Editorial

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Rapid Targeted Genomic Testing: A Powerful Tool for Diagnostic Evaluation of Critically Ill Neonates and Infants With Suspected Genetic Diseases

Genetic diseases and congenital malformations have been found in approximately 14% of all hospitalized children in neonatal intensive care units in developed countries [1, 2]. These afflictions are the leading cause of a neonatal mortality of 20%–34% [3, 4], and patients with genetic diseases require longer hospitalization than those without genetic diseases [5]. In 2020, the Korean Ministry of Health and Welfare reported that congenital malformations, chromosomal abnormalities, and genetic diseases are among the leading causes of death in children during the first year of life [6]. According to the same report, 115 infants under the age of 1 year died from congenital malformations and chromosomal abnormalities, accounting for 17.1% of the total deaths for this age group [6].

Diagnosing genetic diseases based on the clinical presentation of critically ill newborns and early infants is challenging. The symptoms and features of known genetic syndromes may not be present at birth, may change rapidly, and may be difficult to observe in a child on life support [7]. The standard genetic diagnostic workup for sequential testing of disease-associated genes considered in preliminary diagnosis is time-consuming, often referred to as a "diagnostic odyssey." Routine genetic diagnostics for children with suspected genetic diseases include molecular and cytogenetic testing to identify large and structural chromosomal variations, as well as single-gene and gene-panel testing [8]. Turnaround times (TATs) of these diagnostic procedures range from 2 to 8 weeks or more, and more time is required to make a final diagnosis if multiple consecutive tests are needed. There is an urgent need to accelerate this process in critically ill children, as diseases can progress rapidly and require timely clinical interventions to reduce morbidity, suffering, and mortality.

Genome-scale testing methods such as whole-genome sequencing (WGS) or whole-exome sequencing (WES) have been developed for the diagnosis of genetic diseases [2, 9-11]. Rapid WGS or WES, which reduces sequencing and interpretation times, has proven to be a useful diagnostic test for critically ill neonates and infants suspected of having genetic diseases, with reported diagnostic yields of 30% to 57% [2, 7, 9, 12]. This evidence has led to calls for implementation of rapid WGS or WES in national healthcare systems as the new standard of care. However, widespread deployment of rapid WGS or WES has led to several ethical issues pertaining to the interpretation of variants of uncertain significance (VUS), discovery of incidental findings related to adult-onset conditions by examining sequence information of the whole genome or exome, and implementation of medical therapies with minimal information on risks and benefits [9, 13]. Time is another essential factor when treating critically ill children in neonatal and pediatric intensive care units, limiting

the use of genome or exome sequencing in acute care.

In this issue of *Annals of Laboratory Medicine*, Kim and colleagues [14] report the design of a rapid targeted sequencing panel called NEOseq_ACTION containing 254 actionable genes with therapeutic options to meet clinical needs and overcome ethical concerns. They further developed a machine learning–based prediction model to support variant interpretation, which is expected to shorten the TAT and efficiently predict the pathogenicity of VUS [14]. Prospective validation tests were performed using dried blood spot samples from critically ill neonates and infants with suspected genetic diseases based on abnormal neonatal screening findings, neonatal hypotonia, seizures, complex metabolic phenotypes, skeletal dysplasia or joint problems, and neurodevelopmental delays. In this study of 111 children who underwent NEOseq_ACTION panel sequencing, 13.5% (15/111) had a genetic diagnosis, including 14 patients with autosomal recessive disease and one patient with X-linked recessive disease. The majority of patients (11/15) who received a genetic diagnosis were asymptomatic and showed abnormal findings in neonatal screening [14]. The average time from blood collection to reporting was 3.4 days, and medical management was applied for all patients (15/15) with a diagnosis [14].

Evidence is rapidly accumulating to clarify the role of rapid genomic sequencing in the diagnosis and timely treatment of neonates and infants in neonatal and pediatric intensive care, and efforts to integrate rapid genetic diagnosis into the clinical setting continue. As one such endeavor, rapid targeted sequencing could be a powerful tool for the diagnostic evaluation of critically ill neonates and infants with suspected genetic diseases, with an expected significant improvement on clinical decision-making.

AUTHOR CONTRIBUTION

Jang MA contributed to the manuscript writing.

CONFLICTS OF INTEREST

None declared.

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