Impact of Rapid Whole Exome Sequencing on Pediatric Intensive Care Patients with Acute Cardiomyopathies

Tameemi Abdalla Moady[1], Tova Hershkovitz[1,2], Clair Habib[1], Ori Attias[3], Amir Hadash[3,4], Galit Tal[3,5], Asaad Khoury[3,6], Josef Ben-Ari[3,4], Tamar Paperna[1], Karin Weiss[1,3]

רמב"ם
הקריה הרפואית לבריאות האדם

- Pediatric CM are very rare but significantly influence morbidity and mortality

- Genetic CM can be primary affecting only muscle myocardium structure and function or could be part of a wider multisystem disorder including rasopathies, mitochondrial and metabolic and neuromuscular disorders

- Pediatric CM can present with rapid deterioration especially in infants under 1Y and rapid work up is crucial in these patients

- NGS has significantly reduced the turnaround time (TAT) to get results and has higher molecular diagnosis

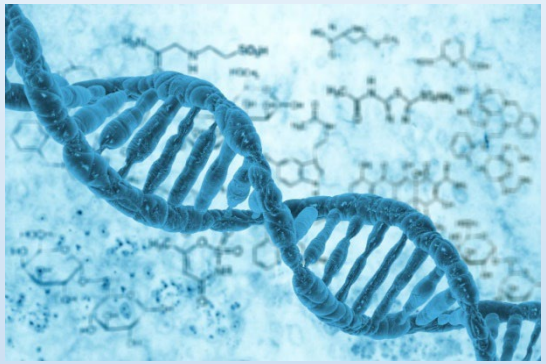
✓ Better
✓ Cheaper
✓ Faster

- Rapid (7–21days) and ultra-rapid (24 hours-7 days) rWES/rWGS is beneficial as first tier work up in infants and children suspected to have a monogenic disorders in urgent settings

- The diagnostic yield and benefits reported widely vary depending on the phenotype

- Very few studies on rapid sequencing impact in pediatric CM

Impact of Rapid Whole Exome Sequencing On Pediatric Intensive Care Patients with Acute Cardiomyopathies



Retrospective study
0-18y admitted to PICU
From 2021 to 2023
Patients with major heart malformations or previous medical issues were excluded

Major outcomes: TAT, diagnostic yield, impact on management
Minor outcomes: Family segregation, PND, secondary findings

Results

patient	Gender	age	cardiac manifestaion	TAT	Exome results	FU
1	M	6W	DCM+NC	8 days	ACTC1: c.664G>A, DN, LP	palliative
2	F	10d	HCM	7days	MYBPC3:c.3491-2A>C ,HOM, P	palliative
3	M	1 Y	HCM+DCM	10 days	IARS2: c.3G>T ,HOM,VUS ?	HT
4	F	6m	DCM	14days	CDH2:c.970A>T, HET, VUS, GSD3 carrier	waiting HT
5	F	11m	DCM	9 days	none	palliative
6	M	13d	HCM+arrythmia	5days	MYBPC3:c.1504C>T, HET,P + CACNA1C:c.1252C>T, HET,VUS	cardiac FU
7	M	11.5 Y	RCM+HCM+VF	14days	TNNI3 : c.509G>A;p.Arg170Gln,DN,P	ICD+cardiac FU
8	F	6W	NC+VSD+ASD	9days	NKX2-5:c.693dup, HET,P	cardiac FU

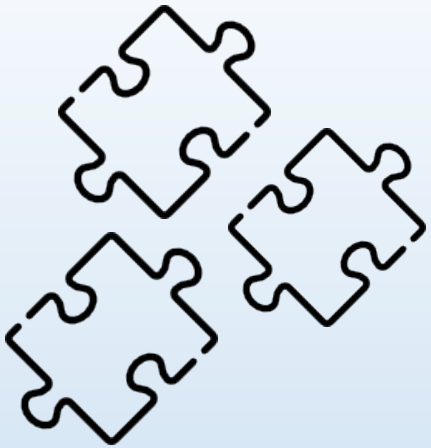
7/8 cases presented by age 1 year
Family history in one case only
M=F

- TAT ranged from 5-14 days (average of 9 days)
- The diagnostic yield was 5/8 (62.5%)

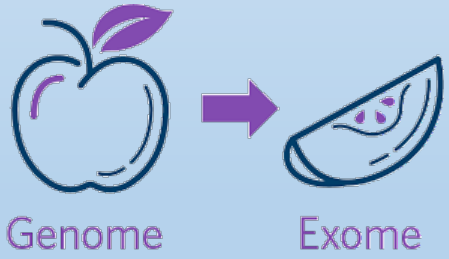
patient	Gender	age	cardiac manifestaion	TAT	Exome results	Impact
1	M	6W	DCM+NC	8 days	ACTC1: c.664G>A, DN, LP	palliative passed 4.5m
2	F	10d	HCM	7days	MYBPC3:c.3491-2A>C ,HOM, P	palliative passed 45d
3	M	1 Y	HCM+DCM	10 days	IARS2: c.3G>T ,HOM,VUS ?	HT
4	F	6m	DCM	14days	CDH2:c.970A>T, HET, VUS, GSD3 carrier	waiting HT
5	F	11m	DCM	9 days	none	palliative
6	M	13d	HCM+arrythmia	5days	MYBPC3:c.1504C>T, HET,P + CACNA1C:c.1252C>T, HET,VUS	cardiac FU
7	M	11.5 Y	RCM+HCM+VF	14days	TNNI3 : c.509G>A;p.Arg170Gln,DN,P	ICD+cardiac FU
8	F	6W	NC+VSD+ASD	9days	NKX2-5:c.693dup, HET,P	cardiac FU

- 2 families with no history started cardiac FU (2,6)
- 2 DN cases no cardiac FU needed for family members (1,7)
- Family segregation in case 8
- Accurate recurrence risk estimation and PND and/or PGD
- Secondary findings: MYBPC3 carriers
  - One incidental finding (AGL)

Limitations



- Retrospective study
- Small sample size (rare)
- Single analysis compared to trio (cascade screening)
- WES compared to WGS



- Lack of health care funding and resources (Baby4Kid)

Conclusions

Rapid exome sequencing integration as part of routine clinical practice for patients with CM in acute settings is recommended:

- High molecular yield
- Clinical utility in identifying the genetic diagnosis and impacting immediate and long-term management
- Impact on family members (cardiac FU)
- Impact on future family planning

ACKNOWLEDGMENTS

Human Genetics Institute staff
Molecular Lab staff

PICU staff

Metabolic unit

Pediatric Cardiology unit