Impact of CFTR-gene sequencing on outcomes of newborn screening for cystic fibrosis in Ontario

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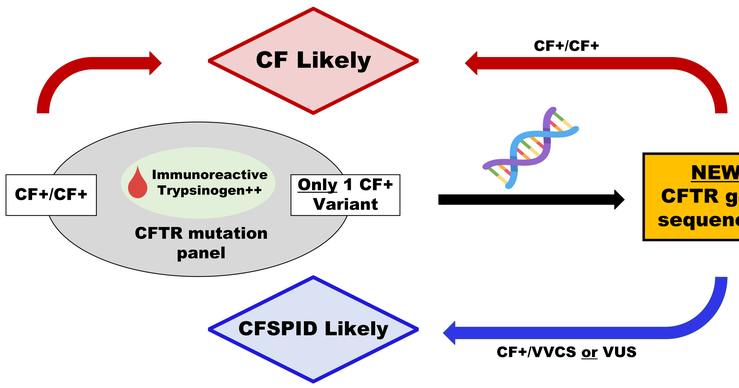
Background

- Cystic fibrosis (CF) is a multi-organ disease with 1/3600 incidence in Ontario.
- CF newborn screening (NBS) was introduced in Ontario in 2008 to identify CF early.[1]
- As an unintended effect, some infants are also identified as CFSPID based on inconclusive genetic and clinical testing or as false positive screens. CFSPID are followed in clinic to monitor potential development of CF.
  - **CF: Positive mutation panel screen AND 2 CF-causing gene mutations AND/OR high clinical sweat chloride value.**
  - **CFSPID: Positive mutation panel screen AND 2 gene mutations where 1 may cause CF, with normal sweat chloride OR 2 CF-causing gene mutations, with intermediate sweat chloride.**
  - **False positive: Positive mutation panel screen AND no CF causing mutation (discharged).**



- As of March 2020, CFTR-gene sequencing was introduced to reduce the volume of false positive screens and identify those with gene mutations with unknown outcomes for CF.[2]
- The uncertainty of CF and related disorders associated with CFSPID diagnosis can exacerbate stress and have psychological impact on families.

Aim

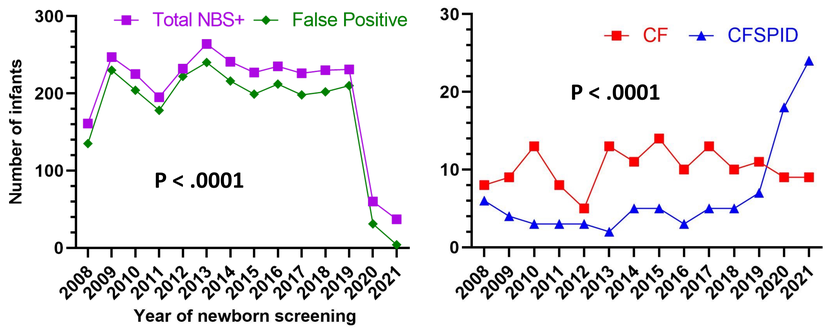
Our **aim** was to evaluate if the introduction of CFTR gene sequencing to Ontario's CF newborn screening algorithm in 2020 impacted patient outcomes in the province.

Methods

- Analysis and statistical testing using
  - CF Newborn Screening clinical trial data on 72 CFSPID participants from Ontario hospitals.
  - Canadian CF Registry for longitudinal data on 10 CFSPID participants from Ontario sites.
  - SickKids referral data where CF Registry data between 2020-22 was not available.
- Mutation significance determined per CFTR2 database (April 2022 version)

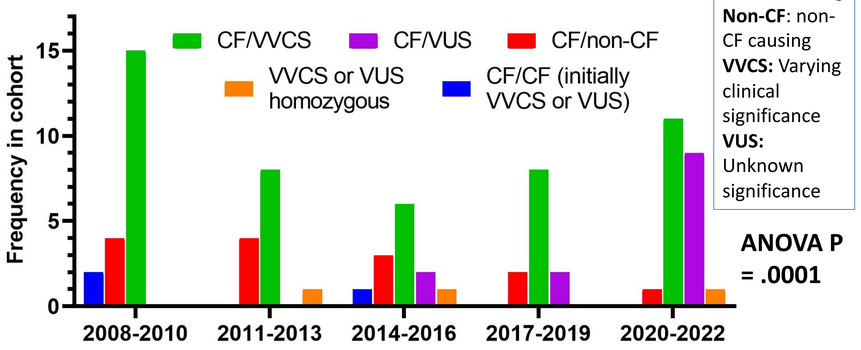
Results

1. Annual screening volume at SickKids NBS Ontario site



- 200% increase in CFSPID at SickKids since 2020, 94% decrease in discharged (false positives).
- 1.7% (42) of positive mutation panel screens diagnosed CFSPID during 2008-19, 45% (50) diagnosed CFSPID since 2020.

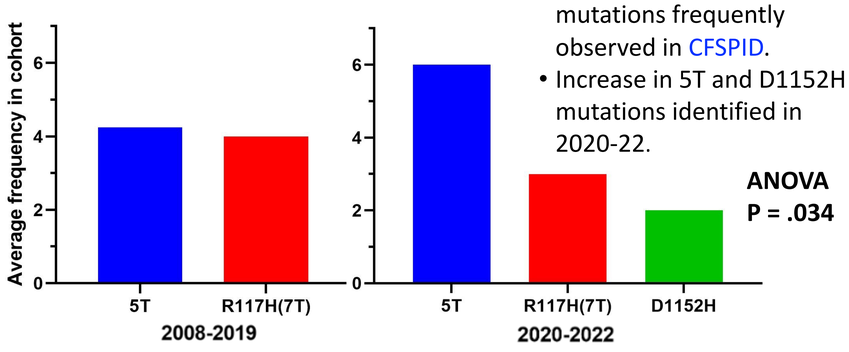
2. Mutation variation in CF NBS clinical trial and CF Registry CFSPID cohorts



CF: CF-causing
Non-CF: non-CF causing
VVCS: Varying clinical significance
VUS: Unknown significance

- Increase of CF/unknown and varying clinical significance combination in 2020-22 CFSPID cohort.
- Decrease in CF/Non-CF combination (false positive carriers).

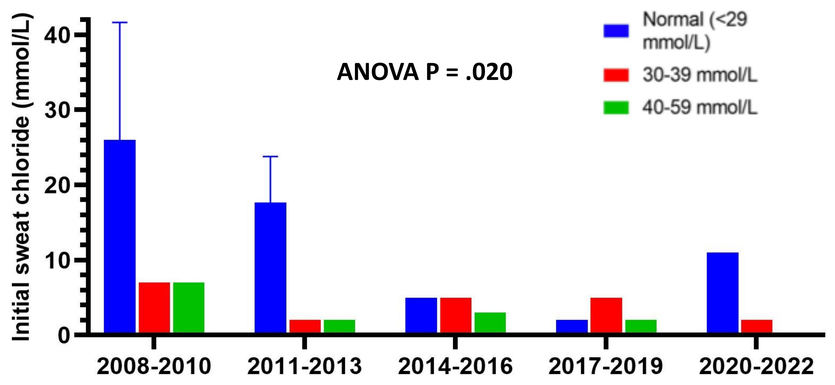
3. Most frequent mutations of varying significance in CFSPID cohorts



- CFTR alleles 5T, R117H(7T) mutations frequently observed in CFSPID.
- Increase in 5T and D1152H mutations identified in 2020-22.

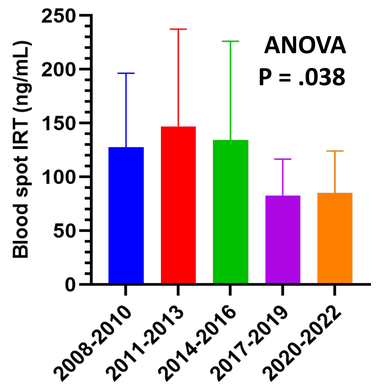
Results (cont.)

4. Comparison with clinical measurements in CF NBS Study and CF Registry CFSPID cohorts



- Most CFSPID had normal first sweat chloride test (86% from 2020-2022, 62% from 2008-19).
- Since 2020, none had high sweat chloride values (>40 mmol/L).
- Significant decrease in mean initial sweat chloride from CFSPID cohort.

- Moderate decrease in median blood spot immunoreactive trypsinogen (IRT).



Conclusions

- Number of false positives decreased, however, CFSPID numbers increased by identifying those carrying 1 unknown mutation with normal sweat chloride test.
- While the introduction of CFTR-gene sequencing achieved aim of reducing false positives, demand on counselling and clinical monitoring of CFSPID has significantly increased.
- We are currently establishing a clinical algorithm to re-stratify ongoing follow-up of CFSPID children regarding risk of developing CF.

References

1. "Newborn Screening Manual." (2018). Newborn Screening Ontario, 2(1), 43.

2. Bergougnoux, A., Lopez, M., & Girodon, E. (2020). The role of extended CFTR gene sequencing in newborn screening for cystic fibrosis. International Journal of Neonatal Screening, 6(1), 23.