Newborn Screening for Cystic Fibrosis

Three States' Experience with IRT/IRT/DNA

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Colorado's CF Newborn Screening History with IRT/IRT

- Historic false negative rate (*non Meconium Ileus*)
  - 18/327 = 5.5% (3.5 – 8.5, 95% CI) – *Sontag et al J Peds 2005*
  - Approximately 1 infant every 1-2 years
  - Suggestions other infants may have been missed
- How can we improve the sensitivity of the CF Newborn Screen?
  - Can we improve the sensitivity without increasing the burden of the screen?

Our Goals for a new screen in Colorado

- Minimize false negatives
- Reduce the number of false positives
- Provide a more specific diagnosis, ie DNA
- Minimize the need for genetic counseling for detection of carriers
- Reduce parental stress
  - Reduce the time to a diagnosis
  - Reduce the number of children/parents recalled for testing
- Reduce costs of screening and follow-up

IRT/IRT$_{1\uparrow}$/DNA in Colorado

- Decrease 1st screen cutoff
  - 105ng/ml (99.7 %ile) to 97th %ile (60ng/mL)
- **Link** 1st and 2nd screen specimens for each baby – SpecimenGate
- Test 2nd screen ONLY if first screen > 60ng/mL
- Mutation analysis if BOTH first and second screen results > 60ng/mL

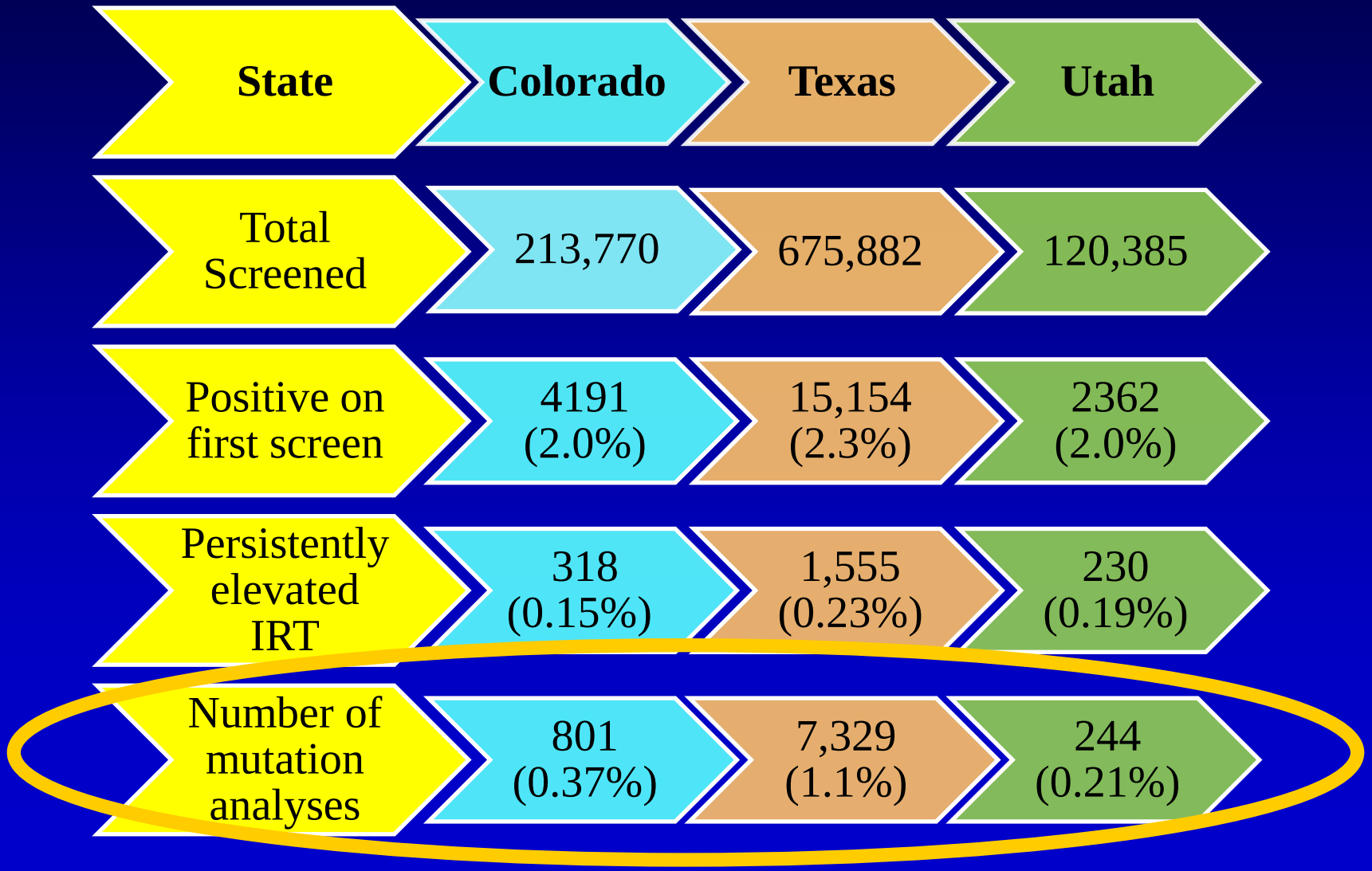
Implementation of IRT/IRT/DNA

- Currently being used in 3 states:
  - Colorado (June 2008) – Appx 70,000 births/yr
  - Utah (January 2009) – Appx 60,000 births/yr
  - Texas (January 2010) – Appx 400,000 births/yr

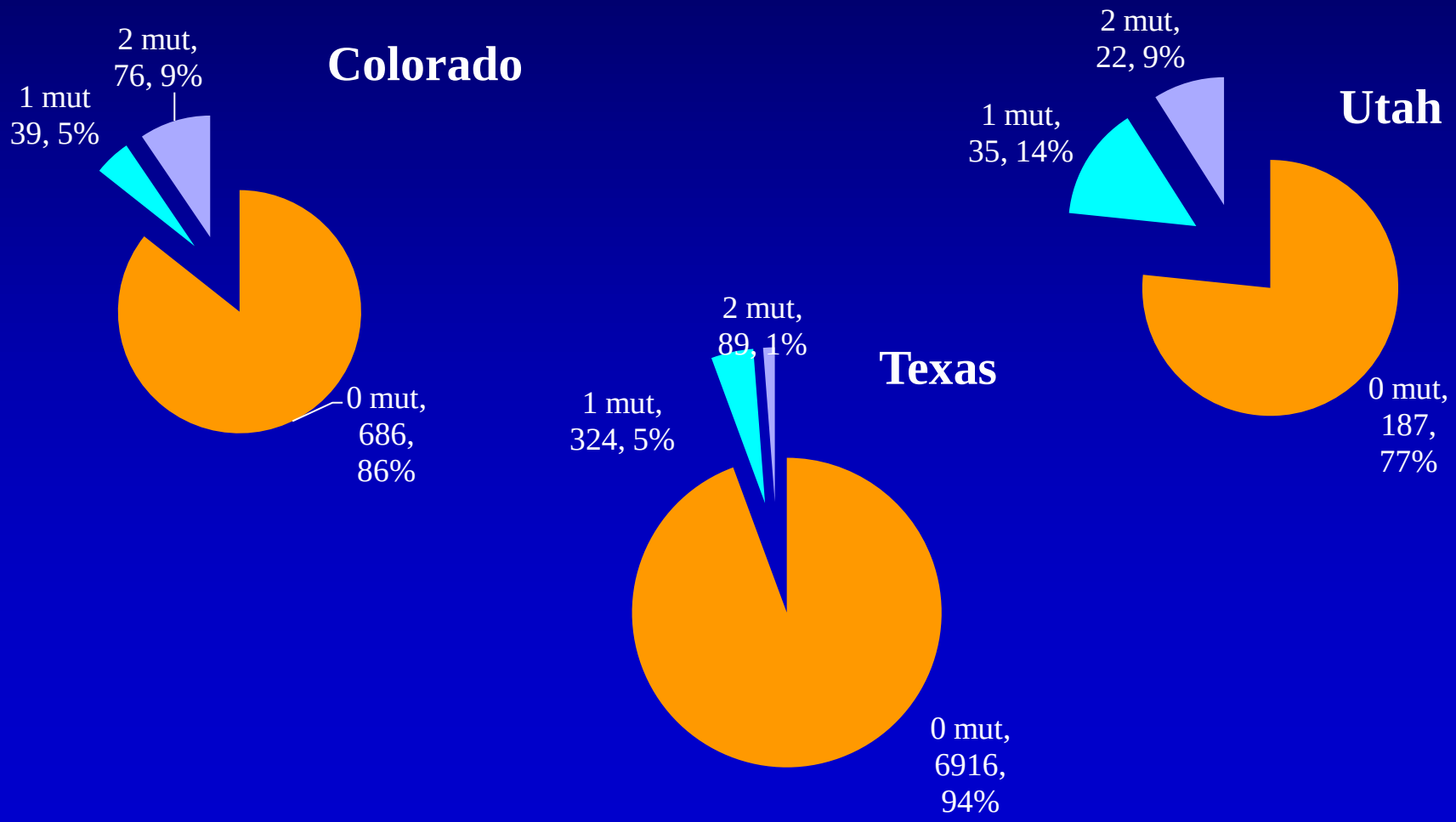
Basic Algorithms – similarities and differences

	Colorado	Texas	Utah
Cutoffs (1st/2nd)	60/60ng/mL	60/60ng/mL	60/60ng/mL
Other cutoffs		46.5ng/mL – over 30 days	>97%ile prior to 6/1/10
Testing all 2nd Screens	NO	YES	NO
Number of mutations	32	40	32
Ultra-high cutoffs	>150 ng/mL	>150 ng/mL	NONE
Dates reported	7/1/08 – 8/1/11	12/1/09 – 8/31/11	1/1/09 – 3/31/11

Results of IRT/IRT/DNA algorithm



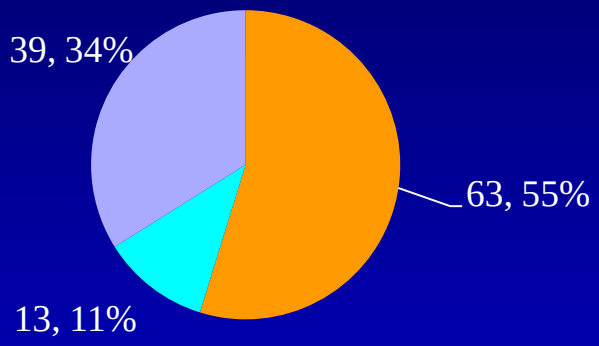
Results of mutation analyses performed



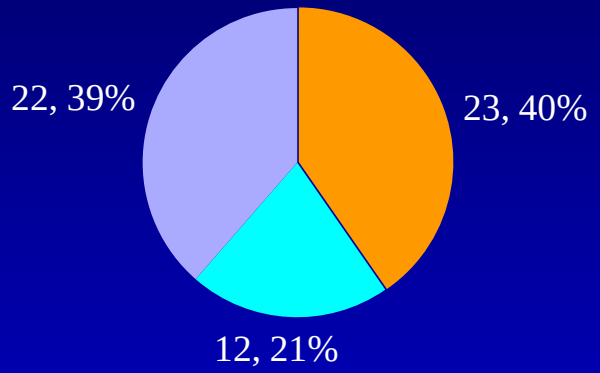
Of those with at least one mutation….

PPV of ≥1 CFTR mutation
CF: Carrier Ratio

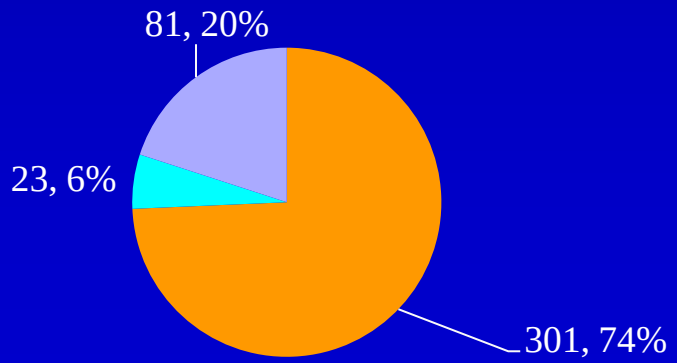
Colorado
PPV = 45%
1: 1.2

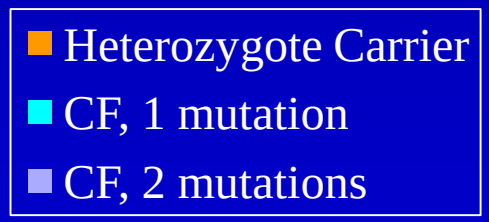


Utah
PPV = 59.6%
1:0.67

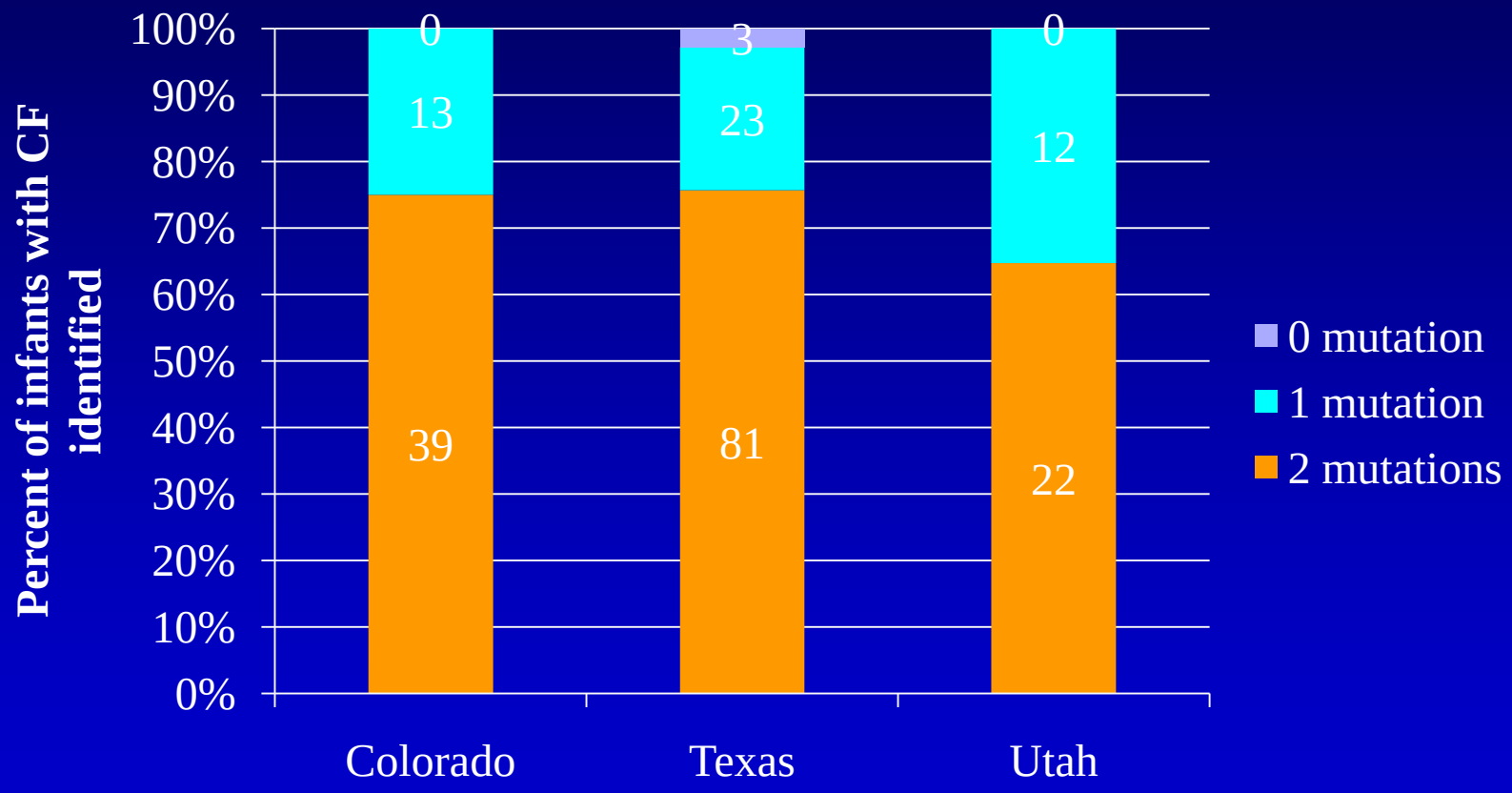


Texas
PPV = 25.7%
1:2.9





Over 60% of CF Cases identified had 2 mutations on the panels



Missed Cases

State	Colorado	Texas	Utah
Missed on screen	2	6	1
Missed by IRT	2 (52, 55ng/mL)	4 (19, 42 , 43and 48 ng/mL)	N/A
Missed by DNA	0	1	1 (Q943X)
False Negative Rate	4.2% (1.3-14.0)	4.7% (2.1-10.5)	2.9% (0.7-14.5)

The new algorithm in Colorado is accurately identifying more babies with CF

- 5/52(9.6%) Babies with IRTs <105 ng/mL and >60 ng/mL have been identified cases that would not have been identified by an IRT/IRT algorithm
- Two other babies were missed by Colorado's program: - hypothetical total missed case to date (had cutoff not changed): 7/52 (13.5%, 95% CI: 6.7 – 25.3%)

80% of cases in the new cutoff window of IRT/IRT/DNA (60-105ng/mL) in Colorado were pancreatic insufficient

First IRT (ng/mL)	Second IRT (ng/mL)	Genotype	Pancreatic Status
98	87	R347P/UNK	Sufficient
98	99	F508/G542X	Insufficient
68	127	F508/F508	Insufficient
78	79	F508/F508	Insufficient
76		663delT/G551D	Insufficient
55		N1303K/2789+5G->A	Sufficient
50		F508/R117H	Sufficient

Would have been missed with 105 ng/mL cutoff

Missed with 60 ng/mL cutoff

Two IRTs (Always vs. Selective)

- Colorado and Utah test IRTs on second specimens if the first specimen is above threshold
- Texas tests IRTs on ALL first and second specimens
  - Has identified 2/107 (1.8%) babies with CF on second screen that had normal first IRTs (<60ng/mL)
- Balancing cost of additional tests with sensitivity of tests

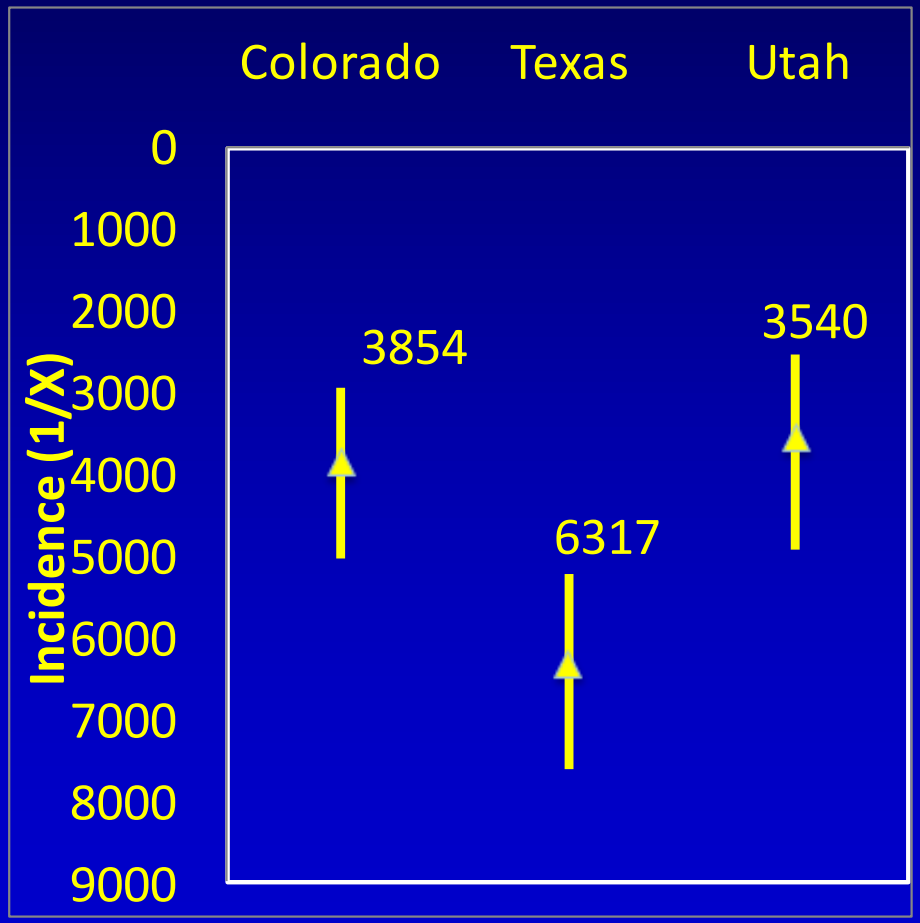
Ultra-high algorithm

- Recalling infants with persistently *extremely* elevated IRTs (>99.9%ile) and no mutations on panel
- Texas and Colorado
  - 150ng/mL w/no mutations=> Sweat test
  - Texas has identified 2/107 babies (1.9%) with ultra-high algorithm
- Especially useful if mutation panel may miss some race/ethnicity groups

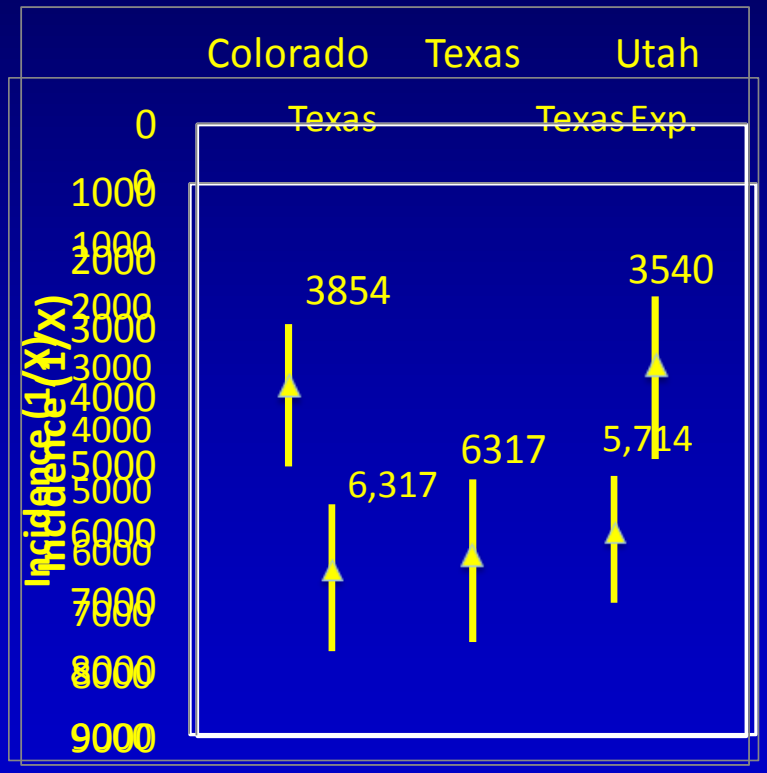
Unlinked samples

- If first sample has elevated IRT AND second sample is not received, or not ‘linkable’ the 1st sample can be tested for CFTR mutations
- Colorado identified 2/52 (3.8%) cases by testing DNA on first sample.

Incidence of CF
Newborn screening across 3 states



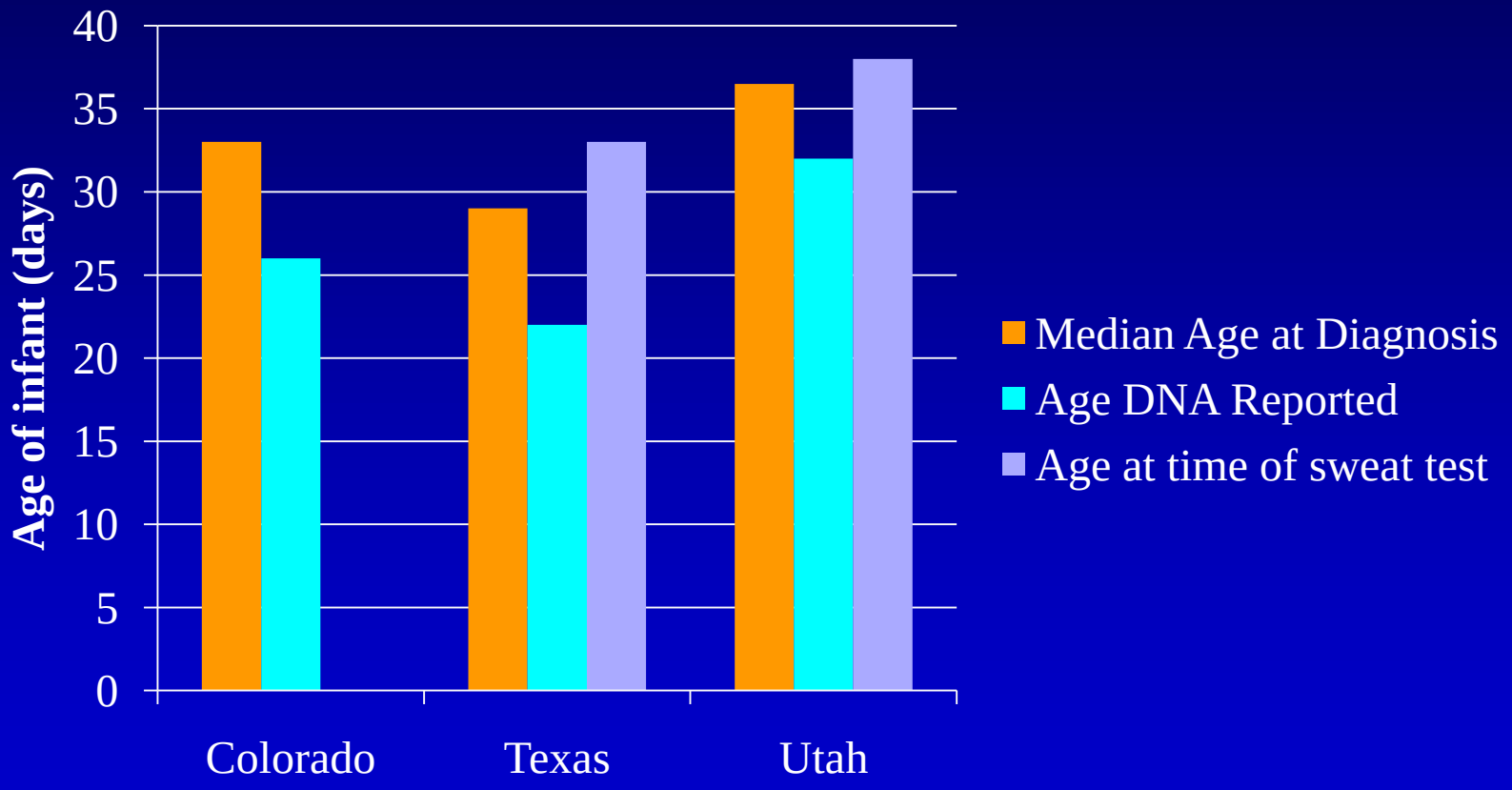
What would the *Expected* number of children with CF be in Texas?



Identified 107

- Applying published disease frequencies:
  - Caucasians: 1/3,600
  - Hispanics: 1/6,500
  - African American: 1/29,000
  - Native American: 1/2,700
    - *Colorado disease frequencies from: Sontag et al J Pediatr 2005;147*
- Texas Vital Statistics (2008)
  - 34% Caucasian
  - 50% Hispanic
  - 11% African American
  - 5% Other
- **675, 882 births => Expected 118 babies**

Age of infant at time of diagnosis, sweat test



Median age of diagnosis in Colorado has changed from 35 days (2008) to 31 days (2009) to 28 days (2010)

Challenges to IRT/IRT/DNA analysis

Specific to IRT/IRT/DNA

- Requires 2 samples
- May increase time to diagnosis
  - There are many steps that can be taken to shorten time to diagnosis
- Linking the samples

DNA challenges alone

- Clinicians ‘trust’ DNA
  - Need to educate clinicians that mistakes can happen in all tests
- Identification of carriers requires counseling
- May miss individuals with rare mutations

Advantages to IRT/IRT/DNA

Specific to IRT/IRT/DNA

- More specific test
  - Lower number of false positives identified and referred to sweat testing
- More sensitive test than IRT/IRT
  - Lower cutoffs
- May be more sensitive than IRT/DNA in some situations
  - TX – repeating IRT on infants x2 identified infants

DNA advantages alone

- Offers a more specific result in many cases
  - >60% of CF cases identified had 2 mutations.
- Can provide additional genetic information
  - Allow genetic counseling of parents of carriers

Conclusion

- IRT/IRT/DNA is a sensitive algorithm for the identification of CF
- Identifies fewer carriers than reported values for programs employing IRT/DNA
- May have longer time to diagnosis but can still be achieved <1 month
- Should be considered by states with 2 DBS collections

Thank You for Sharing Data

- Texas
  - Lynette Borgfeld
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  - Barbara Chatfield
- Colorado
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  - Laura Taylor
  - Elin Towler

The new face of the infant with cystic fibrosis