REFINEMENT OF NEWBORN SCREENING FOR CYSTIC FIBROSIS WITH NEXT GENERATION SEQUENCING

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April 9, 2022

Abstract

Background: Newborn screening (NBS) for cystic fibrosis (CF) has been underway universally in the USA for more than a decade, as well in most European countries, and algorithms have been evolving throughout this period with quality improvement projects as immunoreactive trypsinogen determinations alone have been transformed to a 2-tier strategy with DNA analyses. Objective: To apply next generation sequencing (NGS) as a method for expanding the DNA tier for identifying variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene with minimization of unintended outcomes. Design: Sequential quality improvement project in three phases using plan coupled to statewide follow up and analysis of screening outcomes in comparison to other NBS programs that use CFTR sequencing. Results: After demonstrating feasibility in the first phase, we studied an IRT/NGS algorithm that included CFTR Variants with Varying Clinical Consequences (VVCCs). This revealed a high identification of CF patients with 2-variants detected through screening, but for every CF case there were 1.4 with cystic fibrosis metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). This led us to a third phase of quality improvement in which the VVCCs were eliminated except for R117H, resulting in 94% 2-variant detection of patients and 0.44:1 ratio of CRMS/CFSPID to CF. Conclusion: NGS can be used with IRT as an effective method of identifying infants at risk for CF without an appreciable increase in detection of either carriers or CRMS/CFSPID cases.

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Figure 6

All NBS specimens

IRT analysis

Infants with top 4% of daily IRT values

CFTR variant analysis

JUL1994 to DEC2000

F508del only

JAN2001 to APR2016

ACMG panel of 23 variants

Optimization of variant analysis via NGS

Pilot project of NGS performed in parallel with ACMG 23 variants

Phase 1: OCT2012 to MAR2016

Phase 2: APR2016 to DEC2019

Phase 3: JAN2020 to present

NGS: pathogenic variants and VVCCs

<table>
<thead>
<tr>
<th>CRMS:CFSPID:CF ratio</th>
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<td>1.4:1</td>
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<td>0.44:1</td>
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Continuous quality improvement

1. NGS: pathogenic variants + R117H
2. Reanalyse for all variants if serum Cr ≥50 mmol/L