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Opportunities and Challenges of Cystic Fibrosis Newborn Screening Using Comprehensive *CFTR* Sequencing

Background and Objectives: Newborn screening (NBS) for cystic fibrosis (CF) traditionally combines biochemical markers with limited *CFTR* variant panels to balance sensitivity and specificity while minimizing detection of carriers and children with inconclusive diagnoses (CFSPID). Expanding variant panels improves sensitivity but typically increases CFSPID rates and reduces positive predictive value (PPV), often necessitating additional screening tiers. This talk aims to evaluate whether comprehensive *CFTR* sequencing can overcome these limitations and to define its clinical, structural, and ethical implications.
Results: Evidence from international screening programs indicates that integrating comprehensive *CFTR* sequencing can further increase sensitivity and reduce reliance on predefined variant panels. It allows improved detection across diverse populations and may decrease false negatives associated with rare variants. At the same time, sequencing does not eliminate key trade-offs: CFSPID cases remain a major challenge, and broader genetic information introduces complexities in interpretation, counseling, and follow-up. Programs implementing sequencing strategies show heterogeneous approaches to variant classification, reporting policies, and management pathways, reflecting the absence of standardized frameworks.
Conclusion and Outlook: Comprehensive *CFTR* sequencing has the potential to refine CF NBS algorithms but does not resolve the fundamental balance between sensitivity, specificity, and clinical relevance. Its implementation requires robust strategies for CFSPID management, harmonized variant interpretation, and clear communication frameworks. Future efforts should focus on international outcome data, standardization of reporting, and evaluation of long-term clinical impact to determine whether sequencing-based approaches provide a net benefit in population-based screening.