REFINEMENT OF NEWBORN SCREENING FOR CYSTIC FIBROSIS WITH NEXT GENERATION SEQUENCING

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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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`Phases of NGS final.docx` available at https://authorea.com/users/475154/articles/564656-refinement-of-newborn-screening-for-cystic-fibrosis-with-next-generation-sequencing

Figure 1

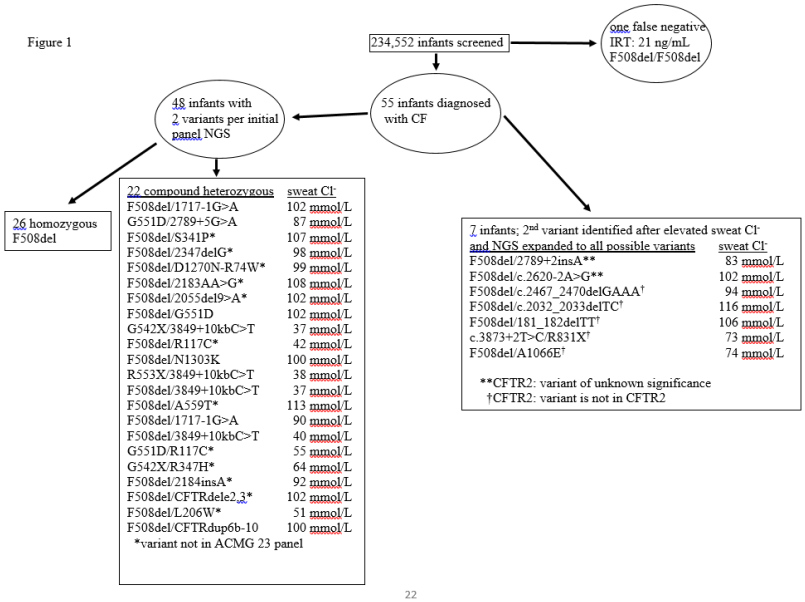

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Figure 2

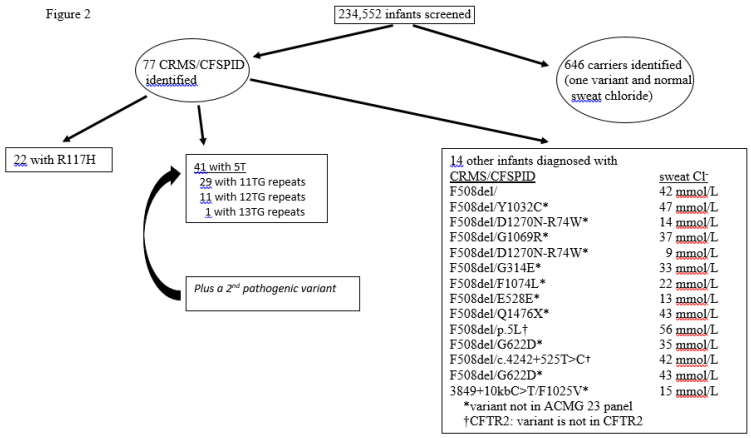

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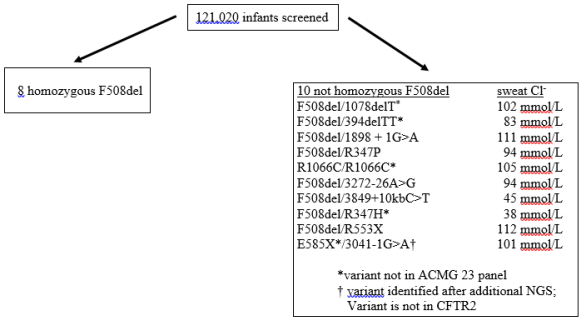
Figure 3



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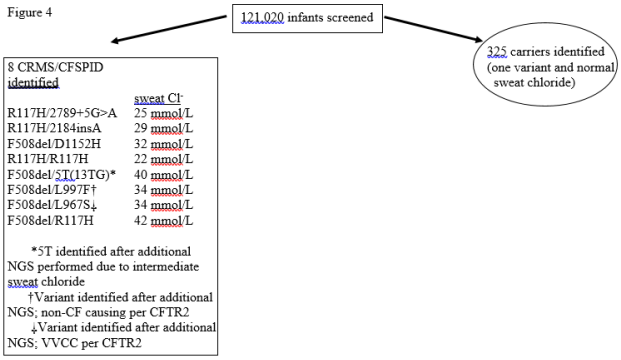
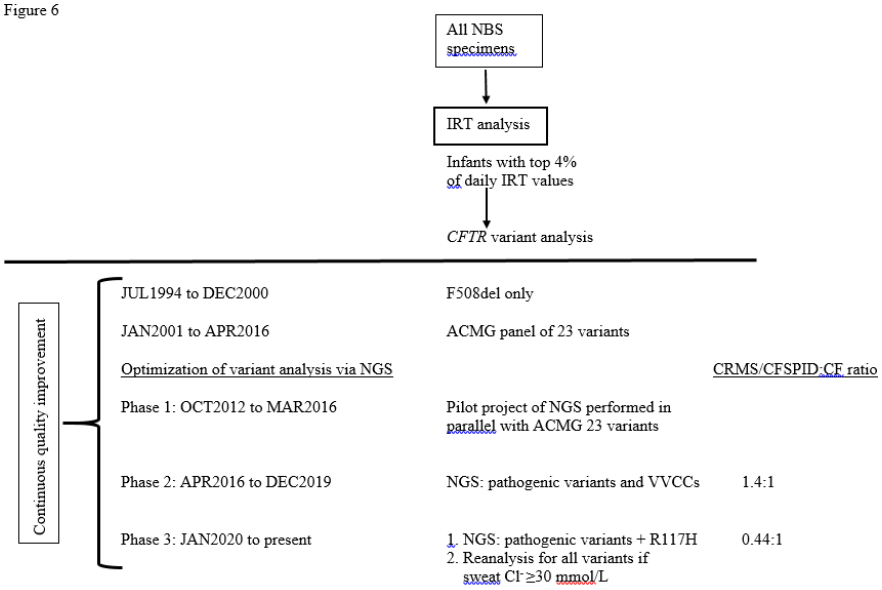


Figure 6



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