Does IRT/IRT/DNA Really Work?

Review of Cystic Fibrosis Newborn Screening in Texas

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TX NBS Specimen Load

- To test each infant twice:
  - 24 to 48 hours of age &
  - 1 to 2 weeks of age
- 2013: Received ~753,000 specimens
  - ~ 2,450 specimens per day (6 days per week)
  - ~ 7,400 unsatisfactory specimens (0.99%)

Cystic Fibrosis NBS

- Implemented statewide December 1, 2009
- IRT/IRT/DNA methodology
  - 1st screen elevated IRT/2nd screen elevated IRT/DNA
  - IRT fixed cutoff:
    - 60 ng/mL in blood for infants <21 days at the time of specimen collection
    - 46.5 ng/mL in blood for infants 21 days or older at the time of specimen collection
  - CFTR mutation panel – Hologic (40+2)
    - 1 or 2 mutations identified – Abnormal CF screen
    - 0 mutation identified - Normal

‘Failsafe’ Protocols

- Ultra-high IRT levels (>150 ng/mL blood) but 0 mutations
- If 1st screen is elevated & no or unacceptable second specimen received by 30 days of age, the first screen is reflexed to DNA
- 1st normal IRT or no 1st screen with 2nd screen elevated IRT is reflexed to DNA

Cystic Fibrosis Screening

December 1, 2009 – December 31, 2013

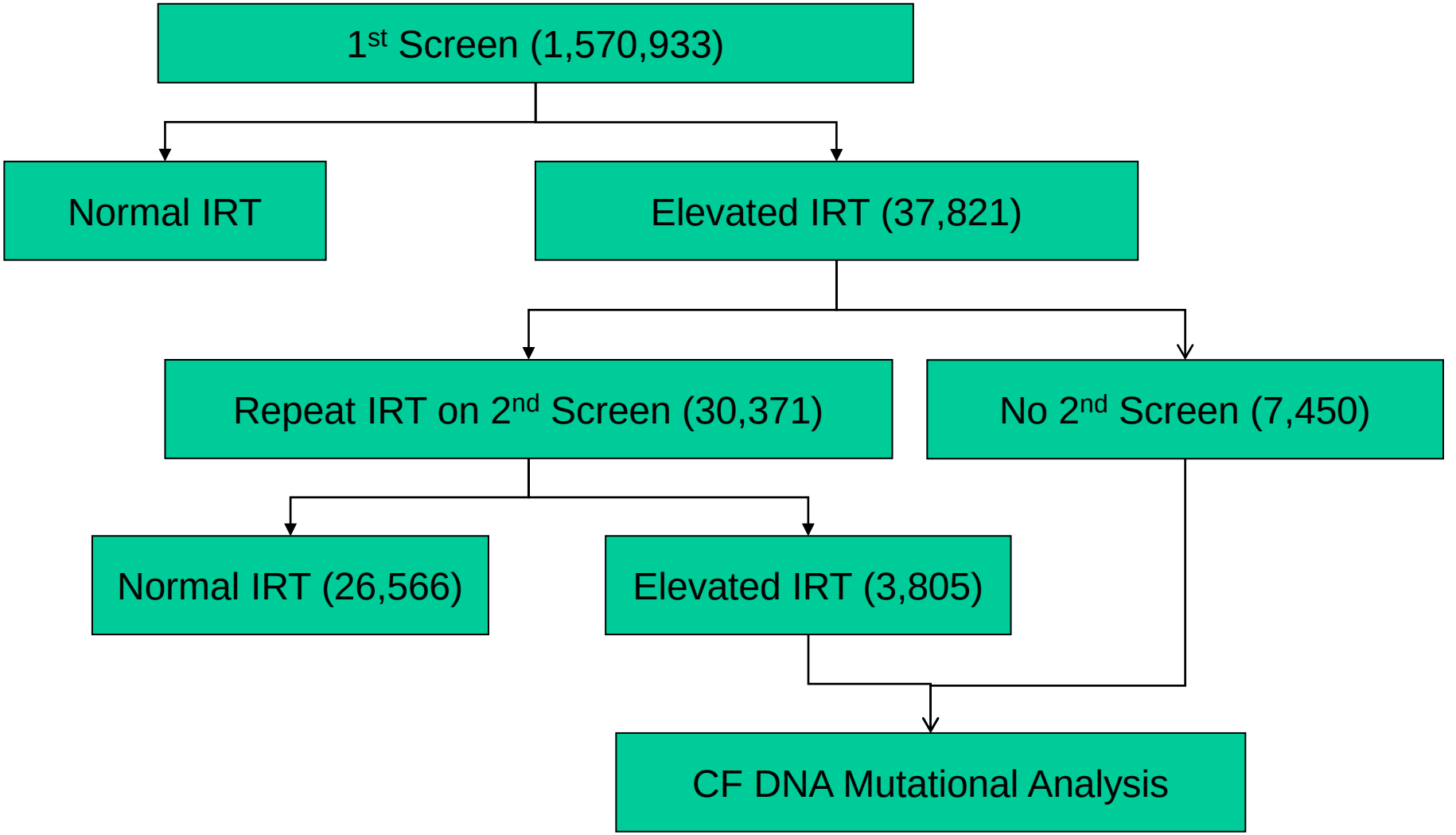
	Specimen Received	IRT Screen Elevated
First Screen	1,570,933	37,821
Follow-up Screen	1,534,469	12,360
Total	3,105,402	50,181

2.4% of the total 1st newborn specimens were elevated for IRT.

0.8% of the total follow-up specimens were elevated for IRT.

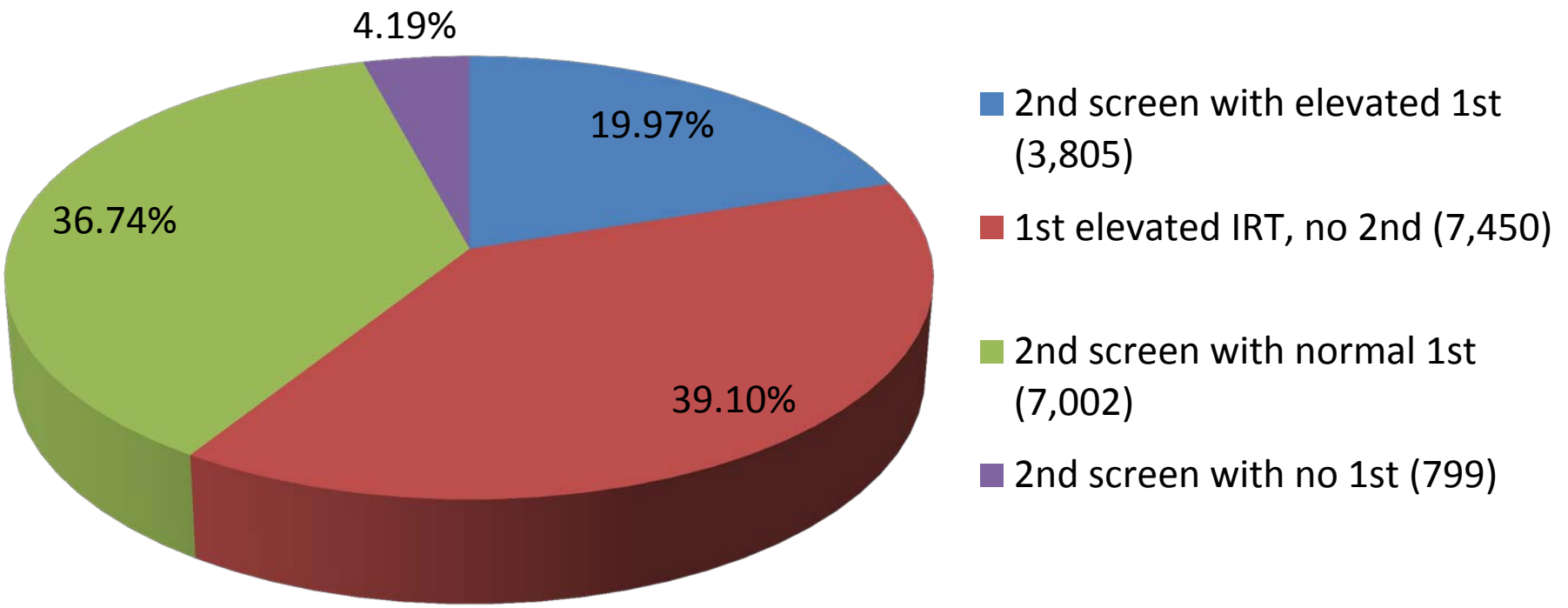
IRT/IRT/DNA Algorithm

December 1, 2009 – December 31, 2013



CF DNA Specimen Type

(December 1, 2009 – December 31, 2013;
Total DNA tests performed = 19,056)



Cystic Fibrosis DNA Test

December 1, 2009 to December 31, 2013

	# of newborns	# of diagnosed cases	# of missed cases
2 mutations found	199	176	4
1 mutation found	915	64	2
0 mutation, very elevated IRT	468	6	0
0 mutation found	17,474	3	3
Total	19,056	249	9

- 1,582 newborns had presumptive positive CF screening results.
- “0 mutation found” is reported as normal CF screening results.

Mutation Distribution (249 CF cases)

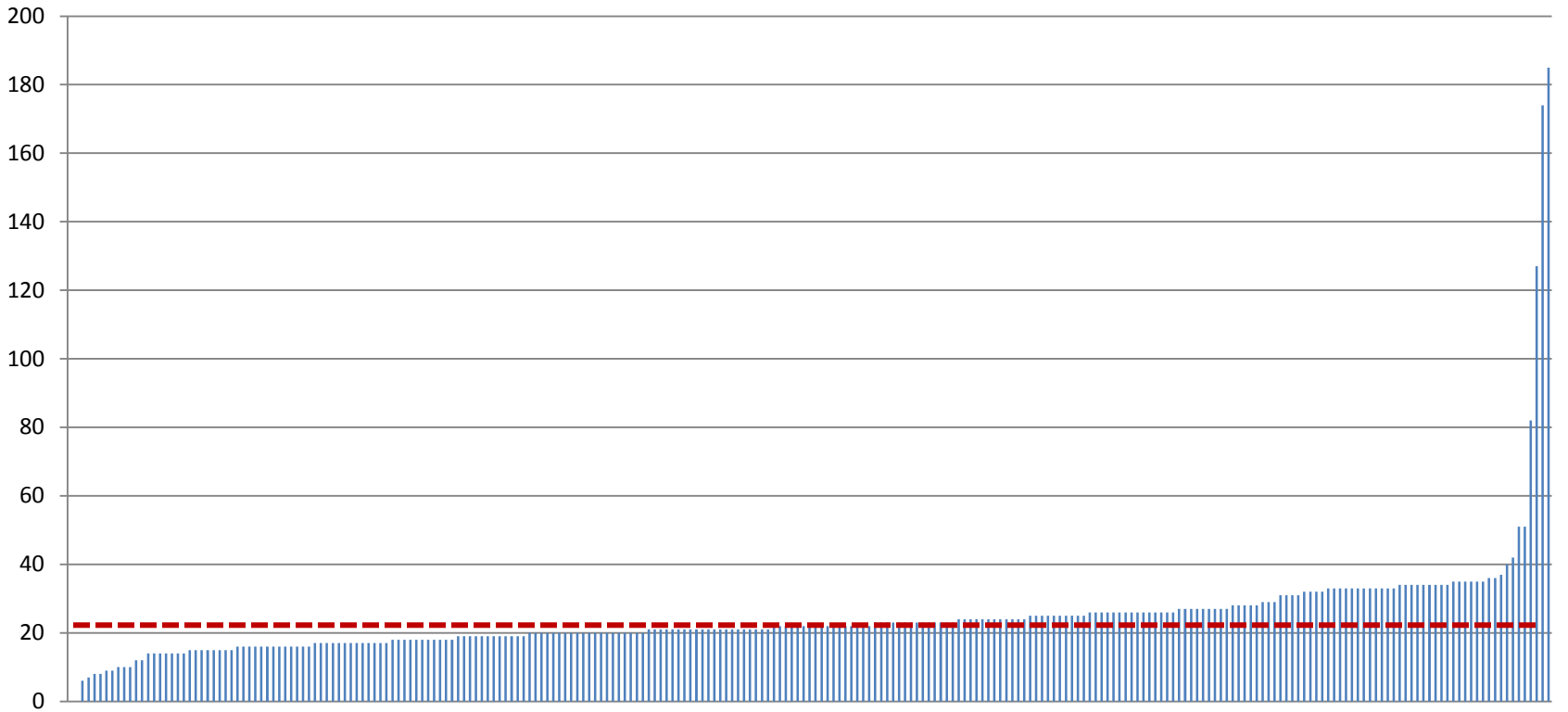
Mutation Name	# of Alleles	Mutation Name	# of Alleles
deltaF508	316	**3120+1G>A**	3
G542X	16	**3849+10kbC->T**	3
R117H	14	D1152H	3
G551D	10	S549N	3
1717-1G->A	6	3876delA	3
N1303K	5	3905insT	3
621+1G>T	4	**W1282X**	2
deltaI507	4	**A455E**	1
R1162X	4	**R347P**	1
R553X	3	**3659delC**	1
2789+5G->A	3	2183A A->G	1
R334W	3	394delTT	1
1898+1G>A	3	V520F	1
		TOTAL	**417**

- Mutation detection rate using Hologic 40+2 panel is ~84% (417/498).
- 32 other mutations were identified. L206W, A559T, and W1089X were the most prevalent.

‘Failsafe’ Protocols

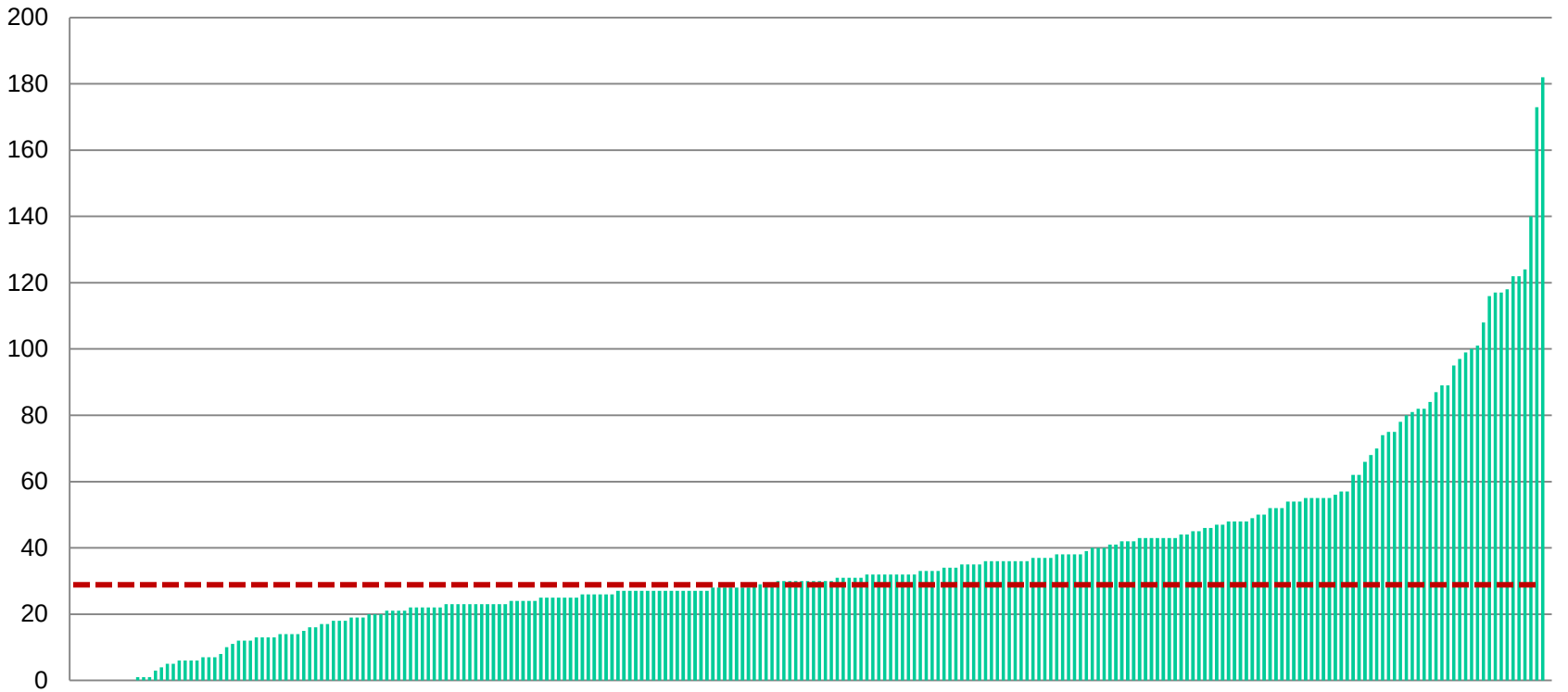
- Ultra-high IRT levels (>150 ng/mL blood) but 0 mutations = 6
- If 1st screen is elevated & no or unacceptable second specimen received by 30 days of age, the first screen is reflexed to DNA = 29
- 1st normal IRT or no 1st screen with 2nd screen elevated IRT is reflexed to DNA = 13

Age of Presumptive Positive Result Notification (Days)



Range = 0-186 Days
Medium = 22 Days
82% (203/249) notified within 30 days of age
98% (243/249) notified within 40 days of age

Age of Diagnosis (Days)



Range = 0-182 Days
Medium = 30 Days
52% (129/249) diagnosed within 30 days of age
87% (217/249) diagnosed within 60 days of age

9 Missed Cases

- Definition - Cystic Fibrosis cases with normal screening results
  - 7 due to IRT below cutoff
  - 2 due to mutation panel (both African American)
- 4 with history of Meconium Ileus
- Age of Diagnosis ranged from 6 days to 173 days (average 69 days)
- Based on data from two missed cases, older baby cutoff was re-evaluated and changed from 30 days to 21 days (DOB to DOC) using cut off ≥46.5 ng/mL

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Summary

- # of newborn screened: 1,570,933
- # of newborn tested by CF DNA: 19,056 (1.2%)
- # of newborn with presumptive positive results: 1,582 (0.1%)
- # of newborn diagnosed with CF: 249
- # of missed cases: 9
- # of carriers identified: 851
- # of CFRMS identified: 23

Summary (continued)

- Positive Predictive Value - 15.7%
- Sensitivity - 96.4% (False negative rate – 3.6%)
- Specificity - 99.9%
- Overall Incidence Rate – 1 in 6,308
  - White - 1 in 3,505
  - Hispanic – 1 in 10,150
  - African American – 1 in 11,803
  - Others – 1 in 19,888
- Need system-wide education on timing of specimen collection, esp. 2nd screens.

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Thank you