



# **USING EVIDENCE BASED CRITERIA TO IDENTIFY CRITICALLY ILL NEONATE CANDIDATES FOR GENOMIC TESTING**

Jess Scott Schwoerer

May 31, 2024 @11:30

**USING EVIDENCE BASED  
CRITERIA TO IDENTIFY  
CRITICALLY ILL NEONATE  
CANDIDATES FOR  
GENOMIC TESTING**

1. Describe clinical presentations in CIN that indicate ES/GS testing
2. Identify clinical presentations in CIN that indicate other genetic testing
3. Discuss challenges and solutions to implementing genomic medicine in a NICU setting

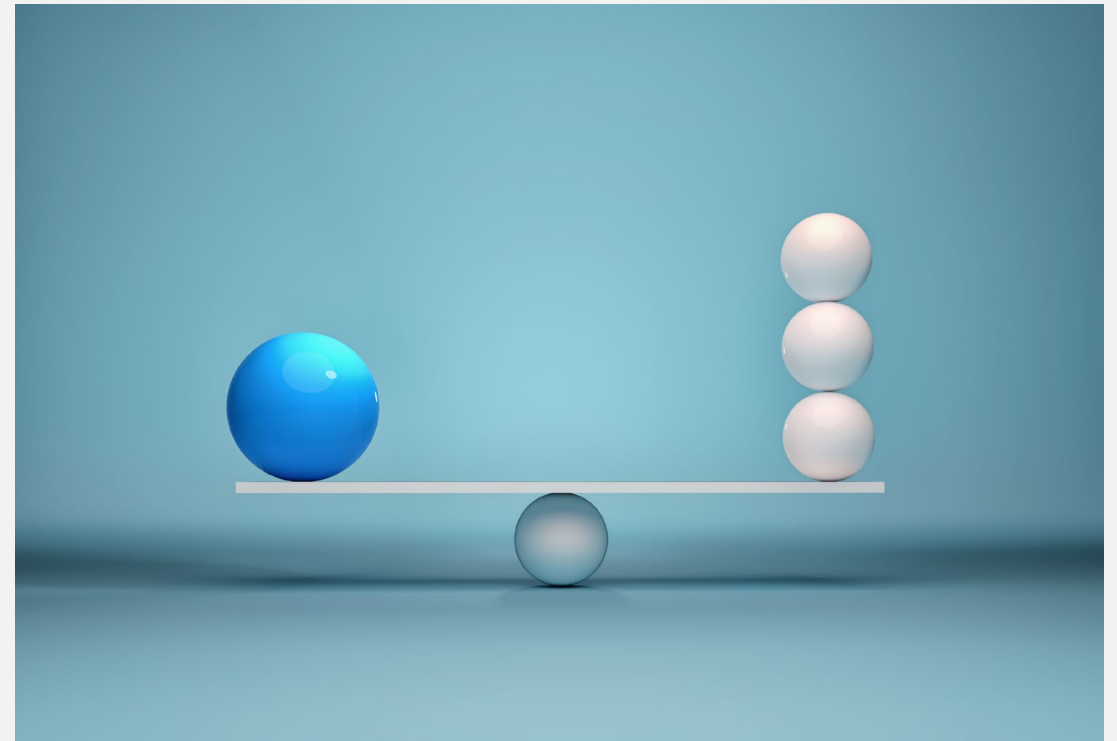
# BBN PATIENT SELECTION CRITERIA

Want:

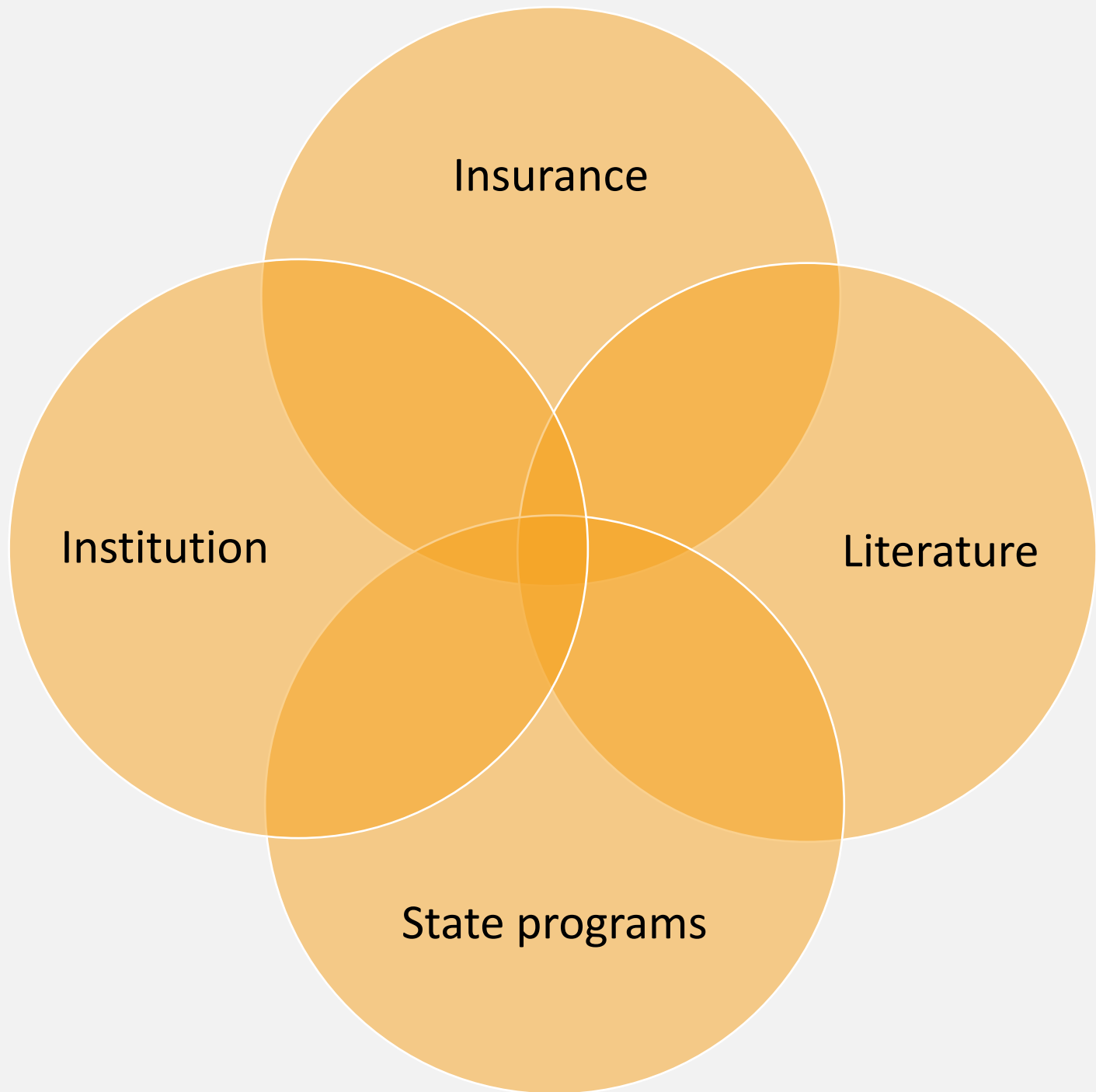
- Good diagnostic yield
- Good clinical utility

The Balance:

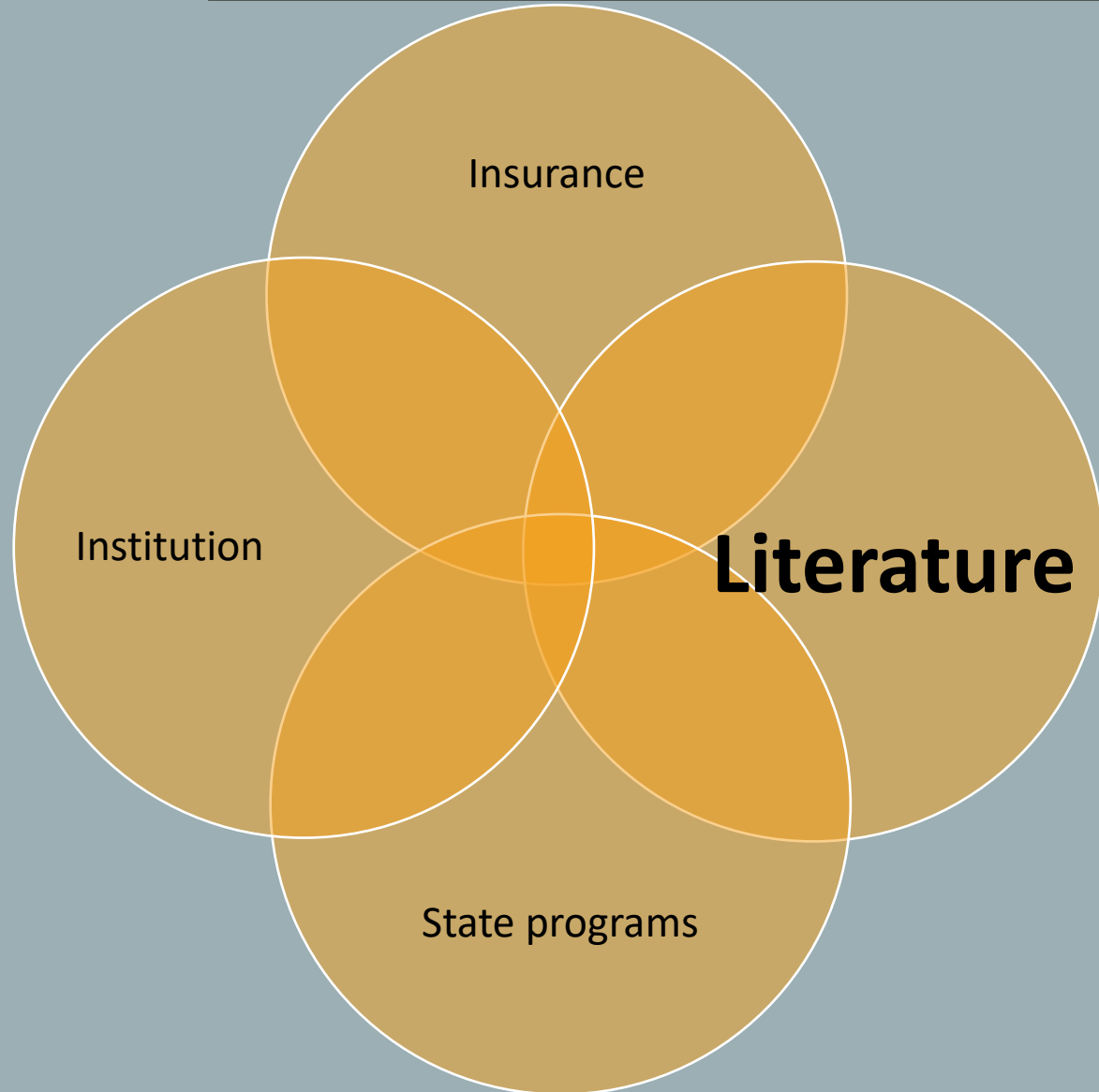
- If the patient criteria is too strict, will miss neonates that can benefit from a genetic diagnosis
- If the patient criteria is too loose, overuse (and expense of testing)



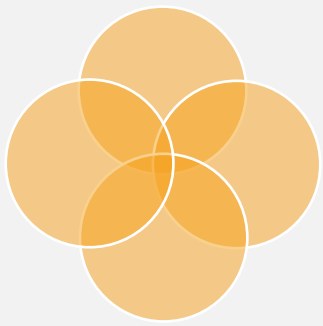
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# BBN PATIENT SELECTION CRITERIA



- Pilot studies
- Phenotype selection
- Reviews

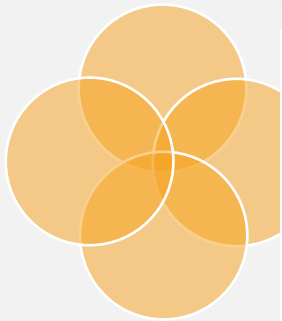


# BBN Patient selection criteria: Literature

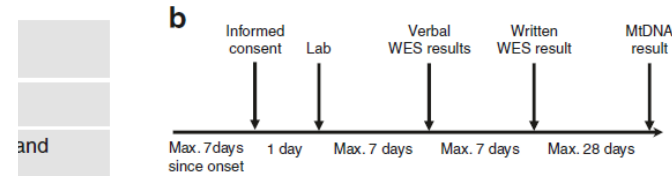
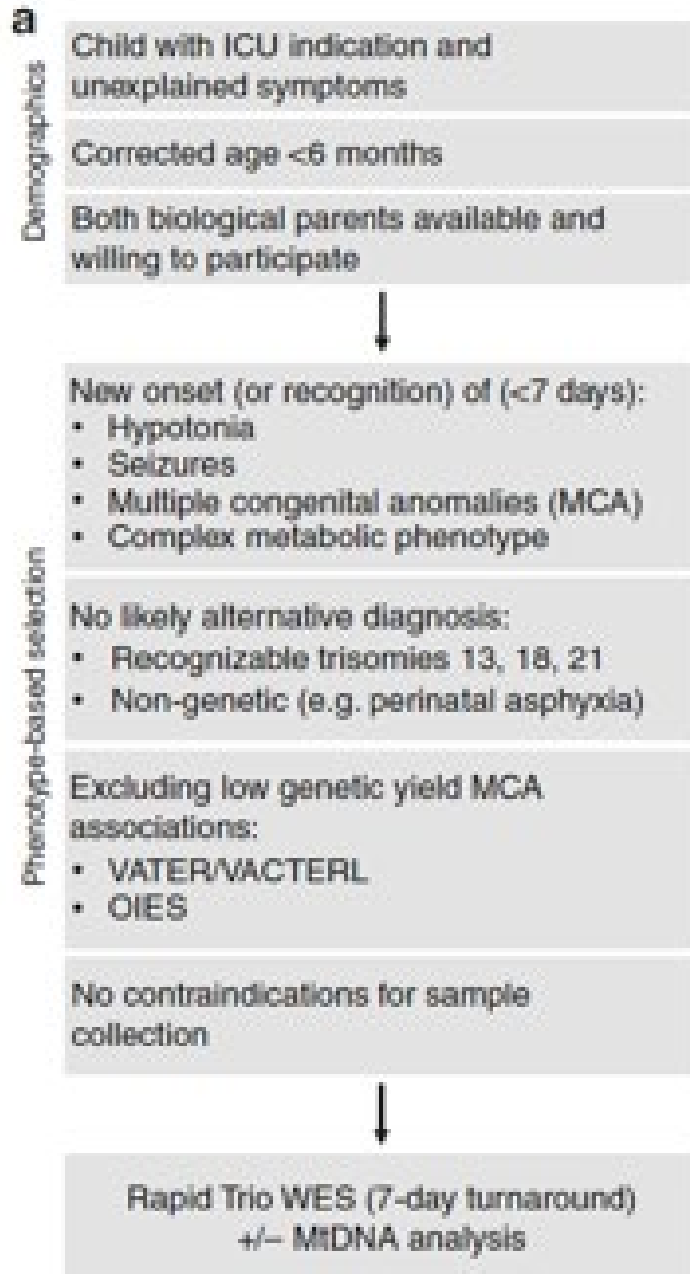
**Table 2** Rapid exome/genome sequencing studies in ICU infants

	Child <4 months, acute illness with suspected genetic cause	By research team	
Wil Me	Child <100 days, referred for exome sequencing on clinical basis	By clinical provider (retrospective analysis)	: rapid (8%)
var et al	Critically ill children <1 year old in NICU or PICU with MCA or neurological symptoms	Multidisciplinary working group	
Pet et al	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	Screening of NICU census	
Far et al	Acutely ill infants <1 year old, nominated by clinical provider	By clinical provider (retrospective analysis)	
Me Bot et al	PICU and CICU patients	By multidisciplinary research team	
Fre			
Elic	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	Clinician/ research team	
CICU	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	care unit.

Gubbels CS, VanNoy GE, Madden JA, Copenheaver D, Yang S, Wojcik MH, et al. Prospective, phenotype-driven selection of critically ill neonates for rapid exome sequencing is associated with high diagnostic yield. *Genetics in Medicine*. 2020 Apr;22(4):736–44.



# nt selection criteria: Literature

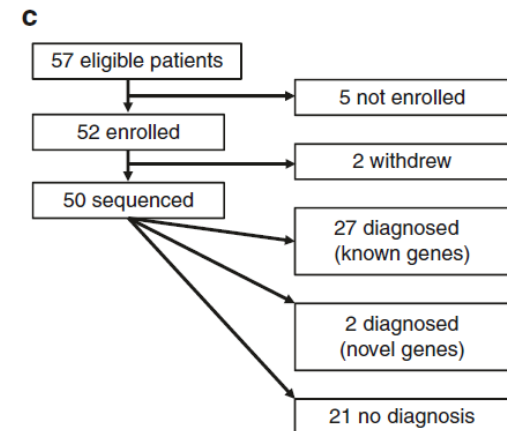


days):

MCA)

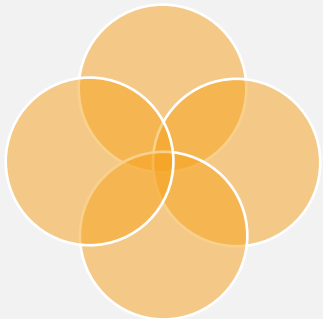
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selection protocol. (b) Timeline for screening, enrollment, sendoff, and return of results. (c) are unit, *mtDNA* mitochondrial DNA.

penheaver D, Yang S, Wojcik MH, et al. Prospective, II neonates for rapid exome sequencing is associated with  
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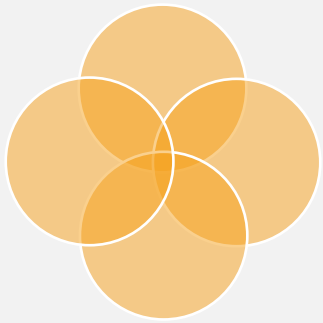


# PATIENT SELECTION IN STATE MEDICAID PROGRAMS/BABY ANIMAL PROGRAMS

- Variable criteria
- May be based on:
  - Policy
  - Legislation

State Medicaid Coverage for rWGS

State	Policy	Criteria
Arizona Medicaid	AHCCCS Reimbursement for Rapid Whole Genome Sequencing	≤ 1 year; ICU (NICU/PICU/CVICU)
California Medi-Cal	AB133 and reflected in Provider Bulletin 573	≤ 1 year; ICU (NICU/PICU/CVICU)
Florida Medicaid	Laboratory Services Coverage Policy (Agency for Health Care Administration)	≤ 1 year; ICU (NICU/PICU/CVICU)
Georgia Medicaid	January 2024 Update Laboratory Services	Not yet issued
Louisiana Medicaid	SB 154	≤ 1 year; ICU (NICU/PICU/CVICU) or Pediatric Care Unit Louisiana Senate Bill 154 also requires that all private health plans cover rWGS subject to medical necessity criteria.
Maryland Medicaid	Lab Testing Policy	
Michigan Medicaid	Lab Policy MSA 21-33, State Plan Amendment # MI-21-0010	≤ 1 year; ICU (NICU/PICU/CVICU)
Minnesota Medicaid	Lab & Pathology Services Provider Manual	No age restriction for pediatric critical care unit; ICU (NICU/PICU/CVICU)
Oregon Medicaid	Prioritized Health Services List	≤ 1 year; ICU (NICU/PICU/CVICU)
Utah Medicaid	Medicaid Information Bulletin November 2023: 23-82 Physician and EPSDT Services Provider Manual Revisions	≤ 1 year; ICU (NICU/PICU/CVICU)



# PATIENT SELECTION IN STATE PROGRAMS

## State Medicaid Coverage for rWGS

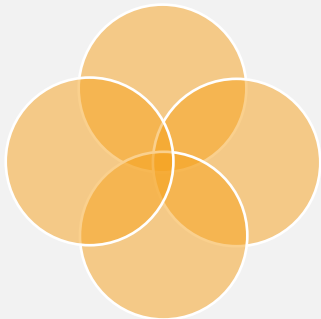
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## FLORIDA

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

**Diagnosis: 40/82 patients**

**Change in care: 36/40 patients**



# PATIENT SELECTION IN STATE PROGRAMS

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## Michigan

**PRECISION MEDICINE IN MICHIGAN TO SAVE LIVES AND RESOURCES**

**INCLUSION CRITERIA**

- > 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

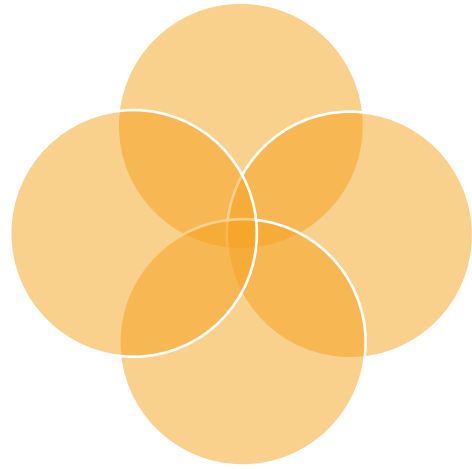
**EXCLUSION CRITERIA**

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

Diagnosis: 39%

Change in care: 27%



# PATIENT SELECTION AT INSTITUTIONS

## Expanded Genome Sequencing In NICU

### Inclusion Criteria

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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

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



# PATIENT SELECTION FROM INSURANCE

## Whole Exome Sequencing (WES)

Whole Exome Sequencing (WES) is proven and medically necessary for the following:

- Diagnosing or evaluating a genetic disorder when the results are expected to directly influence medical management and clinical outcomes and all of the following criteria are met:
  - Clinical presentation is nonspecific and does not fit a well-defined syndrome for which a specific or targeted gene test is available. If a specific genetic syndrome is suspected, a single gene or targeted gene panel should be performed prior to determining if WES is necessary
  - WES is ordered by a medical geneticist, neonatologist, neurologist, or developmental pediatrician
  - One of the following:

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

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Effective 04/01/2024

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- Clinical history strongly suggests a genetic cause and **one** or more of the following features are present:
  - Multiple congenital anomalies (must affect different organ systems)
  - Moderate, severe, or profound Intellectual Disability diagnosed by 18 years of age
  - Global Developmental Delay
  - Epileptic encephalopathy with onset before three years of age; or
- Clinical history strongly suggests a genetic cause and **two** or more of the following features are present:
  - Congenital anomaly
  - Significant hearing or visual impairment diagnosed by 18 years of age
  - Laboratory abnormalities suggestive of an inborn error of metabolism (IEM)
  - 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 neurologic abnormality
  - Unexplained developmental regression, unrelated to autism 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 features
- Comparator (e.g., parents or siblings) WES for evaluating a genetic disorder when the above criteria have been met and WES is performed concurrently or has been previously performed on the individual
- Reanalysis of WES after at least 18 months when above criteria for initial WES has been met and one of the following occurs:
  - Individual experiences additional symptoms after initial WES that cannot be explained by the results of the initial WES; or
  - New data or new family history emerges which suggest a link between the individual's symptoms and specific genes



## 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 aneuploidy<sup>i</sup>
- Concern for metabolic disorder<sup>ii</sup>
- Hydrops fetalis without clear etiology
- Neonatal seizures without HIE
- 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

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<sup>i</sup> **Common aneuploidies:** Trisomy 21 (Down syndrome), Trisomy 13 (Patau syndrome), Trisomy 18 (Edward syndrome), Monosomy X (Turner syndrome)

<sup>ii</sup> **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

## 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 neonatologist.

Neonatologists are experts to decide on testing:

- Suspect Mendelian disorder
- Abnormal course
- Not typical preemie

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

# WHEN TO ORDER OTHER GENETIC TESTING?

- Concerns for a trisomy, karyotype

Trisomy 21  
Down Syndrome

Trisomy 18  
Edward Syndrome

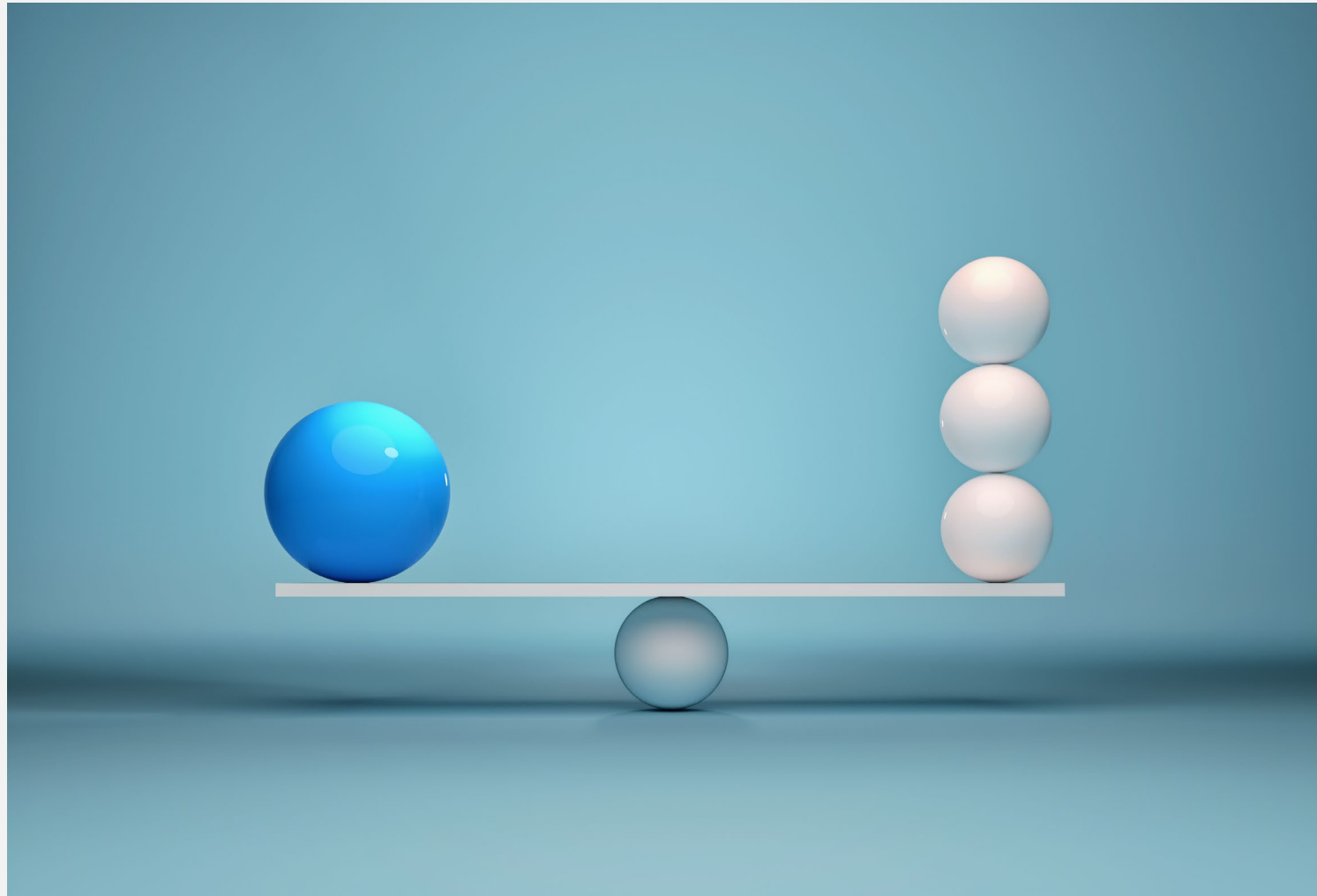
Trisomy 13  
Patau Syndrome

- Family history with genetic diagnosis with specific molecular finding
- Prenatal testing indicating a probable diagnosis
- List is not all inclusive, can always reach out to genetics

# ADVANTAGES TO GENOMIC TESTING

- Genomic testing can be used to evaluate a broad number of genetic conditions:
  - Can find single gene disorders
  - Can find copy number variants
  - Multiple type of variants (and more variants than exome sequencing)
- Using broad testing can improve
  - Eliminates stepwise process
  - Turnaround time


# BBN PATIENT SELECTION CRITERIA




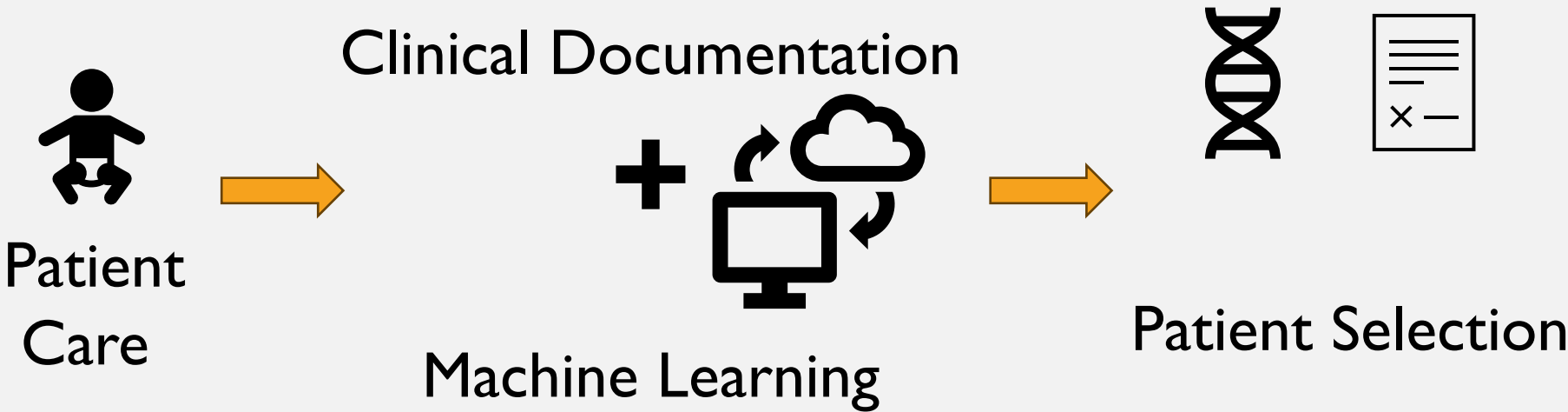
# BBN PATIENT SELECTION CRITERIA

Peterson et al. *Genome Medicine* (2023) 15:18  
<https://doi.org/10.1186/s13073-023-01166-7> Genome Medicine

**RESEARCH** **Open Access**

**Automated prioritization of sick newborns for whole genome sequencing using clinical natural language processing and machine learning** 

Bennet Peterson<sup>1</sup>, Edgar Javier Hernandez<sup>2</sup>, Charlotte Hobbs<sup>3</sup>, Sabrina Malone Jenkins<sup>4</sup>, Barry Moore<sup>2</sup>, Edwin Rosales<sup>3</sup>, Samuel Zoucha<sup>4</sup>, Erica Sanford<sup>3,5</sup>, Matthew N. Bainbridge<sup>3</sup>, Erwin Frise<sup>6</sup>, Albert Oriol<sup>7</sup>, Luca Brunelli<sup>4</sup>, Stephen F. Kingsmore<sup>3</sup> and Mark Yandell<sup>2</sup> 



# CHALLENGES AND SOLUTIONS TO IMPLEMENTING GENOMIC MEDICINE IN A NICU SETTING

CHALLENGES	SOLUTIONS
Workforce concerns in genetics	Collaboration between clinicians, laboratories, hospital administrators, patients/caregivers, patient advocacy groups, policymakers, payers
Health care costs	
Who to test?	
Timing and speed of results	
Communication with family surrounding consent and results.	
Long term follow-up of testing results.	

And more...

