Rapid Sequencing of Known Mendelian Genes in Neonatal ICU Patients (NICU)

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Professor of Pathology, University of Utah

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Objectives

- Describe the state-of-the-art next-generation sequencing technology improving the precision medicine in NICU patients.
- Describe the collaboration between ARUP and Primary Children Medical Center (PCMC) NICU on the rapid sequencing of known Mendelian genes panel (RapidSeq Panel).
- Explain the advantages of rapid turnaround RapidSeq Panel in relation to whole exome and whole genome sequencing.
- Discuss the limitations, case selections, and present the interesting cases.
Case 1

- Two weeks old, Caucasian male
- Respiratory failure, incubated at delivery
- Hypotonia, absence of intentional movements, absence of cranial nerve reflexes, contractures of shoulder, upper and lower limbs
- Mildly dilated hypertrophied right ventricle
Case 1

• Dysmorphic facial features: sparse eyebrows, sloping forehead, thickened nares, recessed jaw

• Small penis and undescended testes

• Born at term with birth weight of 3520 grams (42%) and length at 75th percentile and HC at 17th %

• First child, no family history of the same condition
Case 1

- Normal Laboratory testing
  - brain MRI
  - SMA testing (spinal muscular atrophy)
  - carbohydrate deficient transferrin (CDG)
  - SNP microarray
Neonatal ICU (NICU)

• SOME BABIES NEED SPEICAL CARE
  – If a child is premature or has health problems at birth, such as an infection or respiratory stress, he or she may need to spend some time in the special area with facilities for special care ....

THE NICU
Most Common Diseases in NICU

- Respiratory Distress Syndrome (RDS)
- Transient Tachypnea of the Newborn (TTN)
- Patent Ductus Arterious (PDA)
- Meconium Aspiration Syndrome (MAS)
- Persistent Pulmonary Hypertension (PPHN)
- Wilson-Mikity Syndrome (Pulmonary Dysmaturity)
- Bronchopulmonary Dysplasia (BPD)
- Diaphragmatic Hernia
- Pulmonary Barotrauma and Air Leak Syndromes
- Trans-illumination
- Necrotizing Enterocolitis (NEC)
- Congenital Cardiac Anomalies

10-15% of patients are due to monogenic genetic diseases
NICU - High Mortality

- According to the March of Dimes, about 150,000 babies are born with birth defects each year in the United States.

- 3 out of every 100 babies born in the United States have some kind of major birth defect, severe, NICU

- Birth defects can be caused by genetic, environmental, or unknown factors. For most birth defects, the cause is believed to be an interaction of a number of genetic and environmental factors.

- High mortality
Costs analysis - PCMC at UU

• The median variable cost per day is $1,379, with the 75th percentile at $1,662

• **Median stay in NICU is 35 days**

• Looking at 2013-2016, we average ~38 deaths per year in the NICU

• ~35 per year have support withdrawn

• The reasons given: (table)

Courtesy to Steven Bleyl
### Age when support withdrawn (2013-2016)

<table>
<thead>
<tr>
<th>Mortality Primary Cause of</th>
<th>Patients</th>
<th>Average Age (Days) at death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomaly or Syndrome</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Central Nervous System(CNS) Injury</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>GI/Intra-abdominal Catastrophe</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Inborn Error</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>Massive Hemorrhage/Coagulopathy</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>Multi-organ System failure</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>33</td>
<td>59</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td>139</td>
<td>32</td>
</tr>
</tbody>
</table>

Courtesy to Steven Bleyl
Critical for NICU

- The quick and precise diagnosis of disease
  - Neonatal presentation atypical: hypotonia, respiratory distress, abnormal metabolism

- Effective treatment
  - Many diseases are treatable: metabolic diseases

- Reduce mortality rate
ARUP R&D and Bioinformatics
• Shale Dames
• Rong Mao
• Pinar Bayrak-Toydemir
• Karl Voelkerding
• Brendan O’Fallon
• Erica Cuttitta

ARUP Genetics Counselor and Sequence Analyst
• Chris Miller
• Tatiana Tvrdik

Primary Children Hospital NICU, University of Utah
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• Luca Brunelli (chief of NICU)
• Ted Pysher
• Lorenzo Botto
• Robert Christensen
• Christian Con Yost
• Elizabeth O’Brien
• Stephen Guthery
• Joshua Bonkowsky
• Betsy Ostrander
• Susan Morelli
• Seth Andrews
• Jim Gudgeon
• Roger Faiz
Rapid Genomic Sequencing (RapidSeq Panel) for NICU

• **Content:**
  - 4,503 HGMD genes for inherited diseases
  - 98% Overlapping with OMIM 4000 known disease-causing genes

• **Advantage**
  - Targeted 15 Mb design
  - Consistent performance and high uniformity
  - Cost: 4 days in NICU
Why 4503 Gene Panel?

• Compare 4500 gene panel vs Exome vs whole genome
  – Includes most known disease-causing genes
  – Rapid TAT: 3-4 days of 4500 gene panel vs 24-29 days for exome
  – Cost effective: 1/6 of whole genome sequencing cost
  – Focus on targeted region, deep sequencing 300-500X mean
Rapid Turnaround Time

**Work flow:**
- DNA (Sheared DNA)
- Library prep
- Enrichment (RNA or DNA beads in solution)
- Barcoding
- Cluster generation
- Sequencing
- Data Analysis

**Time Frame:**

<table>
<thead>
<tr>
<th>Exome</th>
<th>RapidSeq</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 days</td>
<td>1 day</td>
</tr>
<tr>
<td>1 day</td>
<td>6 hours</td>
</tr>
<tr>
<td>14 days for paired-end</td>
<td>29 hours</td>
</tr>
<tr>
<td>5-10 days</td>
<td>1-4 days</td>
</tr>
</tbody>
</table>

**Total:**
- 24-29 days
- 3-4 days
RapidSeq Coverage >99% for the targeted regions with 20X
## Comparison RapidSeq vs Exome Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Rapid Seq Panel</th>
<th>Exome Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>4500+</td>
<td>~20,000</td>
</tr>
<tr>
<td>TAT</td>
<td>14-28 days</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>Family Members</td>
<td>Parental samples required (trio)</td>
<td>Proband only, Trio, Trio + other informative family members</td>
</tr>
<tr>
<td>ACMG Secondary Variants</td>
<td>Reported if desired for proband only</td>
<td>Reported if desired for proband and family members</td>
</tr>
<tr>
<td>Sanger Confirmation</td>
<td>When necessary</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Courtesy to Tatiana Tvrzik
**Process Overview**

- **High acuity candidate patient as judged by NICU staff and consultants**

  - NICU/Consultant:
    - Do **Pre-test counseling**
    - Consultant fills out forms:
      - **patient phenotype**
      - **consent documents**
    - Database (REDCAP database) entry by ordering CGI

  - **Testing**

  - **Preliminary results (7 days):**
    - Counseling
    - Management changes
    - Data entry by CGI

  - **Final results (3-4 weeks):**
    - Counseling
    - Management changes
    - Data entry

- **NICU RTIDS committee review of data and results quarterly**

- **NICU, <1 year only (to start)**
- **Trio (parents/child)**
- **Consent and intake done by ordering MD**
Rapid Seq Test Inclusion Criteria

- Patient’s disease is plausibly monogenic
- Making diagnosis will alter acute decision-making
- Alternative testing is not available, more costly or protracted
- Trio (patient and both parents) available

Brunelli et al. 2018, submitted manuscript
Sample Collection

- Submit everything together
  - Trio: proband and parents’ samples
  - Signed consent
  - Completed patient history form
  - Abnormal genomic microarray or MRI results
  - Clinical and genetics summary notes

- Turnaround time won’t start until everything received

Courtesy to Chris Miller
Consent

• Genetic counselor, NICU attending, nurse
• Should be face to face
• We are only examining 4500 genes with known function out of over 20,000 that exist
• Even if genes have known function, some mutations are not detectable with this technology
• Some conditions are not caused by DNA changes
• Not report ACMG secondary finding (Revised)

Courtesy to Chris Miller
Case 2

- 38-day old female
- Hydrops and respiratory failure
- Heart defect: prenatal ultrasound found single ventricle, pulmonary valve atresia, left aortic valve stenosis
- Recently progressive cholestasis, suspect Dx of Alagille syndrome
- Family hx: mother has HCM and carrying MHY7 variant c. 740T>G, p.Phe247Cys (LP)
- Died at 3 months, from congenital heart defect leading to respiratory failure
Case 2

- Results: Negative

MYH7 Variant

F247C/--
HCM

Proband

Mother

Father

c.740T>G, p.Phe247Cys

Results: Negative
Case 2: Secondary Finding

BRCA1 Variant

c.2035A>T, p.Lys679Stop

30's

L679*/--

Proband

Mother

Father
Results Could Be Upsetting

- Results may not be informative
- Child may have a condition that is not treatable
- A parent could carry or be at risk for the same medical condition as child
- Parents may have an increased risk to have additional children with the same condition

Courtesy to Chris Miller
Parental Samples

- Must accompany infant’s sample
- Must know if parent has any birth defects, learning problems, other conditions, etc.
- Full sequencing is performed
- Used to determine significance of variant
  - Is variant de novo?
  - Is variant in healthy adult?
  - Confirm autosomal recessive

Courtesy to Chris Miller
Non-Paternity

- Will be detected
- May render result uninterpretable
- If this is a possibility, tell GC before sequencing
Data Analysis and Interpretation

• Preliminary Report: 7-14 days
  – Disease-causing mutation responsible for patient phenotype
    • Recessive disease: one loss of function mutation and one variant
  – De novo mutations
  – Sanger confirmation when necessary (deletion/insertions)

• Follow-up call to make sure someone received
Data Analysis and Interpretation

- Final Report: 21-28 days

- Positive report: lists gene and variant(s) believed related to phenotype

- Negative for preliminary report, 4500 genes analysis and report based on proband phenotype
  - Uncertain report: several gene variants will be reported that may or may not be causative for phenotype
  - Negative report: no variants detected believed related to phenotype; does not mean genetic cause has been excluded
Storage and Information Sharing

• De-identified DNA stored indefinitely
  – For test validation purposes
• De-identified data shared with national/international databases
  – Aids clinicians understanding of significance of variants

Courtesy to Chris Miller
Case 1

- Perform RapidSeq in two weeks after the baby admitted to NICU
- Trio (proband and parents)
Case 1

- HGMD Matches: 1% frequency, 27 variants

**CHAT gene**

- **Father**
  - V136M/--
  - E555L/--
- **Mother**
  - V136M/E555L
Case 1

Mutation 1 in CHAT

c.406G>A, p.Val136Met
Case 1

Mutation 2 in CHAT

c.1663G>A, p.Glu555Lys

Proband

Father

Mother
Case 1  

CHAT Gene

- **CHAT**: Choline Acetyltransferase (OMIM:254310). It is the biosynthetic enzyme for the neurotransmitter acetylcholine in the central and peripheral nervous systems.
Case 1  CHAT Gene Mutations

• Congenital Myasthenic Syndrome (CMS)
• Autosomal Recessive
• Affect the neuromuscular junction. Presents with muscle weakness between infancy and adulthood: hypotonia, respiratory distress/insufficiency due to muscle weakness, arthrogryposis, etc.
• Treatment: acetylcholinesterase inhibitors: Neostigmine (aniticholinesterase agent)
Case 1

• Preliminary report within 5 days
• Final report in 7 days
• Patient had a trial treatment with Neostigmine, and improved motor function. Discharged from NICU a week later.

Quick diagnosis of the disease can make differences in patient care.

Brunelli, et al, AJMG 201712:1002-1005
Case 3

- A PICU patient
- Clinical information
  - Four months old female, Native American ancestry
  - Acute liver failure and cholestasis
  - No family history of any birth defects, intellectual deficiency
  - Purpose for testing: rule out genetic causes of liver failure. Physician request to pay special attention to *CIRH1A (UPT4)* and *MPV17* genes; autosomal recessive childhood cirrhosis and progressive liver failure
Case 2

- PICU Trio to test:
  - Proband
  - Parental samples
Case 3

- Data review and interpretation
  - *CIRH1A* and *MPV17* gene well-covered by NGS, no rare variants detected
  - A panel of cholestasis and liver failure, well-covered and no rare variants

AGL, ABCB11, ABCB4, ABCB11, ABCC2, ABCG5, ABCG8, AKR1D1, ALDOB, ARG1, ASL, ASS1, ATP7B, ATP8B1, BAAT, BCS1L, CC2D2A, CCR5, CFTR, CLDN1, CPT1A, CYP27A1, CYP7A1, CYP7B1, DGUOK, DHCR7, EPHX1, FAH, FBP1, G6PC, GAA, GBE1, GYS2, HFE, HNF1B, HSD3B7, IFNG, INVS, JAG1, LIPA, MBOAT7, MKS1, MPV17, NOS3, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, NR1H4, PCK1, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PHKA2, PHKB, PHKG2, PKHD1, PRKCSH, POLG, PTPRC, PYGL, SERPINA1, SLC2A2, SLC10A1, SLC25A13, SLC27A5, SLC37A4, SLCO1B3, SLCO1B1, SMPD1, TJP2, TMEM216, TRMU, TYR, UGT1A1, VIPAS39, VPS33B.

Negative result is important prior liver transplantation.
Limitation of RapidSeq Panel

• Regions missing
  - deep intronic region, 5’ and 3’ UTRs, repetitive regions, and pseudogenes

• Genes not included
  • trinucleotide repeats, imprinting genes, etc.

• Detect CNVs: in development, not ready yet
Case 4

- 15 days old, baby girl, Caucasian
- Delivered by emergent C-section at 32 weeks gestation due to non-immune hydrops
- Cyanotic and without respiratory effort
- Thrombocytopenia, possible contractures
- No family history
- In NICU after birth

Courtesy to Tatiana Tvrdik
Case 4

Previous testing

- Normal karyotype
- Normal CMA SNP
- MPS Screen – suggestive of Mucopolysaccharidosis type VII

RapidSeq

- Trio (proband+parents)

Courtesy to Tatiana Tvrdik
Case 4

GUSB c.1A>C, p.Met1? Variant

Poband: Homozygous

Mother: Heterozygous

Father: None?
Case 4

GUSB: Autosomal recessive, Mucopolysaccharidosis VII (MPS7, OMIM:611499)
Case 4

IGV GUSB

Proband

Mother

Father

GUSB

Courtesy to Tatiana Tvrdik
Case 4

CNV Analysis by Depth of Reads (Dr. Wei Shen)

Deletion of exon 1-8
Confirmed by CytoScan XON (Exome Microarray)

9KB deletion including GUSB exons 1-8 (268 markers)

Courtesy to Tatiana Tvrdik and Xinjie Xu
Case 4 Genotype

\[ \text{GUSB} \]

\[ \text{Del exon 1-8/--} \]

\[ \text{M1?/--} \]

\[ \text{M1?/Del exon 1-8} \]
Mucopolysaccharidosis type VII

- Also known as Sly syndrome
- Caused by biallelic pathogenic variants in the *GUSB* gene
- Defect in the enzyme: beta glucuronidase
- Accumulation of GAGs (glycosaminoglycans) causes dysfunction of multiple organs
- Skeletal anomalies and short stature, **pulmonary disease**, cardiovascular complications, **joint stiffness**, **hepatosplenomegaly**, hernias, coarse features, corneal clouding, and varying degrees of intellectual disability, **prenatal hydrops**

Courtesy to Tatiana Tvrdik
Summary of first 50 Cases
Phenotypes

Multiple Anomalies | Neuromuscular | Respiratory Failure | Liver Failure | Heart Defect | Recognizable Syndrome

0 | 0 | 0 | 0 | 0 | 0

18 | 16 | 14 | 12 | 10 | 8

Column 1
RapidSeq Diagnostic Yield and TAT

• Positive: 25/50 (50%)

• Twenty-five positive cases: 13 De Novo, 11 Recessive, 1 dominant (maternal inherited)

• Partially positive 1/50 (2%) – inherited

• Negative 20/50 (40%)

• Uncertain 4/50 (8%)

• All genes are OMIM/HGMD known disease-causing genes

• Average prelim report issued in 9 days, final reports in 16 days (8-37 days)
Other Rapid Tests on the Market

- Baylor: Critical Trio Whole Exome Sequencing, TAT 2 weeks
- GeneDx: XomeDxXpress (WES with a verbal Result in 7 Days), TAT 2 weeks
- Ambry: ExomeNext-Rapid, TAT 8-14 days
- PerkinElmer: WES – STAT – 7-10 days
- Fulgent: Clinical Exome (4681 genes)
- Rady: rapid Whole Genome Sequencing (rWGS) (currently research only)

Courtesy to Tatiana Tvrdik
Rapid Whole Genome Sequencing

Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization

LaRge Farnaes1,2, Amber Hildreth1,2, Nathaly M. Sweeney1,2, Michelle M. Clark1, Shimul Chowdhury1, Shareef Nahas1, Julie A. Cakici1, Wendy Benson1, Robert H. Kaplan3, Richard Kronick4, Matthew N. Bainbridge1, Jennifer Friedman1,2,5, Jeffrey J. Gold1,5, Yan Ding1, Narayanan Veeraraghavan1, David Dimmock1 and Stephen F. Kingsmore1

Rady Children Hospital: rapid Whole Genome Sequencing (rWGS) in NICU, PICU and cardiovascular intensive care unite (currently research only)
Rapid Whole Genome Sequencing

• rWGS performed in 42 cases: 29 trios, 1 quad, 9 mother-infant duos, 3 proband only

• Positive yield: 18 (43%) diagnosed by rWGS, 4 (10%) diagnosed by standard test

• TAT: two weeks

• 18 genes are included in the Rapid Seq 4500+ Gene Panel
Rapid Mendelian Genes Sequencing Panel, Trio

- The panel updated: ~4900 genes
- Specimens: peripheral blood
- TAT: 2-4 weeks
- Only final report (no preliminary report)
- Trio: require proband and parental specimens
- Consent required
Additional Technical Information

- Tests to consider
- Test overview
- Test Interpretation
  - Clinical sensitivity
  - Reporting and interpretation
  - Secondary findings
  - Limitations
  - Analytical sensitivity and specificity

Rapid Mendelian Genes Sequencing Panel, Trio

Mendelian diseases are inherited conditions linked to individual genes. This test entails rapid sequencing of ~4,900 genes of known function from a critically ill individual and both parents to quickly diagnose a Mendelian disease to improve medical management.

TEST OVERVIEW
- Although humans have ~19,000 genes, the function of only ~4,900 genes is known.
  - This test only sequences genes with known function
- See Rapid Mendelian Sequencing Gene List for genes included in this panel.
- Parental specimens are required to identify de novo variants and to determine phase and clinical significance of variants detected in proband.

TESTS TO CONSIDER
Rapid Mendelian Genes Sequencing Panel, Trio 2012849
Method: Massively Parallel Sequencing
Order for rapid diagnosis of a critically ill individual suspected to be affected with a Mendelian genetic condition

See Related Tests
Informed Consent and Patient History

<table>
<thead>
<tr>
<th>INFORMED CONSENT FOR RAPID MENDELIAN GENES SEQUENCING PANEL, TRIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name: ________________________ Date of Birth: ________ Sex: □ F □ M</td>
</tr>
<tr>
<td>Symptoms: □ No □ Unknown □ Yes (please describe): __________</td>
</tr>
<tr>
<td>Test Description and Purpose:</td>
</tr>
<tr>
<td>• The Rapid Mendelian Genes Sequencing Panel involves determining the presence of mutations in genes known to be associated with genetic disorders.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT HISTORY FOR RAPID MENDELIAN GENES SEQUENCING PANEL, TRIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name: ________________________ Date of Birth: ________ Sex: □ F □ M</td>
</tr>
<tr>
<td>Physician: ___________________________ Physician Email: ________</td>
</tr>
<tr>
<td>Practice Specialty: ___________________ Physician Fax: ________</td>
</tr>
<tr>
<td>Genetic Counselor: ____________________ Counselor Phone: __________</td>
</tr>
<tr>
<td>Patient’s Ethnicity (check all that apply):</td>
</tr>
<tr>
<td>□ African-American □ Asian □ Hispanic □ Native American</td>
</tr>
<tr>
<td>□ Ashkenazi Jewish □ Caucasian □ Middle Eastern □ Other: _______</td>
</tr>
</tbody>
</table>

What is the patient’s suspected clinical diagnosis / indication for testing? ____________________________

List specific genes of interest: ____________________________
# Rapid Mendelian Sequencing Gene List

<table>
<thead>
<tr>
<th>Gene</th>
<th>Coding Exons Not Covered</th>
<th>OMIM Number</th>
<th>Gene Aliases</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADK</td>
<td></td>
<td>102750</td>
<td>AK</td>
</tr>
<tr>
<td>ADNP</td>
<td></td>
<td>611386</td>
<td>KIAA0784, ADNP1</td>
</tr>
<tr>
<td>ADORA1</td>
<td></td>
<td>102775</td>
<td>RDC7</td>
</tr>
<tr>
<td>ADORA2A</td>
<td></td>
<td>102776</td>
<td>ADORA2, RDC8</td>
</tr>
<tr>
<td>ADRA1A</td>
<td>NM_001322503.1: 2</td>
<td>104221</td>
<td>ADRA1C, ADRA1L1</td>
</tr>
<tr>
<td></td>
<td>NM_033303.4: 3</td>
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<tr>
<td>ADRA2A</td>
<td></td>
<td>104210</td>
<td>ADRA2, ADRA2R, ADRAR</td>
</tr>
<tr>
<td>ADRA2B</td>
<td></td>
<td>104260</td>
<td>ADRA2L1, ADRA2RL1, ADRARL1</td>
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<tr>
<td>ADRA2C</td>
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<tr>
<td>ADRB1</td>
<td></td>
<td>109630</td>
<td>ADRB1R</td>
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<tr>
<td>ADRB2</td>
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<td>ADRB3</td>
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<td>608222</td>
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<tr>
<td>ADSSL1</td>
<td></td>
<td>612498</td>
<td>FLJ38602</td>
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<tr>
<td>AEBP1</td>
<td></td>
<td>602981</td>
<td>ACLP</td>
</tr>
</tbody>
</table>
Conclusion

- Rapid Mendelian Genes Sequencing Panel with 4900 known disease-causing genes will improve the precision diagnosis of disease in neonatal intensive care.
- Guide for precision treatment
- Reduce the mortality and cost in NICU
- Building the communication between clinicians and laboratorians is critical for the data interpretation and result delivery.
Acknowledgement

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- Shale Dames
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ARUP Genomics Laboratory