

The Importance of Identifying False Negatives: Making the Case for Identifying Cases Missed by Newborn Screening



Marci Sontag PhD,
Colorado School of Public Health

Sara Copeland MD
HRSA/MCHB

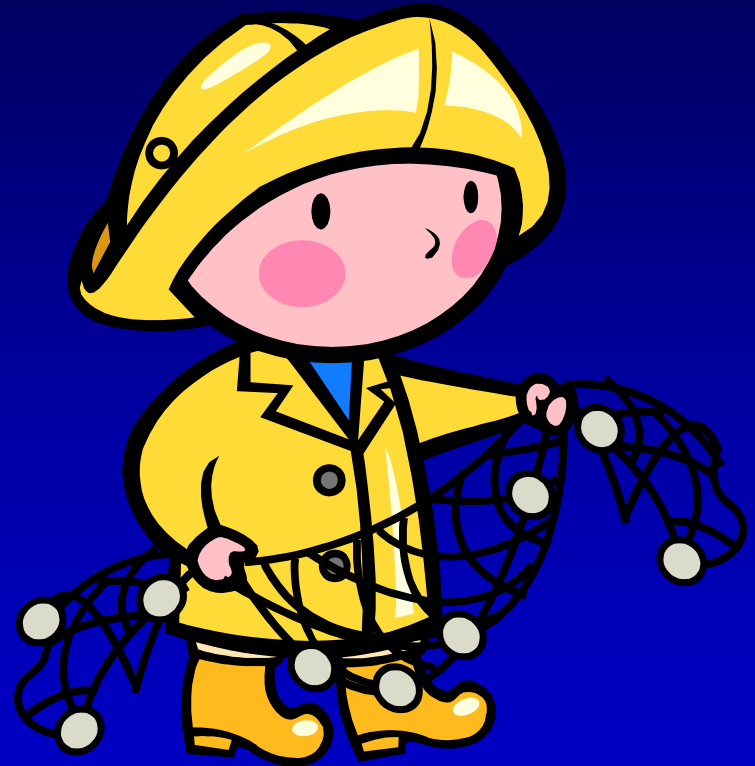
Genetics Services Branch



Public Health

Newborn Screening

- ‘All’ babies are tested
- Cast the net broadly to ensure we capture all babies at risk for having disease
- Try to balance the false positives with the sensitivity of the test
- Missed cases could have devastating outcomes



False Negatives in Newborn Screening

- Public Health Newborn Screening Systems capture most babies with screened diseases in the U.S.
- We are unable to accurately calculate the missed case rate (or 1-sensitivity) because we don't have systems to collect the data
- We *can* calculate positive predictive value, and use PPV as a measurement of newborn screening programs effectiveness (see Zuckerman poster)

Real quotes from the newborn screening community

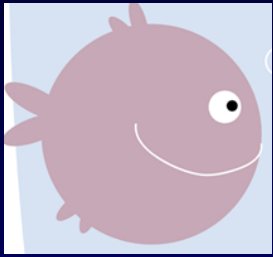
“It is too hard to find false negatives, where are they?”

“We know about the missed cases but I have already closed out my reporting for that year”

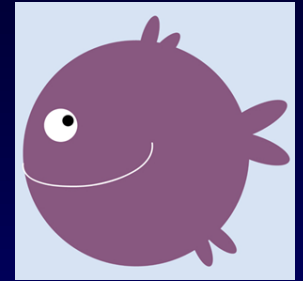
“There aren’t any missed cases for *MY* screening test...they only really miss kids in CF”

“I follow kids in my clinic who were missed on the newborn screen, but I haven’t had time to call the state to report them ”

“PPV is the best we can do. We can’t report anything else”



Fishing for the babies with disease



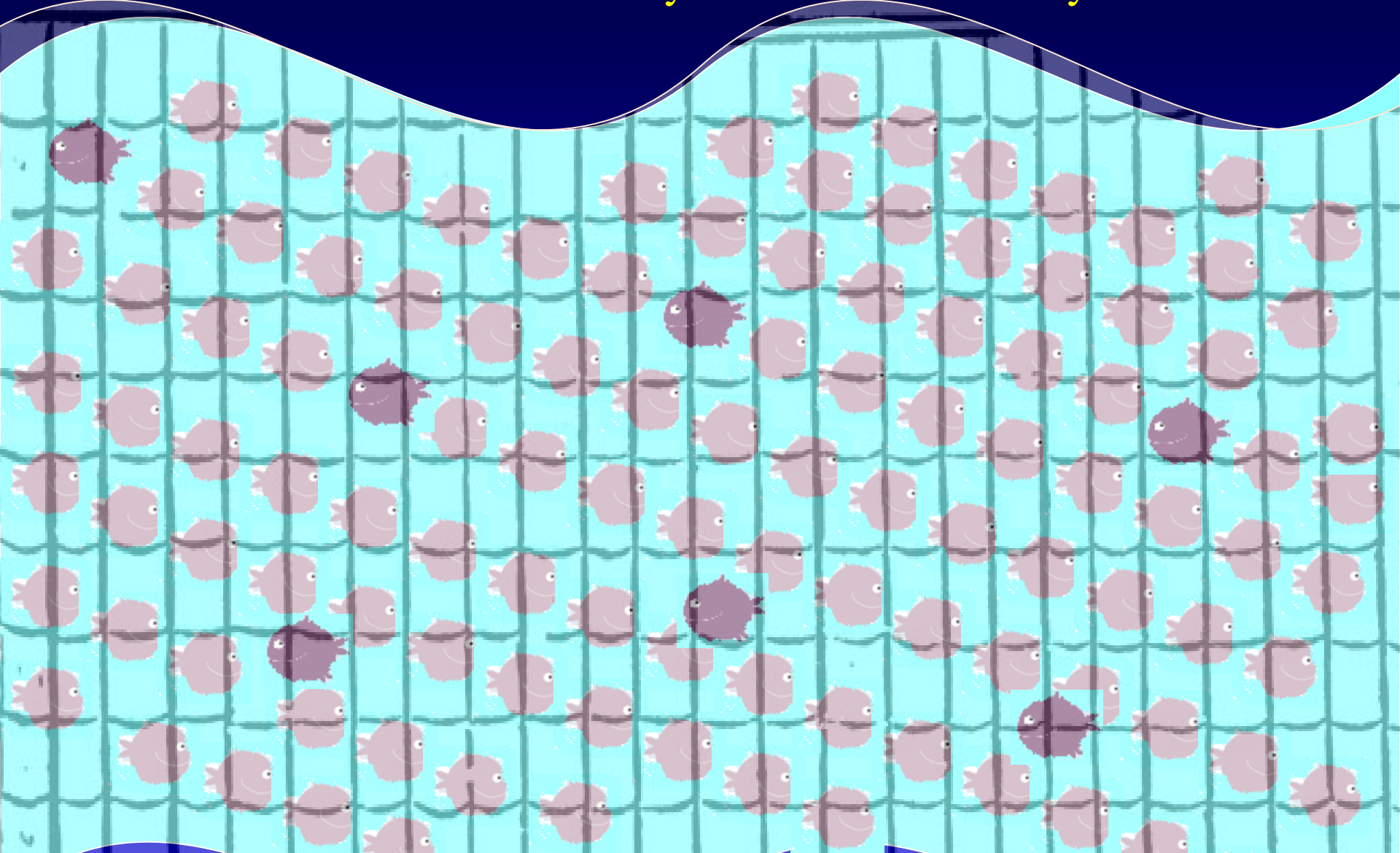
- **False Negative:** Those who have the disease who test negative on the screening test:
 - $c/(a+c)$
 - $1 - \text{sensitivity}$
- **Positive Predictive Value :** The proportion of true positive among all positive tests
 - $a/(a + b)$
 - $\text{true positives}/(\text{all positives})$

		Gold Standard (Disorder +)	
		+	-
Screening Test	+	a	b
	-	c	d

Both depend on 'a' – those WITH disease that are identified by the screening test

Identifying babies with disease

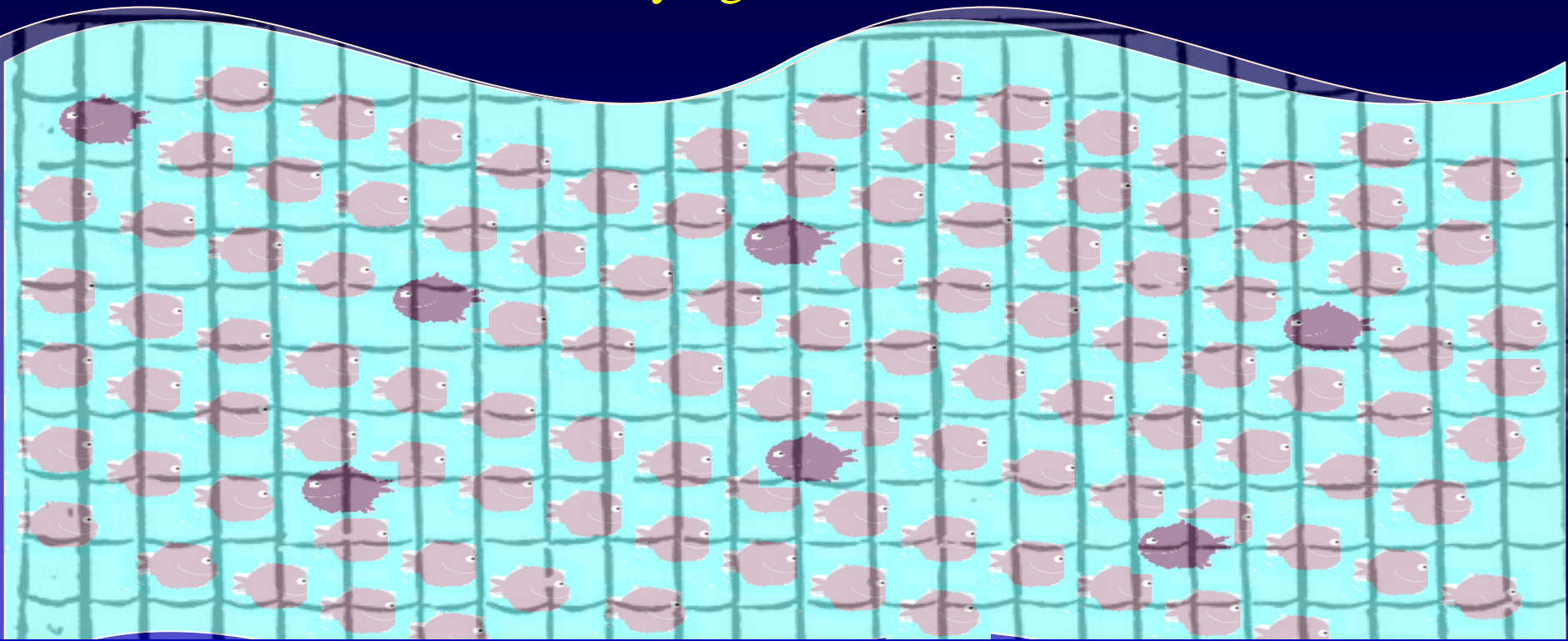
Cast the net broadly – but not too broadly



Identifying babies with disease



Identifying all of the babies



		Disease	
		+	-
Screening Test	+	7	993
	-	0	0

False Negatives =

$$= c/(a+c)$$

$$= 0/(7+0) = 0\%$$

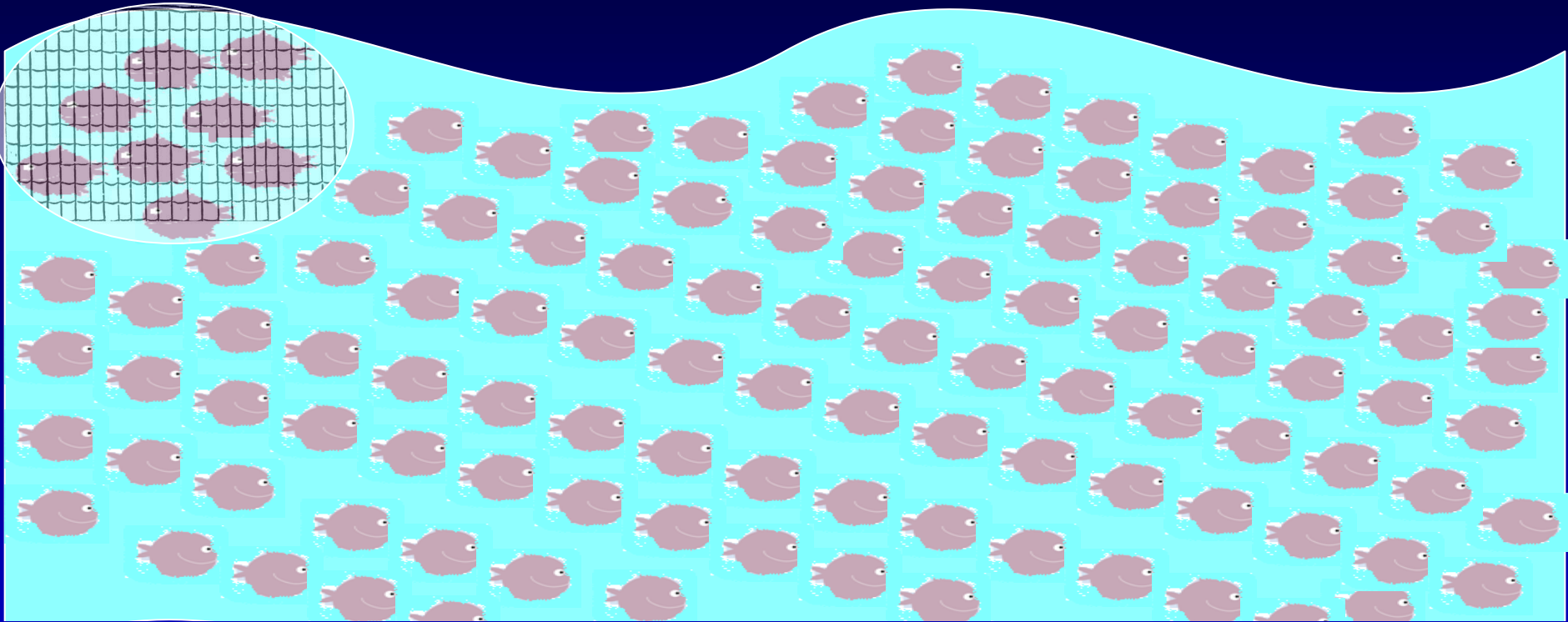
PPV =

$$= a/(a+b) =$$

$$= 7/(7+993) = 0.7\%$$

Identifying babies with disease

Identifying only the babies with the disorder



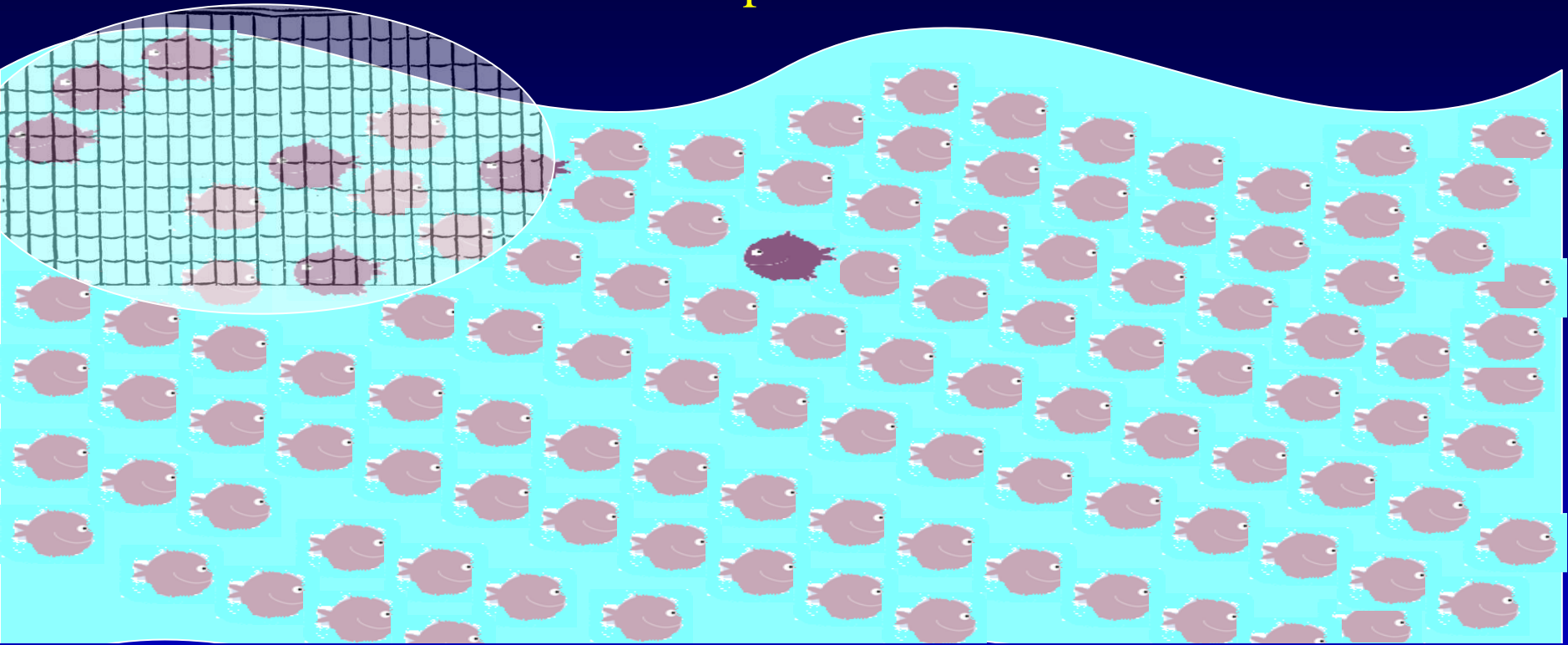
		Disease	
		+	-
Screening Test	+	7	0
	-	0	993

$$\begin{aligned}\text{False Negatives} &= \\ &= c/(a+c) \\ &= 0/(7+0) = 0\%\end{aligned}$$

$$\begin{aligned}\text{PPV} &= a/(a+b) = \\ &= 7/(7+0) = 100\%\end{aligned}$$

Identifying babies with disease

Realistic screen – capture MOST of the babies



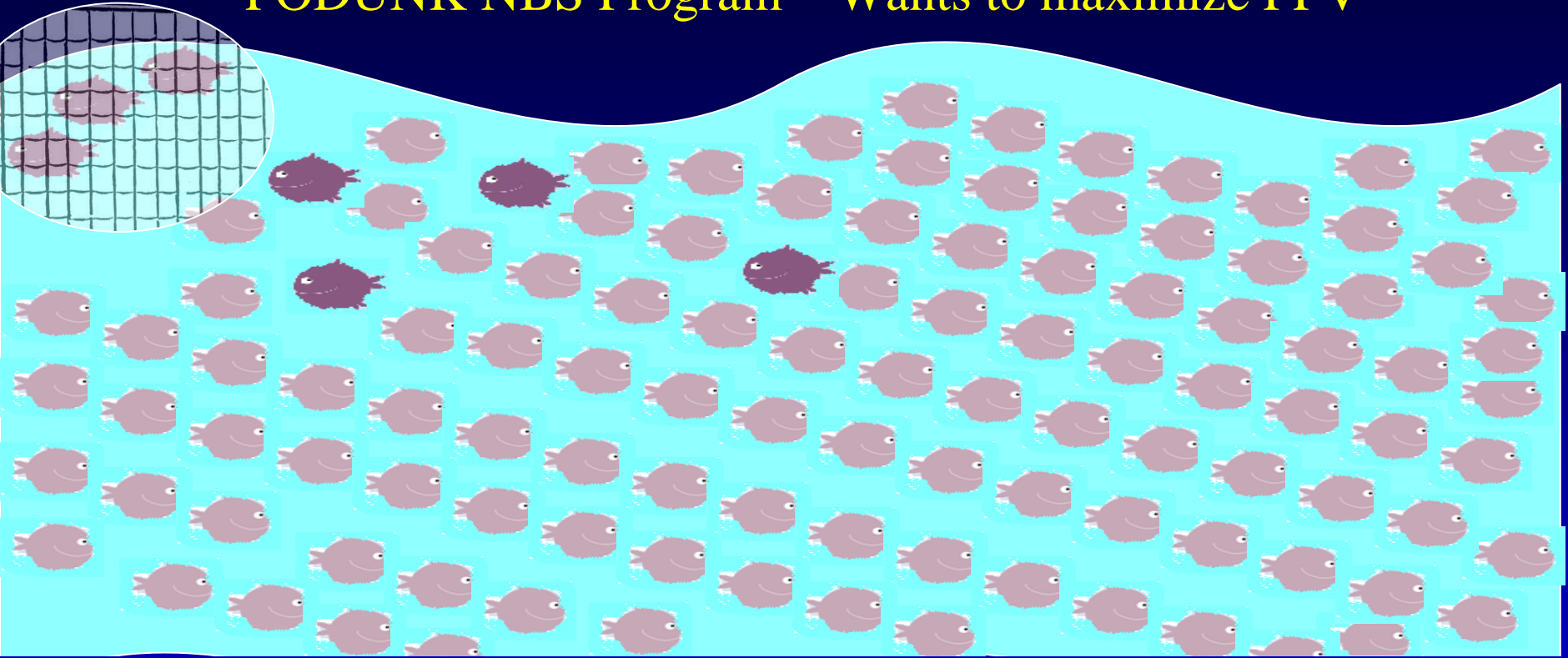
		Disease	
		+	-
Screening Test	+	6	50
	-	1	943

False Negatives =
 $= c/(a+c)$
 $= 1/(6+1) = 14.3\%$

PPV = $a/(a+b) =$
 $= 6/(6+50) = 10.7\%$

Identifying babies with disease

PODUNK NBS Program – Wants to maximize PPV



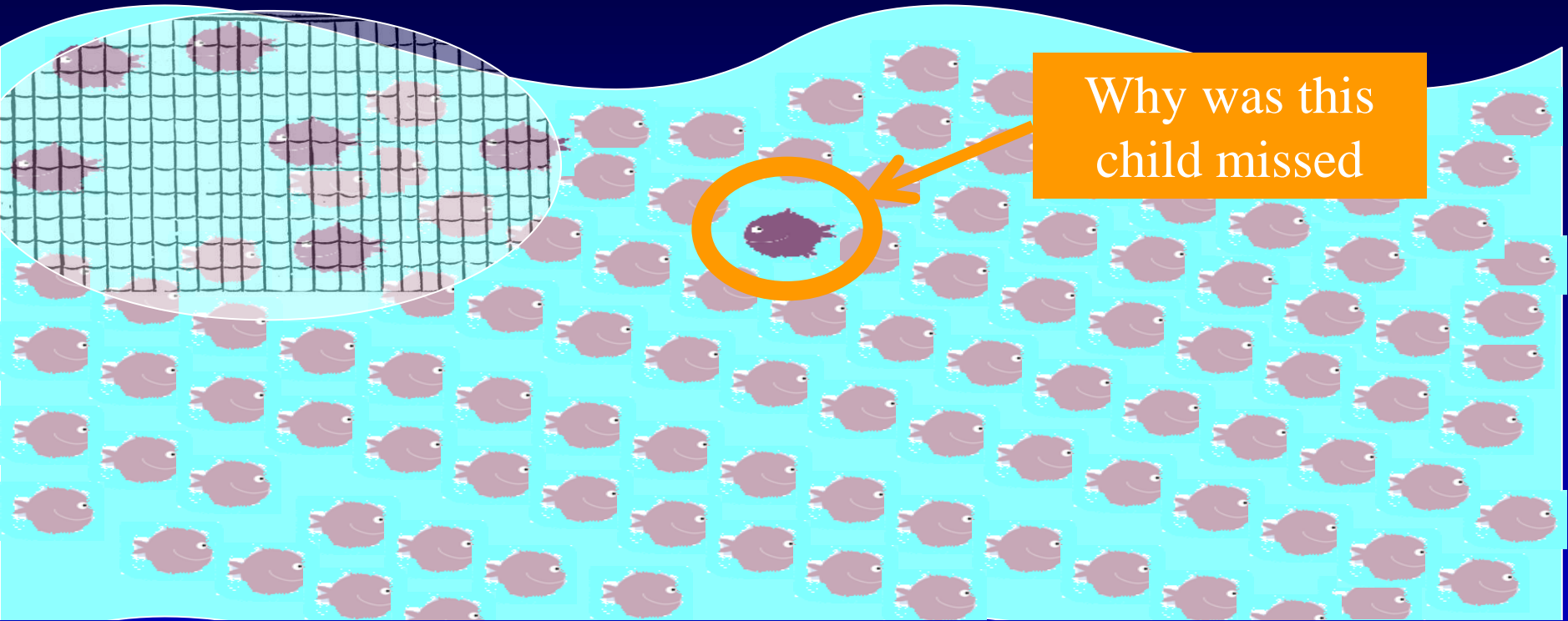
		Disease	
		+	-
Screening Test	+	3	0
	-	4	993

$$\begin{aligned}\text{False Negatives} &= \\ &= c/(a+c) \\ &= 4/(3+4) = 57.1\%\end{aligned}$$

$$\begin{aligned}\text{PPV} &= a/(a+b) = \\ &= 3/(3+0) = 100\%\end{aligned}$$

Identifying babies with disease

Realistic screen – capture MOST of the babies



		Disease	
		+	-
Screening Test	+	6	50
	-	1	943

False Negatives =
 $= c/(a+c)$
 $= 1/(6+1) = 14.3\%$

PPV = $a/(a+b)$ =
 $= 6/(6+50) = 10.7\%$

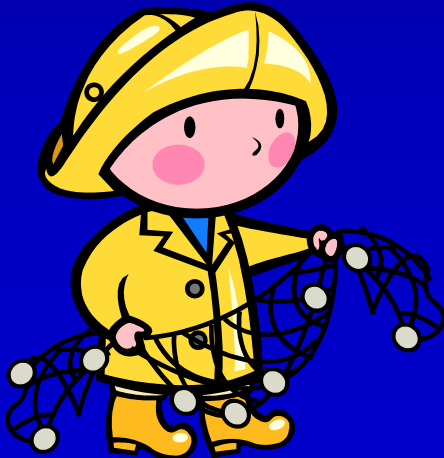
Missed Cases Do Happen

Why are the cases missed?

- True biologic false negative
- Sample mix-ups
- Laboratory errors
- No newborn screen collected

Where can missed cases be found?

- Sub-specialty clinics
- Primary care offices
- Birth defects registries
- Hospital records
- Disease Registries
- Death Certificates



Biologic Examples

Cystic Fibrosis

- Baby with IRT less than the cutoff
- Presents at 6 months of age after struggling with weight gain and respiratory problems.
- Will likely be seen at CF Center – will CF Center report to state?

MCAD (Medium Chain Acyl-CoA dehydrogenase deficiency)

- Well fed or anabolic infants with MCAD may have normal NBS tests.
- Baby may be missed on NBS and if untreated may get sick and die undiagnosed.
- Will the screening program ever know of this baby?

HOW do we solve the problem?

- Awareness of incidence of cases – is the incidence close to what you anticipate?
- Communication SYSTEM with sub-specialty clinics
- Develop relationships with primary care physicians, other state and regional programs
- Search death certificates



Reporting false negatives

- We need a surveillance program with protocols to identify and report false negatives
- Need common definitions
 - WHY were babies missed?
 - Biologic
 - Errors
 - Not screened



Improving newborn screening

- We can only improve newborn screening with all of the information
 - Positive predictive value
 - Missed cases

Thank you to the anonymous
public health professionals

