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

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May 31, 2024 @11:30
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)
USING EVIDENCE BASED CRITERIA TO IDENTIFY CRITICALLY ILL NEONATE CANDIDATES FOR GENOMIC TESTING
BBN PATIENT SELECTION CRITERIA

- Pilot studies
- Phenotype selection
- Reviews

- Insurance
- Institution
- State programs
- Literature
PATIENT SELECTION IN STATE MEDICAID PROGRAMS/BABY ANIMAL PROGRAMS

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

### State Medicaid Coverage for rWGS

<table>
<thead>
<tr>
<th>State</th>
<th>Policy</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona Medicaid</td>
<td>AHCCCS Reimbursement for Rapid Whole Genome Sequencing</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU)</td>
</tr>
<tr>
<td>California Medi-Cal</td>
<td>A 133 and reflected in Provider Bulletin 572</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU)</td>
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<tr>
<td>Florida Medicaid</td>
<td>Laboratory Services Coverage Policy (Agency for Health Care Administration)</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU)</td>
</tr>
<tr>
<td>Georgia Medicaid</td>
<td>January 2024 Update Laboratory Services</td>
<td>Not yet issued</td>
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<tr>
<td>Louisiana Medicaid</td>
<td>SB 154</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU) or Pediatric Care Unit; Louisiana Senate Bill 154 also requires that all private health plans cover rWGS subject to medical necessity criteria.</td>
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<tr>
<td>Maryland Medicaid</td>
<td>Lab Testing Policy</td>
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<tr>
<td>Michigan Medicaid</td>
<td>Lab Policy MSA 21-32, State Plan Amendment if ME-21-0010</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU)</td>
</tr>
<tr>
<td>Minnesota Medicaid</td>
<td>Lab &amp; Pathology Services Provider Manual</td>
<td>No age restriction for pediatric critical care unit; ICU (NICU/PCU/CVICU)</td>
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<tr>
<td>Oregon Medicaid</td>
<td>Prioritized Health Services List</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU)</td>
</tr>
<tr>
<td>Utah Medicaid</td>
<td>Medicaid Information Bulletin November 2023; 23-82 Physician and EPSDT Services Provider Manual Revisions</td>
<td>≤ 1 year; ICU (NICU/PCU/CVICU)</td>
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</tbody>
</table>
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

Michigan

Diagnosis: 39%
Change in care: 27%
## 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 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)
United-Healthcare Commercial and Individual Exchange Medical Policy
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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 gene
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
- Concern for metabolic disorder
- 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

\(^1\) 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
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
Automated prioritization of sick newborns for whole genome sequencing using clinical natural language processing and machine learning

Peterson et al. Genome Medicine (2023) 15:18
https://doi.org/10.1186/s13003-023-0166-7

RESEARCH Open Access

Patient Care -> Clinical Documentation + Machine Learning -> Patient Selection
<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>SOLUTIONS</th>
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<tr>
<td>Workforce concerns in genetics</td>
<td>Collaboration between clinicians, laboratories, hospital administrators, patients/caregivers, patient advocacy groups, policymakers, payers</td>
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<tr>
<td>Health care costs</td>
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<tr>
<td>Who to test?</td>
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<td>Timing and speed of results</td>
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<td>Communication with family surrounding consent and results.</td>
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<td>Long term follow-up of testing results.</td>
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</table>

And more...