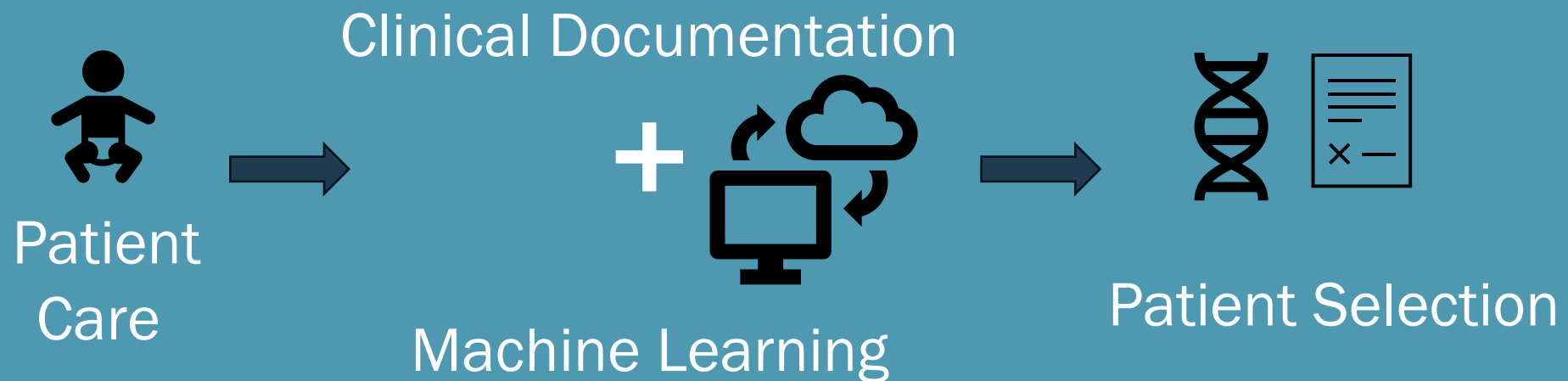


Patient selection criteria – the future?



Primary outcomes comparing Phase 1 and 2:

- More WGS
- Increase diagnostic yield
- Decrease time from admission to nomination



Patient Selection Criteria

- Continues to be a work in progress to determine the best criteria to include patients who would benefit from testing.
- There are different approaches in the literature for patient selection criteria.
 - Most literature has reviewed inclusion criteria.
 - One study is looking at using only exclusion criteria (Seqfirst)



Indications for ES/GS in Critically Ill Neonates

These criteria do not exclude completion of other genetic testing or consultation in the hospitalization for indications not listed here.

- Neonatal encephalopathy without inciting event
- Multiple congenital anomalies not suggestive of aneuploidy¹
- Concern for metabolic disorder²
- Hydrops fetalis without clear etiology
- Neonatal seizures without hypoxic ischemic encephalopathy
- Abnormal neurologic exam including significant hypotonia/hypertonia, weakness
- Complex congenital heart disease
- Growth abnormality including Intrauterine Growth Restriction (IUGR), Small for Gestational Age (SGA), micro/macrocephaly or overgrowth without clear etiology
- Dysmorphic features

¹ Common aneuploidies: Trisomy 21 (Down syndrome), Trisomy 13 (Patau syndrome), Trisomy 18 (Edward syndrome), Monosomy X (Turner syndrome)

² Signs of Acute Metabolic Disorders in the Neonatal Period: Sudden, gradual or insidious onset of sepsis-like features including poor feeding, vomiting, lethargy, seizures, hypoglycemia and lactic acidosis, abnormal urine organic acids, hyperammonemia

BBN Patient Selection criteria



How do you apply patient selection CRITERIA?

Criteria are to be guidelines to help in evaluation of patients

Identifying patients depends on clinical expertise of NICU providers. They are experts to decide on testing:

- Suspect Mendelian disorder
- Abnormal course
- Not typical preemie

*****Absolutely can choose patients which do not fit this criteria*****



Patient selection criteria resources

Baby Badger Network

The Baby Badger Network (BBN) is a collaboration between Wisconsin healthcare providers to increase access to genomic testing for critically ill neonates in Wisconsin NICUs. The information on this page is intended for BBN Participants, but others may find it useful.

Principal Investigators

- Jessica Scott Schweener, MD | Medical College of Wisconsin | Pediatrics
- April Hall, PhD, MS, CGC | UW Madison Center for Human Genomics and Precision Medicine

Related Pages

- BBN ECHO Training Details
- BBN ECHO Training Recordings & Resources

Collaborators

- Krishna Acharya, MD | Medical College of Wisconsin | Neonatology
- Donald Basel, MD | Medical College of Wisconsin | Pediatrics - Genetics
- Ryan McAdams, MD | UW School of Medicine and Public Health | Neonatology
- Stephan Mayn, MD/PhD | UW Madison Center for Human Genomics and Precision Medicine
- Sara Zoran, MS, CGC | Genetic Systems Integration (GSI) Initiative



geneticsinwisconsin.wisc.edu/baby-badger-network/



www.evicore.com/sites/default/files/clinical-guidelines/2025-12/MOL.TS_.306.C_Genome%20Sequencing_V1.0.2026_Eff01.01.2026_Pub09.26.2025_Upd12.08.2025.pdf

Rady Children's
Institute for Genomic Medicine

Providing Rapid Diagnostics to Guide Pediatric Treatment

Every child deserves a chance to live their story

RIDGM offers comprehensive rapid and ultra-rapid WGS to help physicians assess for most genetic diseases in one test. RIDGM empowers clinicians to intervene quickly with precision care and make disease-specific treatment decisions to improve the lives of critically ill babies, children with complex medical issues, and their families.

To help expand access to diagnostic genome sequencing, RIDGM has partnered with Infection Medicine, an independent company focused on supporting clinical adoption and innovations in patient identification, ordering, workflow tools, billing support, and clinical utility.

Radygenomics.org/clinical-genome-services



www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/whole-exome-and-whole-genome-sequencing.pdf

GeneDx

Genetic tests | How to order | Resources | Biopharma | Company

Rapid whole genome sequencing in the NICU

Paid genome sequencing in the NICU enables earlier diagnosis and guides medical management for critically ill infants with suspected genetic conditions.

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Genedx.com/providers/indications/nicu

