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Rapid Genomic Testing in the Diagnosis of Mendelian Disorders

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Role of ultra-rapid exome sequencing in critically ill infants and children (Lunke et al., 2020)

This study was conducted in Australia to evaluate the feasibility of ultra-rapid exome sequencing in critically ill pediatric patients. A total of 108 sick children with a median age of 28 days, underwent exome sequencing. Fifty five out of 108 patients (51%) received a molecular diagnosis within the median time of 3.3 days. Additional 11 children (20%) received a diagnosis by supplementary genetic tests like copy number analysis of exome data, mitochondrial genome sequencing, RNA analysis and additional phenotyping. Of the 55 patients who received a diagnosis, 42 patients had a significant change in management. Negative results also lead to changes in management in 6 out of 53 (11%) cases. Based on the positivity rate and clinical utility, the authors suggested that ultra-rapid exome sequencing is a feasible testing option in critically ill pediatric patients with suspected monogenic conditions in the Australian public health care system.

Clinical utility of rapid next generation sequencing: physicians' perspectives (Dimmock et al., 2020)

As a part of the Newborn Sequencing Genomic Medicine and Public Health 2 (NSIGHT2) study, 189 seriously ill infants with diseases of unknown etiology were randomised to exome versus genome sequencing, initially as solo, and then as trios. The diagnostic yield was similar between both groups [exome sequencing: 18/95 (19%) and genome sequencing: 18/94 (19%)]. The time taken to report was also comparable in both groups (exome sequencing: 11.2 days and genome sequencing: 11 days). However, analytic performance of genome sequencing was better. Of the 153 cases who had negative results by solo sequencing, trios were performed in 104 infants. Only one extra patient was diagnosed by trio exome sequencing. Apart from this, 24 neonates who were considered too sick to await results for 10 days, underwent ultra-rapid trio genome sequencing. The diagnostic yield was better than exome or genome (11/24; 46%) and the mean time for report was 4.6 days.

Clinicians involved in direct care of newborns (intensivists, pediatricians) were interviewed on the clinical utility of rapid next generation sequencing. Clinician responses were available for 201 cases. Overall, clinicians believed rapid next generation sequencing was useful in 154 out of 201 cases (77%), including positive and negative results. Even though positive results were associated with more changes in outcome (42/45; 93%), 112 of 156 (72%) cases with negative results were also considered to have clinical utility. This emphasizes the role of rapid next generation sequencing in providing directions for care when a result is available and also to narrow down differential diagnoses when the result is negative.

Rapid exome sequencing in fetuses with congenital anomalies (Deden et al., 2020)

Fifty four pregnancies with multiple congenital anomalies detected by ultrasound in the fetus with a likely genetic diagnosis, were recruited for rapid exome sequencing. These fetuses were grouped into 3 groups – skeletal dysplasia, multiple major congenital anomalies, and intracerebral structural anomalies. Overall, 18 of the 54 fetuses (33%)

received a diagnosis with a median time of 10 days, of which skeletal dysplasia constituted the majority (11 of 54; 20%). In a survey, physicians indicated that rapid exome sequencing results influenced clinical decision making in 68% of cases. Rapid exome sequencing improves prenatal diagnosis of fetuses with congenital anomalies, and aids in prenatal and peripartum parental and clinical decision making.

Parents' perspective (Cakici et al., 2020)

As a continuation of the NSIGHT2 study, parents of children who underwent rapid next generation sequencing were interviewed on their perceptions on the utility, consenting and harms involved with rapid next generation sequencing. Out of 161, 156 (97%) parents believed testing was somewhat useful on a Likert scale, even though molecular diagnosis was made only in 23% infants. Only a few parents (~5%) reported harm, stress or confusion. Positive results were useful in managing symptoms of their infants. Rapid next generation sequencing was perceived as beneficial by parents in infants with unknown diagnosis in the intensive care unit.

Extra counseling support for parents (Hill et al., 2020)

Forty critically ill children with a likely monogenic disorder were recruited for trio rapid genome sequencing in the Rapid Paediatric Sequencing (RaPS) study. Face-to-face and telephonic interviews were conducted for 11 parents and 19 professionals to assess their perspectives on rapid genome sequencing. Both the parents and professionals believed rapid genome sequencing had clinical benefits in the form of obtaining diagnosis, ruling out differentials and future pregnancy planning. In addition, professionals opined rapid genome sequencing influenced patient management, deciding palliative care and reduction of unwanted invasive procedures that lead to reduction in cost. Psychological benefits reported by parents included relief, reassurance, and greater certainty. However, additional psychosocial support is recommended by authors to parents as they are likely to have increased stress, especially in a critical setting, and when waiting for results.

References

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