



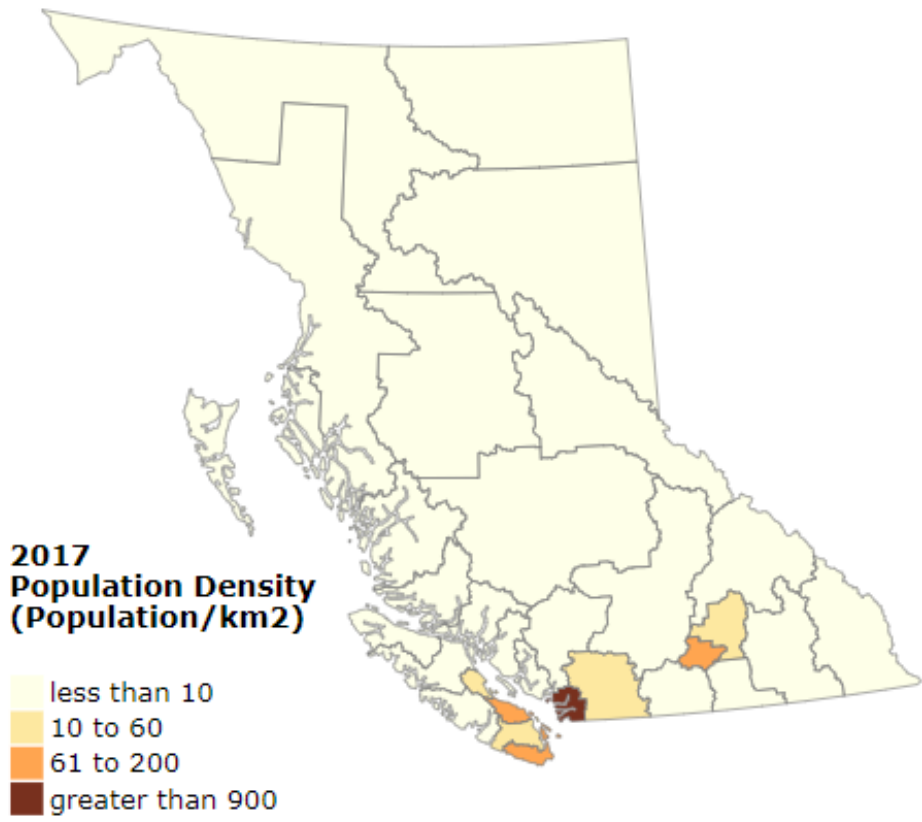
Performance of a three-tier (IRT-DNA-IRT) Cystic Fibrosis screening algorithm in British Columbia

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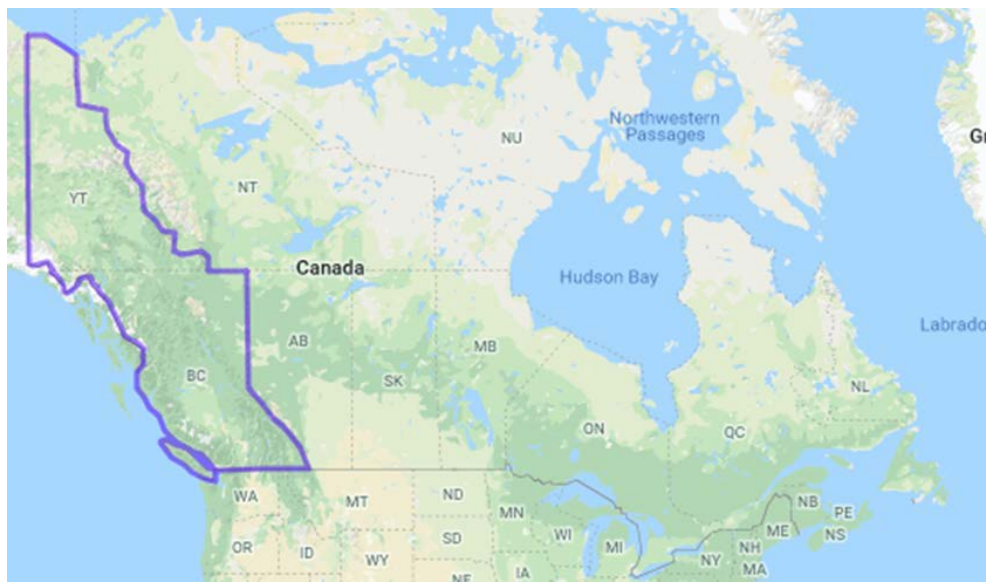
Department of Pathology and Laboratory Medicine, University of British Columbia

Issues of Geography



Illinois = 85 people/km²
BC = 5 people/km²

<http://www.env.gov.bc.ca/soe/indicators/sustainability/bc-population.html>



<http://mapfrappe.com>

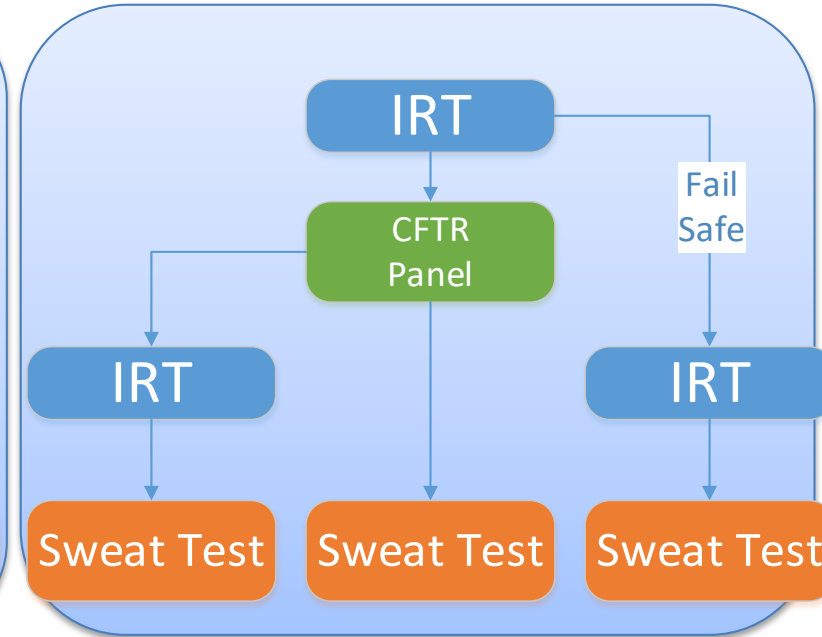
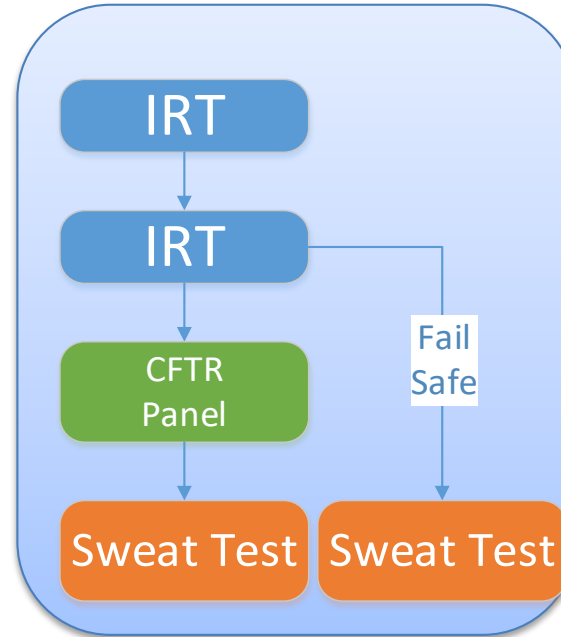
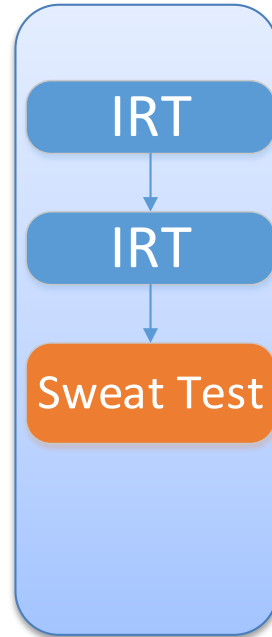
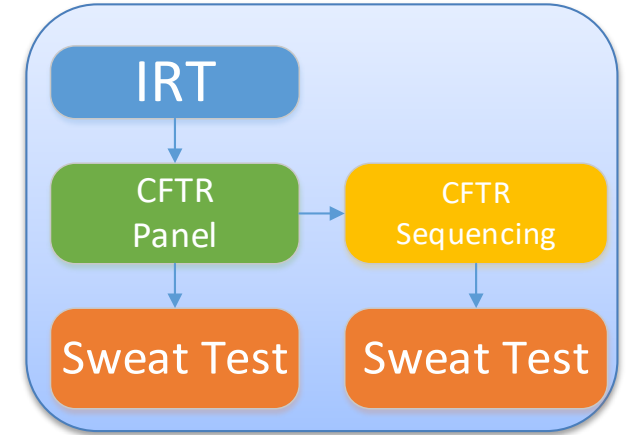
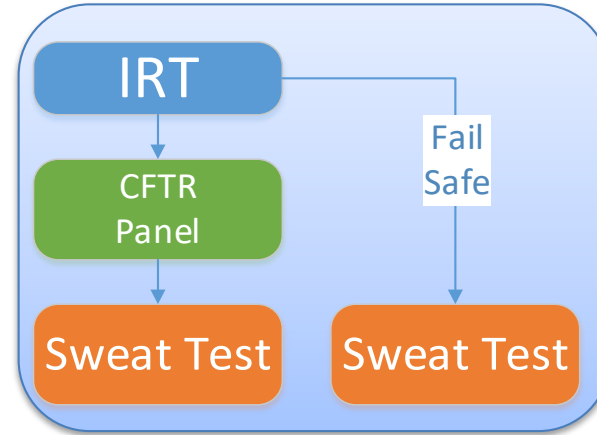
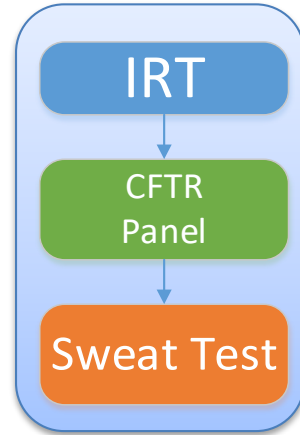
- None to declare

1. Discuss the challenges of CF screening and diagnosis
2. Compare the BC CF screening algorithm to other approaches
3. Review the outcomes of CF screening in BC
4. Present future considerations

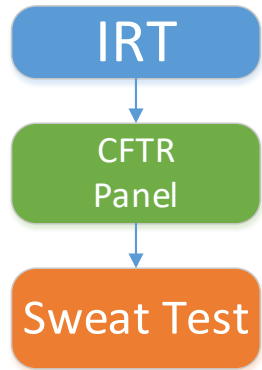
CF Screening Algorithms



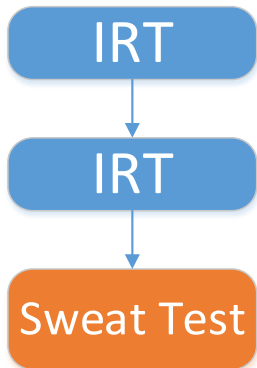
Steps to deal with the low specificity of the IRT



IRT-IRT vs IRT-DNA



Pros	Cons
Single Bloodspot	CFTR Test Expensive
CFTR can be diagnostic	Carrier Detection
	High Sweat test rate

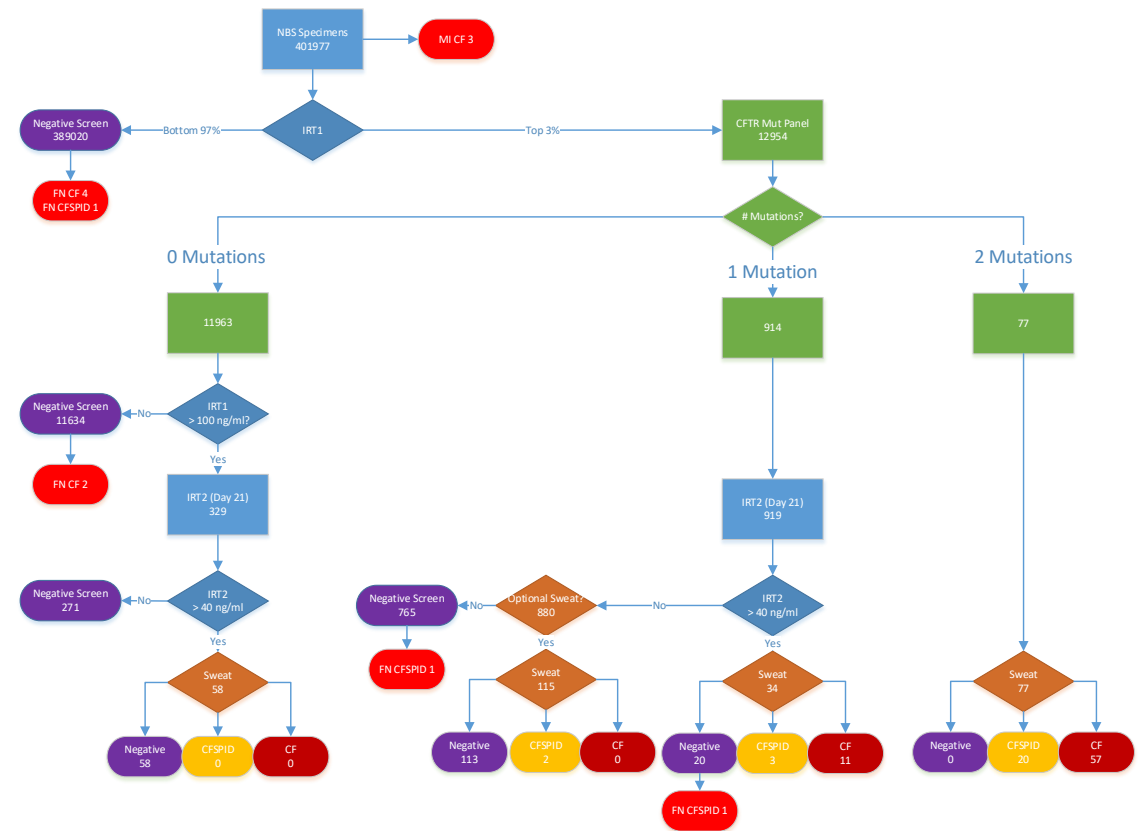
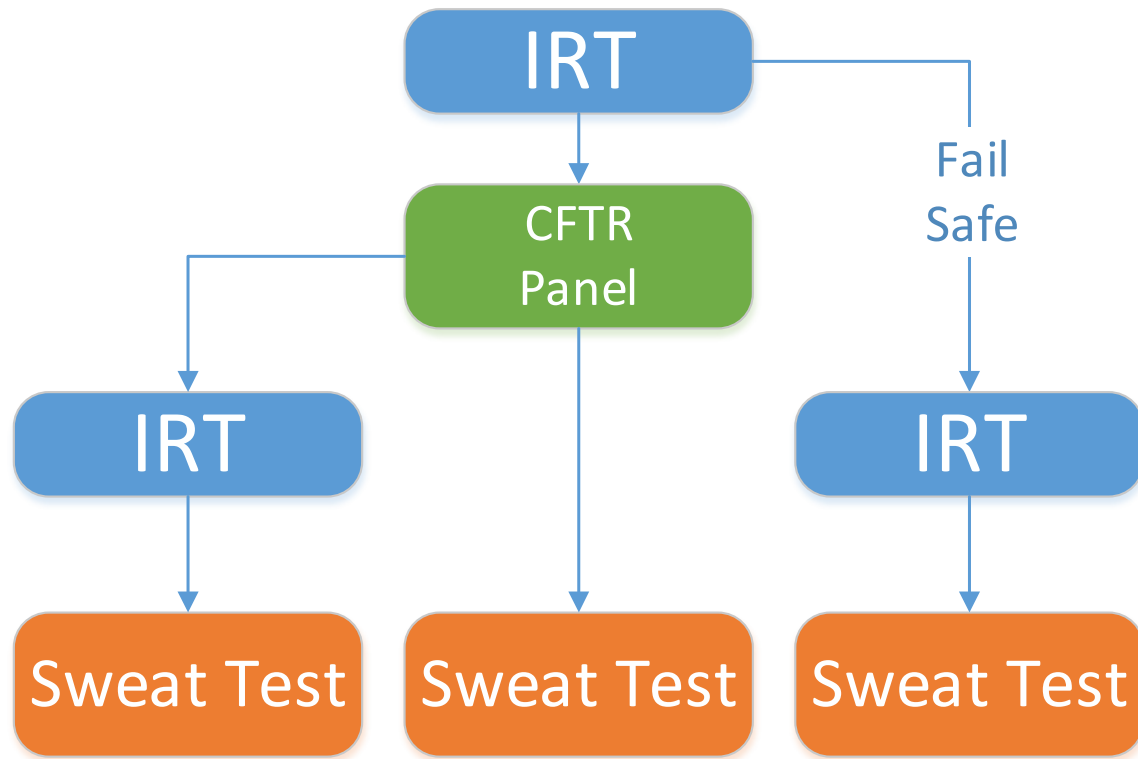


Pros	Cons
IRT is inexpensive	Two samples required
Reduced Sweat test rate	IRT specificity issues
Reduced carrier detection	

CF Foundation Consensus Guidelines (Farrell et al 2017)

		CFTR (based on CFTR2.0)	Sweat Chloride
CF	Cystic Fibrosis	1 or 2 CF-causing mutations	>60
CFSPID	CF Screen Positive Inconclusive Diagnosis	2 mutations (<2 CF-causing)	<30
		<2 mutations	30-60
CRMS	CF Related Metabolic Syndrome	2 mutations	<30
		<2 mutations	30-60

BC Cystic Fibrosis Algorithm



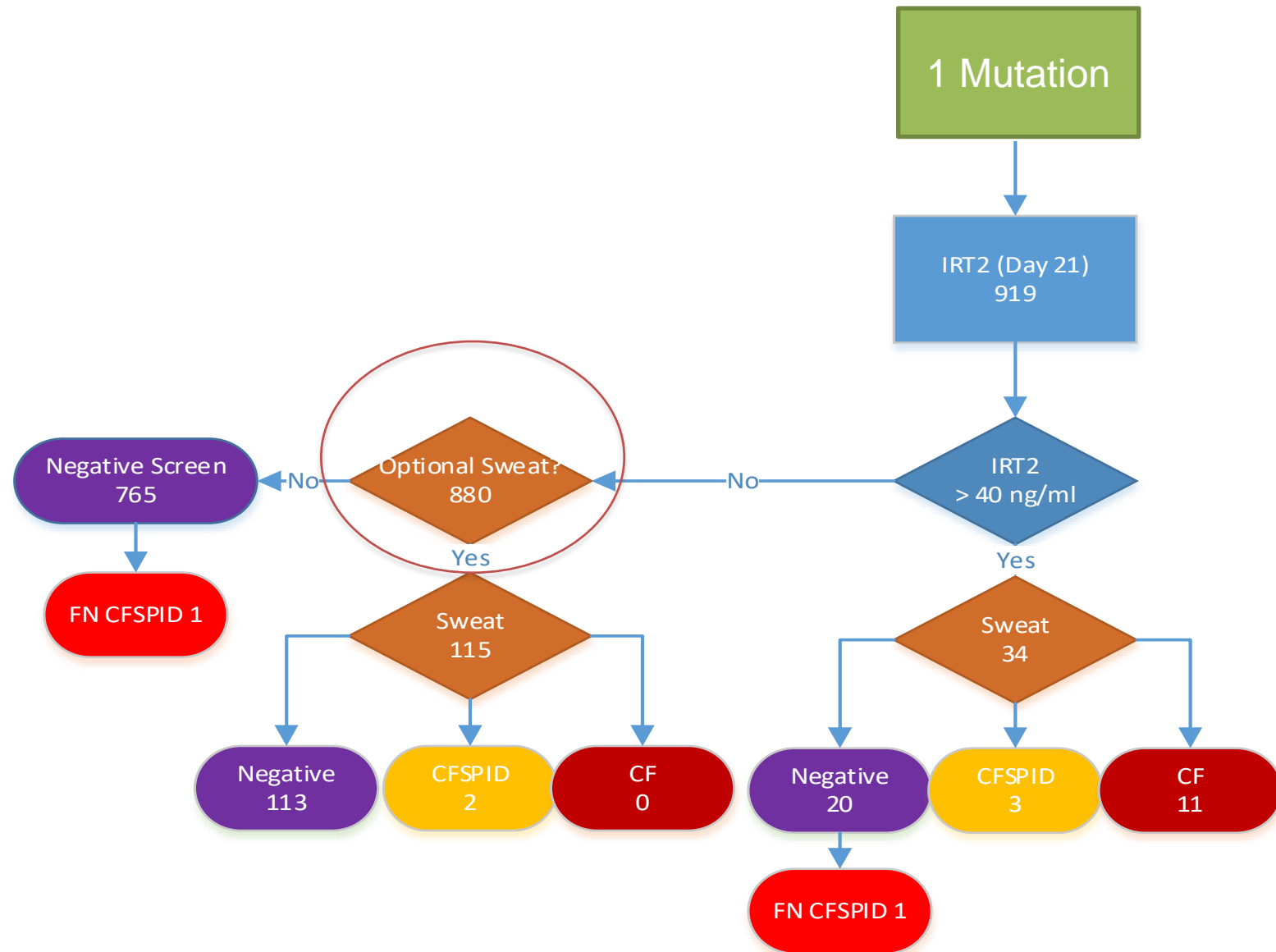
Second IRT for all Carriers

If second IRT elevated

- CF = 32%
- CFSPID = 12%
- Referred for sweat

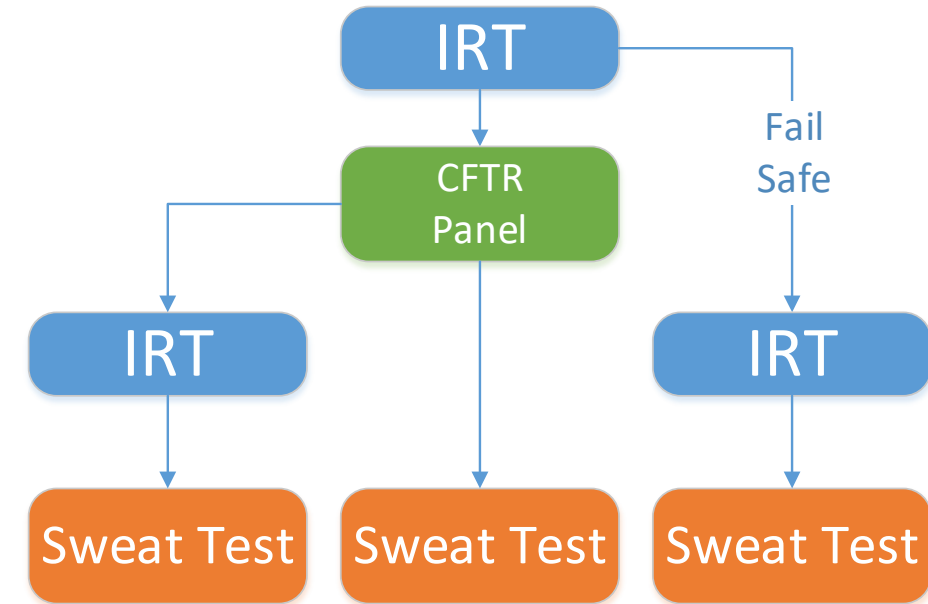
If second IRT Normal

- CF = 0%
- CFSPID = 0.3%
- Optional Sweat test
 - Uptake 13%



N=401,977 over 9 years

	CF	CF +CFSPID
Total Cases	77 (1/5220)	102 (1/3940)
PPV 2 mut	74%	100%
PPV 1 mut + High IRT2	32%	44%
PPV 1 mut + Normal IRT2	0%	0.3%
PPV V. high IRT + High IRT2	0%	0%



**1036 sweat tests avoided
(78% reduction)**

False Negative	CF (% of cases)	CFSPID (% of cases)
Normal IRT1	4 (5.2%)	1 (4%)
0 CFTR Mut.	2 (2.6%)	0
1 Mut., Normal IRT2	0	1 (4%)
1 Mut., High IRT2, Normal Sweat	0	1 (4%)
Total	6 (7.8%)	3 (12%)

Initial IRT Cutoff = 97th %ile or > 60 ng/ml

- Missed cases IRT = 21-42 ng/ml (59th-94th %ile)

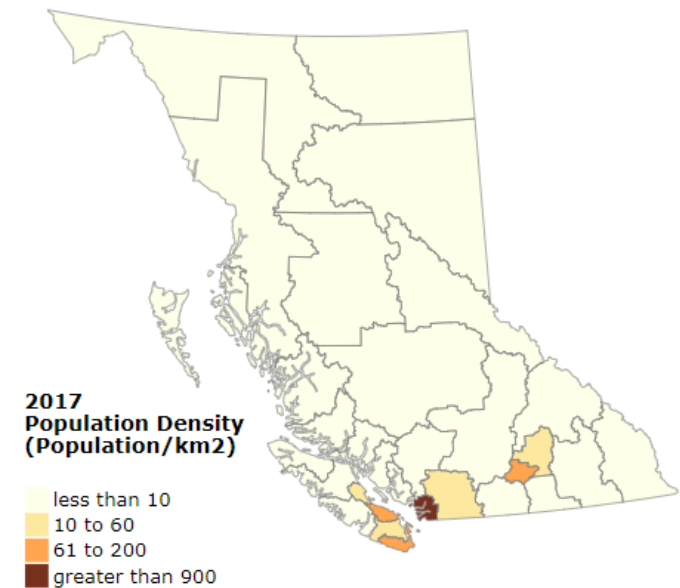
Mutation Panel

- 2009-2010 = 23 mutations (Luminex)
- 2010-2015 = 38 mutations (Third Wave)
- 2016-Current = 130 mutations (Illumina NGS)
- 1 of 2 missed cases would be detected by current pannel

877 carriers detected

Optional Sweat testing

- 880 apparent carriers (normal IRT2) given option to come to Vancouver for a sweat test.
 - 13% uptake (115)
 - 2 CFSPID cases confirmed (no CF)
- Reasons for opting in:
 - NOT geography
 - First Child
 - Parental anxiety (residual risk of CF)



- Most attempts to reduce False Negative enrich for CFSPID cases.
 - Lowering initial IRT cutoff
 - Mean CF IRT1 = 144 ug/L
 - Mean CFSPID IRT1 = 77 ug/L
 - Expanded CFTR analysis
 - BC CF:CFSPID = 3.1:1 (130 mutations)
 - California CF:CFSPID = 2:3 (Third tier extended sequencing)
- Implications of CFSPID
 - 5-15% of CFSPID cases convert to CF over time
 - Changes in CFTR2 mutation definition
 - Changes in sweat results



<http://www.emdocs.net/diagnostic-uncertainty>

Next Generation Sequencing

- Implemented Illumina CF NGS Kit in 2016
 - MiSeqDx 139 CF-causing mutations
 - Only 1 of 2 missed cases would be picked up with this expanded panel
 - Option to include extended mutation panel
 - all of CFTR 2 as a lab developed assay
 - Concerns:
 - diminishing returns for CF
 - enrichment for CFSPID



1. An IRT-DNA-IRT protocol significantly reduces sweat test numbers (78% reduction)
2. High PPV for carriers with high IRT2 = 32%
 - Negative PV of normal IRT2 is near 100%
3. The “fail safe” arm has near zero PPV for CF
4. Initial IRT remains the main cause of false negatives

- BC Newborn Screening Program
 - Hilary Vallance (Medical Director)
 - Daisy Baulcomb (Supervisor)
 - Technologist Team
- BC CF NBS Team
 - Mark Chilvers (Respirologist)
 - Vanesa McMahon, Carolyn Burgess (Nurses)

