

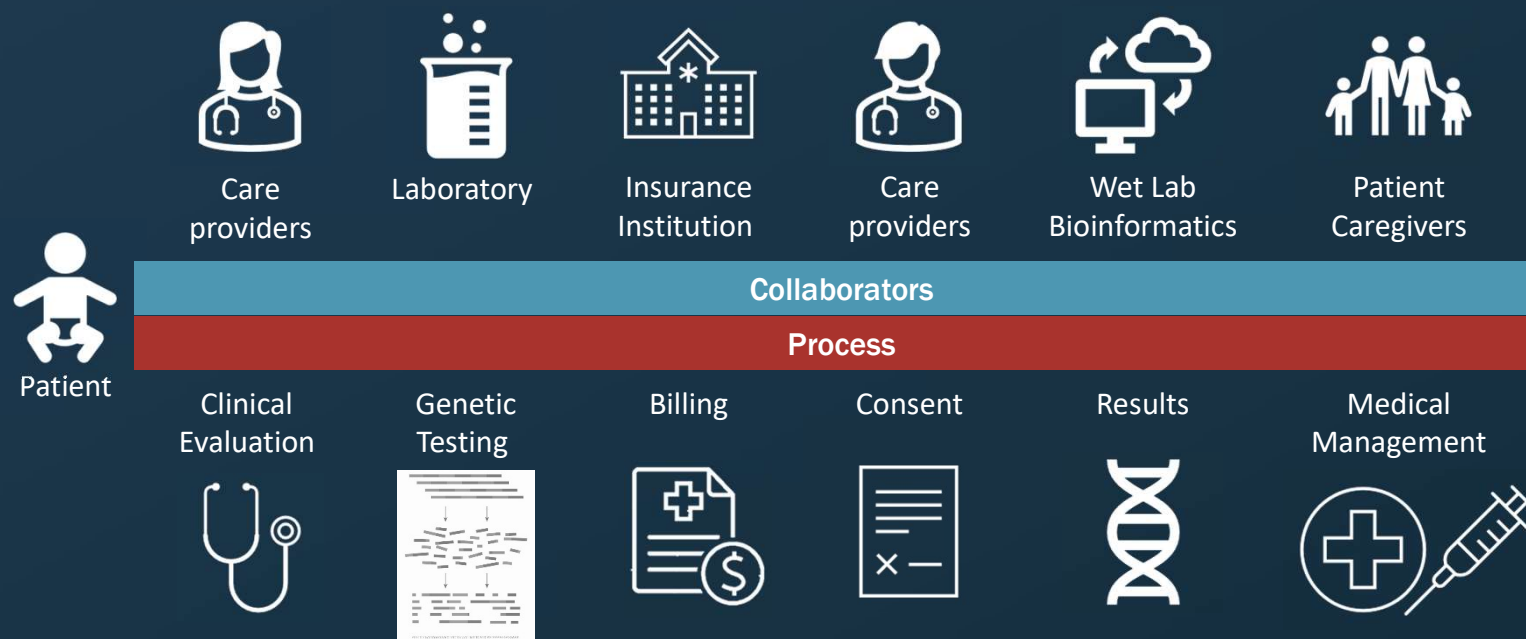
Patient Selection Criteria

Evaluate Every Infant for Genomic Testing

Jessica Scott Schwoerer, MD



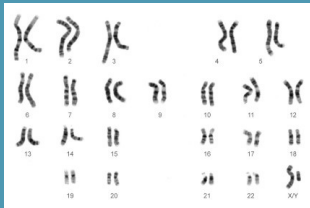
Barriers to Genomic Testing Implementation



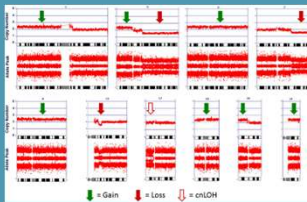
Current Genetic testing options

Routine testing

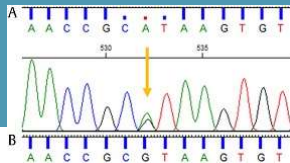
Karyotype



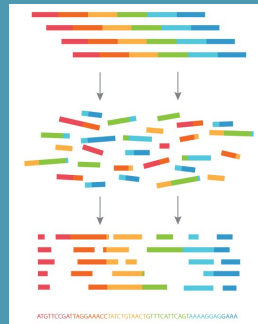
Microarray



Single gene sequencing



Next Gen sequencing



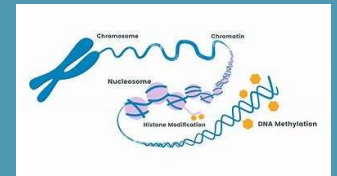
Gene Panels

Exome Sequencing

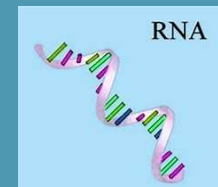
Genome Sequencing

Future

Methylation



RNA expression



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 types of variants (and more variants than exome sequencing)
- Using broad testing can improve
 - Eliminates stepwise process
 - Turnaround time



When to order routine 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



BBN Patient Selection criteria

Want:

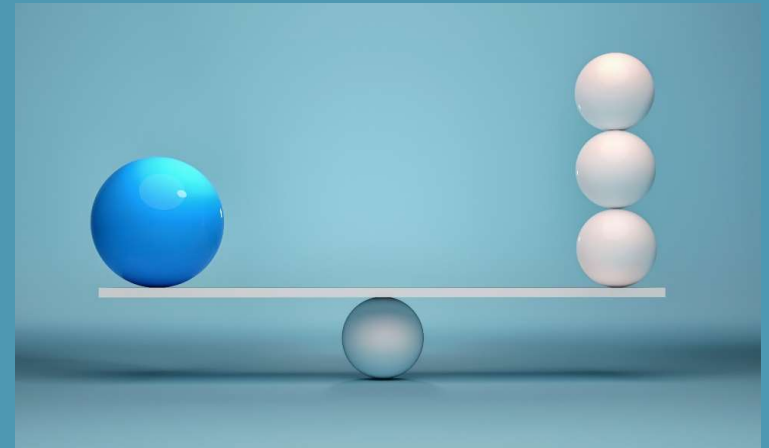
- High diagnostic yield and clinical utility

The Balance:

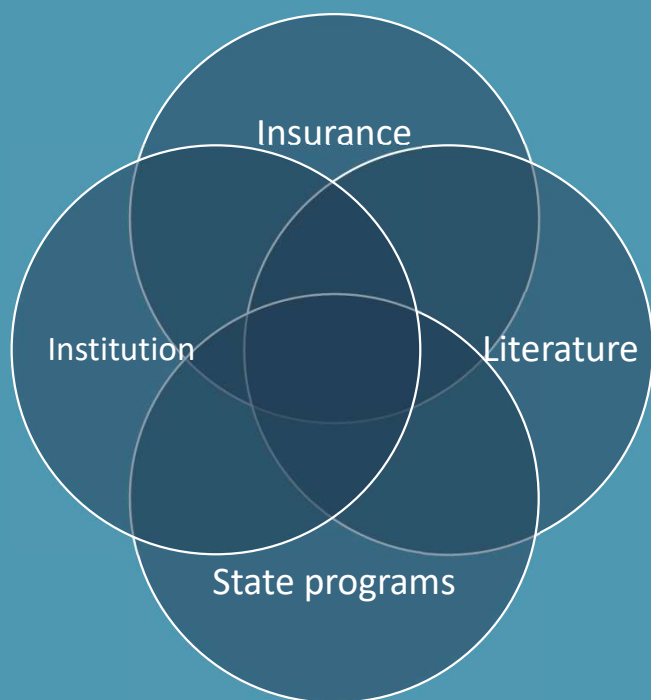
- If the patient criteria is too strict, will miss neonates that can benefit from a genetic diagnosis
- If the patient criteria is too loose, overuse (and expense of testing)

Other factors

- Evolving phenotype



Patient Selection Criteria



Literature

- Pilot studies
- Phenotype selection
- Reviews

State programs

Institutions

Insurance



Patient selection can be done various ways

Table 2 Rapid exome/genome sequencing studies in ICU infants

Patients		Selection	Type of sequencing	Diagnostic yield
Willig et al. ⁸	Child <4 months, acute illness with suspected genetic cause	By research team	Trio rapid GS	20/35 (57%)
Meng et al. ⁷	Child <100 days, referred for exome sequencing on clinical basis	By clinical provider (retrospective analysis)	ES, trio ES, rapid trio ES	102/278 (36.7%); rapid trio ES: 32/63 (50.8%)
van Diemen et al. ⁹	Critically ill children <1 year old in NICU or PICU with MCA or neurological symptoms	Multidisciplinary working group	Rapid GS	7/23 (30%)
Petrilkin et al. ¹¹	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	Rapid GS	22/63 (32%)
Farnaes et al. ¹⁰	Acutely ill infants <1 year old, nominated by clinical provider	By clinical provider (retrospective analysis)	Trio rapid GS	18/42 (43%)
Mestek-Boukhibar et al. ¹³	PICU and CICU patients	By multidisciplinary research team	Trio rapid GS with phased analysis	10/24 (42%)
French et al. ⁵	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	Trio rapid GS	40/195 (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



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.

Phenotype Driven Patient Selection

Genetics
inMedicine

ARTICLE

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Prospective, phenotype-driven selection of critically ill neonates for rapid exome sequencing is associated with high diagnostic yield

Cynthia S. Gubbels, MD, PhD^{1,2,3,4}, Grace E. VanNoy, MS^{1,3,4}, Jill A. Madden, PhD, MSc^{1,4}, Deborah Copenheaver, MS⁵, Sandra Yang, MS⁵, Monica H. Wojcik, MD^{1,2,3,4,6}, Nina B. Gold, MD^{1,2,7}, Casie A. Genetti, MS^{1,4}, Joan Stoler, MD^{1,2}, Richard B. Parad, MD, MPH^{2,8}, Sergei Roumiantsev, MD, PhD^{2,9}, Olaf Bodamer, MD, PhD^{1,2,3}, Alan H. Beggs, PhD^{1,2,4}, Jane Juusola, PhD, FACMG⁵, Pankaj B. Agrawal, MD, MMSc^{1,2,4,6} and Timothy W. Yu, MD, PhD^{1,2,3,4}

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	

Table 1 Characteristics of sequenced patients and diagnostic yield

	Number of patients	Number of diagnoses	Diagnostic yield (%)
Overall	50	29	58
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
Combined criteria			
Isolated hypotonia	1	1	100
Isolated seizures	1	0	0
Isolated MCA	11	5	45
Isolated metabolic	7	3	43
Isolated DSD	1	0	0
Hypotonia and seizures	6	6	100 ^a $p = 0.03$
Hypotonia and MCA	15	12	80 ^a $p = 0.04$
Hypotonia and metabolic	4	3	75
Seizures and MCA	6	6	100 ^a $p = 0.03$
Seizures and metabolic	2	2	100
MCA and metabolic	6	4	67

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.

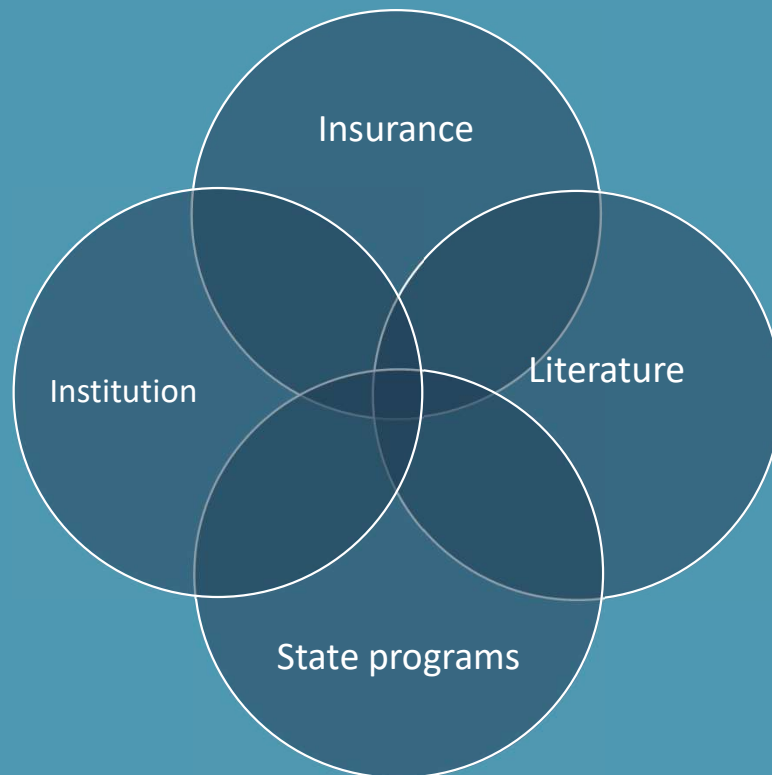
Recently Broader Patient Selection Criteria Have Been Proposed

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

To cite: Helm BM, Hays M, Swaggart KA, et al. Standardized Criteria for Genomic Testing in the NICU. *Pediatrics*. 2025; 156(1):e2024069591



Patient Selection criteria



Literature

- Pilot studies
- Phenotype selection
- Reviews

State programs

Institutions

Insurance



Patient selection in State/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)

Project Baby Bear Selection Criteria



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



Project Baby Deer Selection Criteria



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

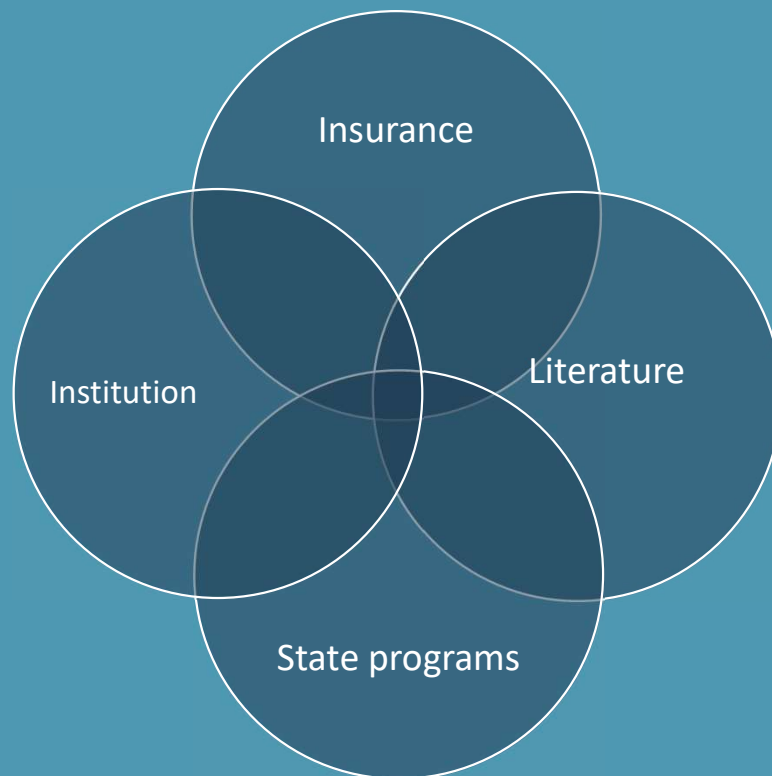
PRECISION MEDICINE IN MICHIGAN TO SAVE LIVES AND RESOURCES

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



Patient Selection criteria



Literature

- Pilot studies
- Phenotype selection
- Reviews

State programs

Institutions

Insurance



Institution Patient Selection Criteria

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



Institution Patient Selection Criteria

Seattle Children's - SeqFirst

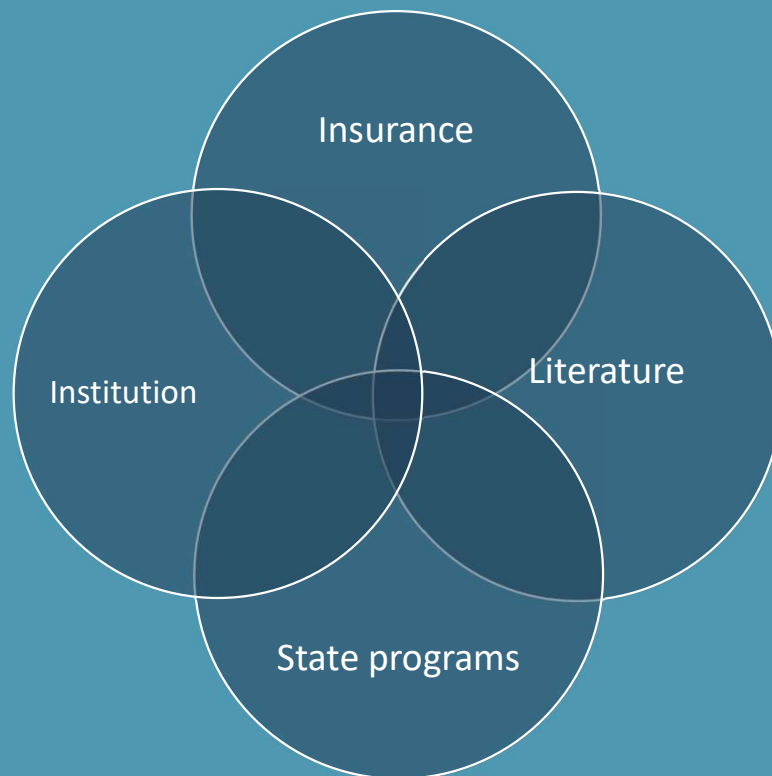
Exclusion criteria included:

- a corrected age >6 months or 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

Diagnostic yield - 50% (compared with conventional care group)



Patient Selection criteria



Literature

- Pilot studies
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Insurance



Insurer Patient Selection Criteria

United
HealthCare

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:
 - 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



Patient Selection Criteria

- 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 aneuploidyⁱ
- Concern for metabolic disorderⁱⁱ
- 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

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

ⁱⁱ 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?



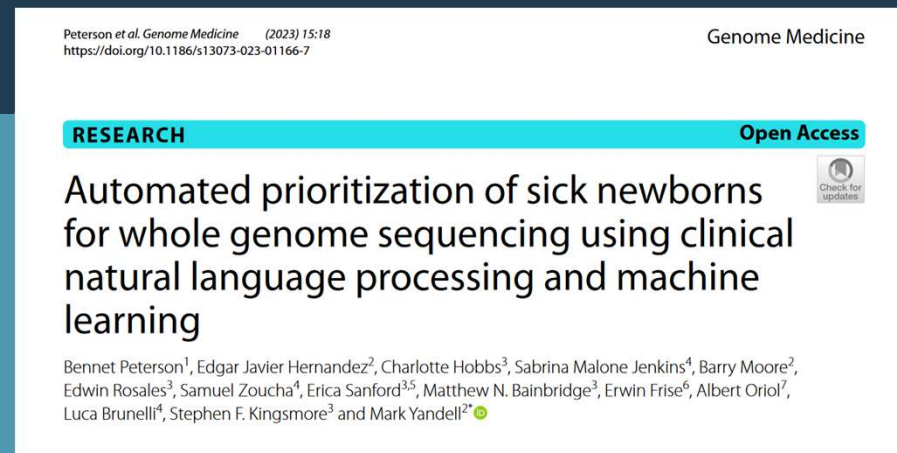
Criteria are to be guidelines to help in evaluation of patients
Identifying patients depends on clinical expertise of neonatologist.
Neonatologists are experts to decide on testing:

- Suspect Mendelian disorder
- Abnormal course
- Atypical preemie

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



Patient selection criteria – the future?



Clinical Documentation

