Cystic Fibrosis (CF) is screened in NYS infants at birth using a three-tier IRT-DNA-SEQ algorithm. **Tier 1**: Immuneoactive trypsinogen (IRT) is tested in all infants. **Tier 2**: A custom second-tier panel targeting 338 clinically-relevant CFTR variants is screened in infants with elevated IRT (top 5%). Variants included on the panel are listed in the table. Each is described using legacy and Human Genome Variation Society (HGVS) nomenclature, with cDNA nucleotide changes with respect to NCBI transcript NM_000492.3, and amino acid changes with respect to NCBI amino acid reference sequence NP_000483.3. 334 of 338 targeted variants are classified as CF-causing by The Clinical and Functional Translation of CFTR database (CFTR2), with the exception of R117H, a varying clinical consequence variant, and three classified as pathogenic. Large deletion/duplications defined as CF causing by CFTR2 are not included on the second-tier panel. **Tier 3**: Other CFTR variants, including pathogenic and likely pathogenic variants not catalogued in CFTR2; variants of varying clinical consequence; and variants of unknown or uncertain significance (VOSU) may be detected via expanded third-tier analysis, in which the complete CFTR coding sequence and other relevant regions are analyzed. Third-tier analysis is only conducted for infants with one second-tier panel variant or ultra-high IRT and no panel variants. Large deletions and duplications may be detected via third-tier analysis.

Variants recommended for population-based CF carrier screening are shown in bold. Most variants with protein effects listed as p.? represent variants that alter splicing. Defined as a variant of varying clinical consequence by CFTR2. If R117H is detected, intron 8 polyT/TG status at c.1210-12T/c.1210-34TG is unmasked.

### References
1. [www.genet.sickkids.on.ca](http://www.genet.sickkids.on.ca). Cystic Fibrosis Mutation Database (CFTR1). Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto.