LABORATORY STANDARDS AND PROCEDURES WORKGROUP

November 3, 2016

Kellie Kelm, PhD, chair
Susan Tanksley, PhD, co-chair

WORKGROUP ROSTER

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Ad Hoc Experts: Ed McCabe

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Co-chair: Susan Tanksley
HRSA staff: Ann Ferrero

Agenda

- Welcome & roll call
- Workgroup roster updates
- Presentations:
  - Strategies to Reduce False Positives in Newborn Screening by Susan Tanksley
  - False Positives in Newborn Screening: What Can We Do About It? By Piero Rinaldo

STRATEGIES TO REDUCE FALSE POSITIVES IN NEWBORN SCREENING

ACHDNC LABORATORY STANDARDS AND PROCEDURES WORKGROUP

Susan Tanksley, PhD

November 3, 2016

Overview

- What is a false positive?
  - Come up with a common definition
- Why do we have false positives?
  - Nature of screening for a rare disorder
- Strategies to reduce false positives
  - Primary screen
  - Second-tier testing

Considerations before Implementation

- Ensure testing platform and methodologies are analytically valid
- Evaluate diagnosed cases to determine appropriateness of the cutoff and analytes
- Determine goal of screening and acceptable clinical sensitivity and specificity
- Need for 2nd or 3rd-tier assays
  - e.g. HPLC, LC/MSMS, mutation panel, sequencing analysis
- Need for a second specimen

Molecular Second-Tier Testing

- Part of screening assay e.g. Cystic fibrosis mutation analysis
- Supplemental, e.g. β-globin and GALT mutation analysis
- Why use a molecular second-tier test?
  - To increase sensitivity without compromising specificity
  - To increase specificity of a complex assay
  - When the primary analyte is transient
  - To speed diagnosis in order to avoid serious medical consequences
  - Significant founder mutations in a population

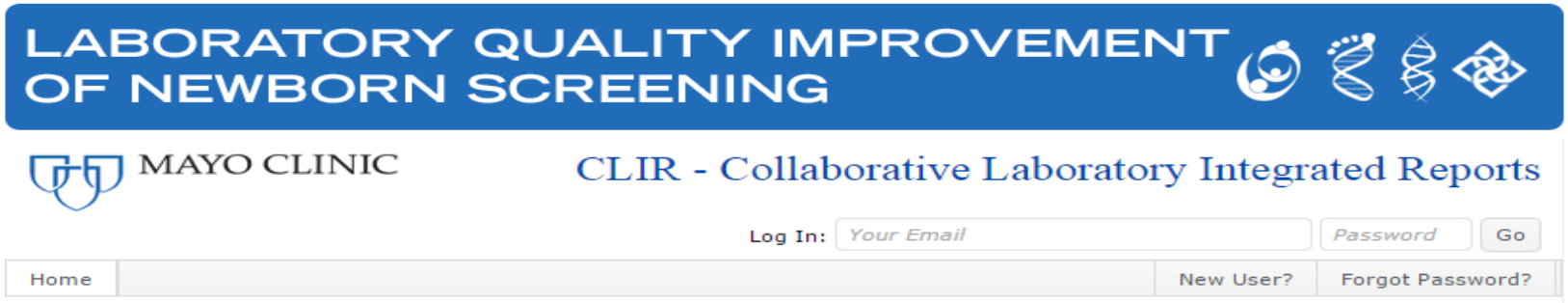
False Positives in Newborn Screening: What Can We Do About It?

Piero Rinaldo, MD, PhD

Professor of Laboratory Medicine

T. Denny Sanford Professor of Pediatrics

Mayo Clinic, Rochester (MN)



The Advisory Committee on Heritable Disorders in Newborns and Children

Lab Standards and Procedures Workgroup (webinar)

November 3, 2016

Outline

- Understanding the problem
- Reduction of false positive (R4S)
- Second tier tests
- Prevention of false positives (CLIR)
- An international call to action

False Positives:
The Dark Side of Newborn Screening

- Recall and repeat analysis (2nd, 3rd, 4th…)
- Disruption of care (premature, sick newborns)
- ER visit(s), admission(s)
- Confirmatory testing ($$$)
- Referral to multiple specialists, 2nd opinions
- Disruption of working parents schedule
- Impact on extended family life (stress)

Addressing the Fallout Of Newborn Screening

Government and Researchers Seek to Reduce False Positives, Improve Physician Education and Follow-Up for Families

By Shirley S. Wang

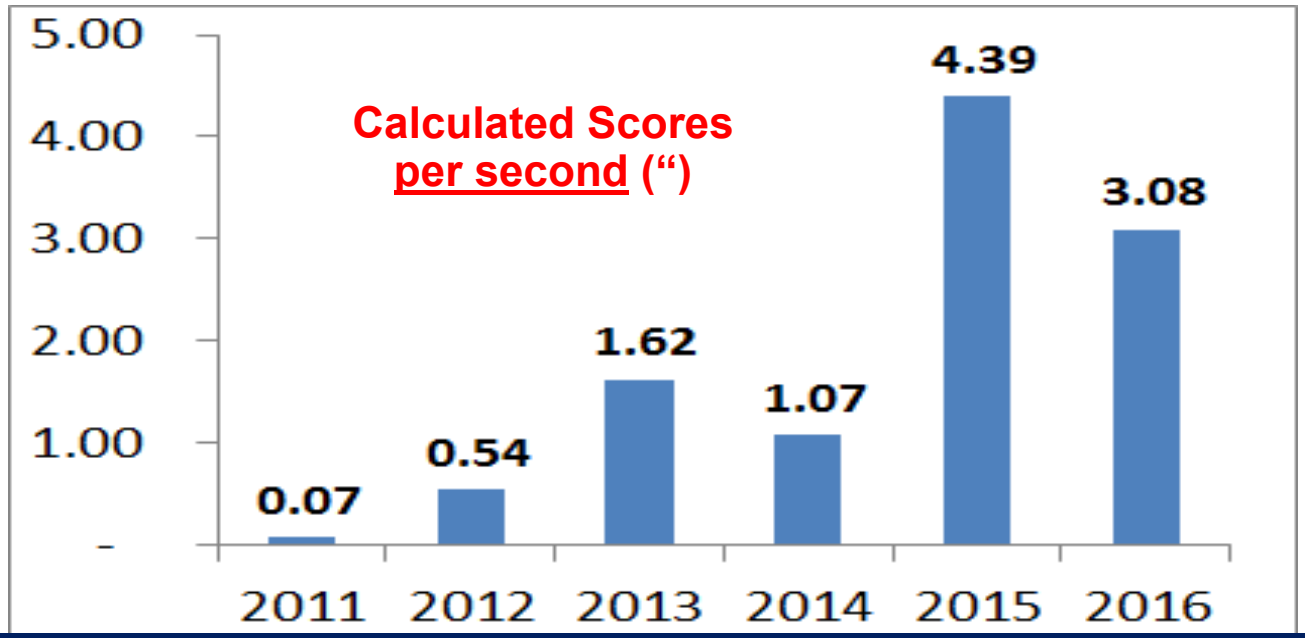
Unintended Impact

help families find treatment. And researchers and health offi-

Why $pecificity Matter$

- A cumulative false positive rate (FPR) of 1.5% means
  - 63,000 false positive (FP) cases per year in the US
  - 1,200 per week
  - 175 per day
- The average cost of short-term follow up (one episode of care) varies between $500 and $2,000
- Assuming an average cost of $1,000, a change of 0.1% of the FPR is equal to ±$4.2M/year of health care expenses
- If we were to add to the RUSP 50 more conditions and "only" double the cumulative FPR, the burden (unnecessary costs) on health care systems could be equal to $126M/year. Worse case scenario could be as high as 5x
- A cumulative FPR (for old and new tests) kept at 0.5% could save $50-100M/year over current health care expenditures

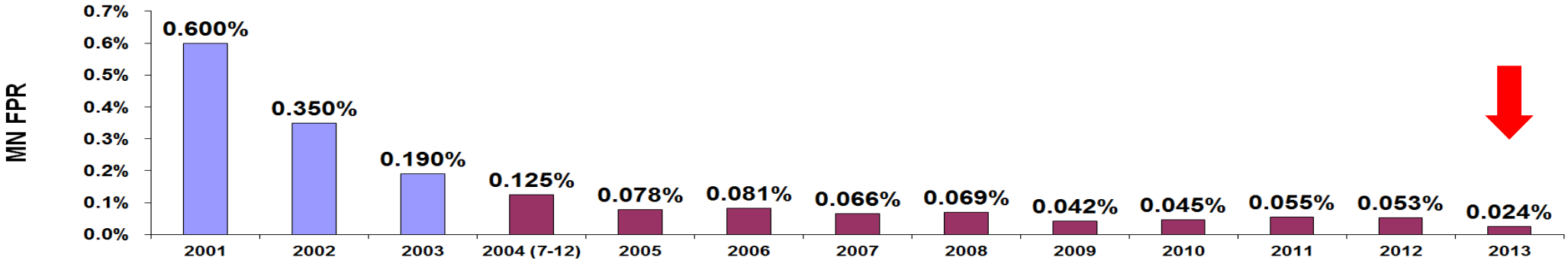
Status of R4S Project
(as of October 31st, 2016)



Do R4S tools improve performance?

Calculated scores with post-analytical tools 321,216,608

MN Performance by MS/MS (False Positive Rate 2004-2013)



Period	2013		
Births	71,207		
Abnormal cases	55*	(N=28)	
True positives	38	USA	
False positives	17	AVERAGE	Delta
Detection rate	1:1,874	1:3,212	+ 42%
FPR	0.024%	0.51%	– 95%
PPV	69%	18%	+ 74%

2nd Tier Tests

J Inherit Metab Dis
DOI 10.1007/s10545-007-0691-y

NEWBORN SCREENING

Reduction of the false-positive rate in newborn screening by implementation of MS/MS-based second-tier tests: The Mayo Clinic experience (2004–2007)

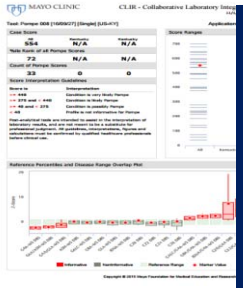
D. Matern · S. Tortorelli · D. Oglesbee · D. Gavrilov · P. Rinaldo

- A cost effective approach to improve specificity when reference and disease ranges overlap considerably
- Same specimen, no additional patient contact
- Normal result overrules primary screening
- Can be regionalized

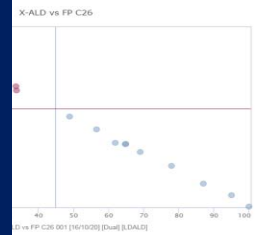
Newborn Screening (10plex) for Pompe MPS-I X-ALD

Plot by Condition (reference and disease ranges of markers and ratios)

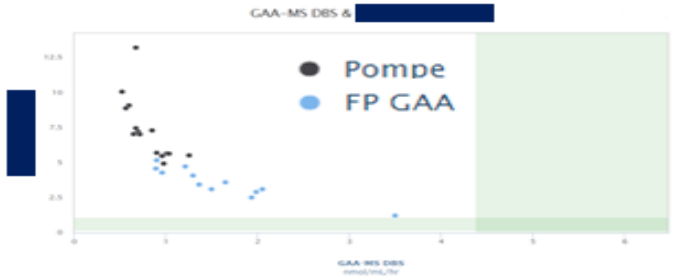
Dual Scatter Plots (INITIAL differential diagnosis true positives vs. false positives)

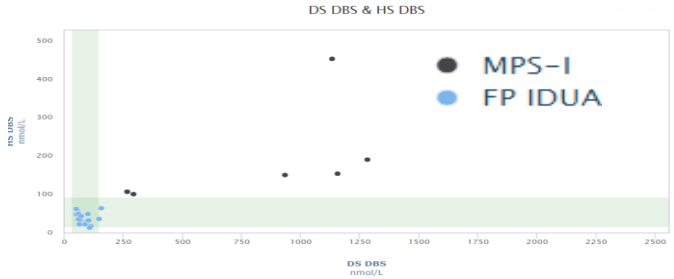


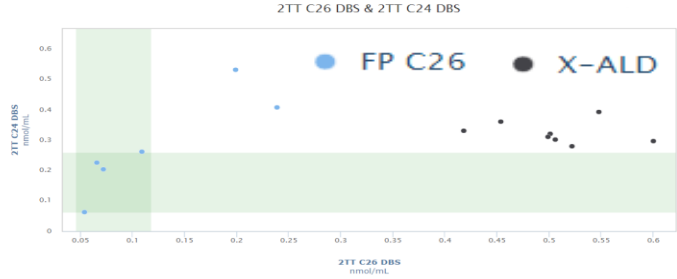
Near 0% FPR
for Pompe, MPS-I, and X-ALD is achievable without additional patient contact and molecular testing



Second tier tests (FINAL differential diagnosis true positives vs. false positives)



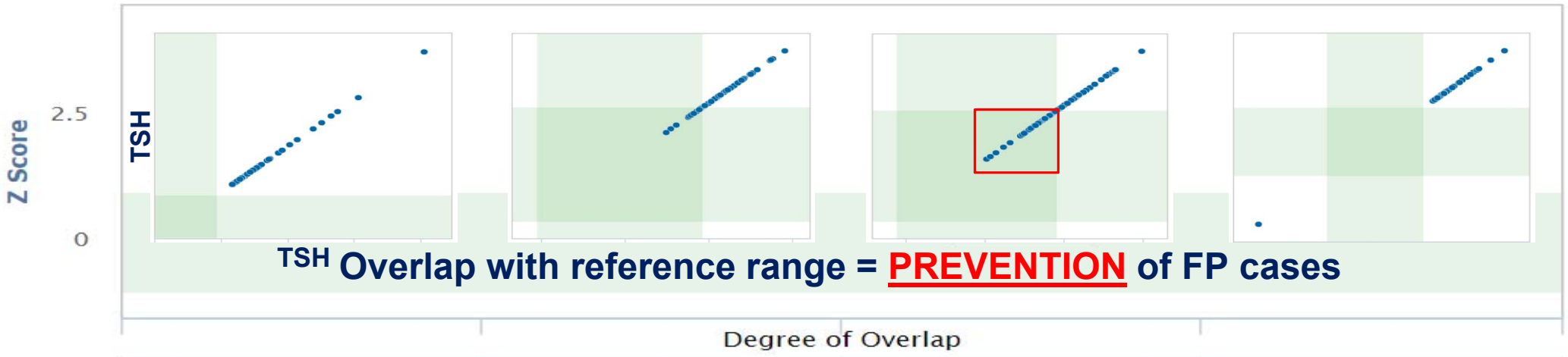




What Does CLIR Do, Exactly?

- Replaces conventional reference ranges
  - With continuous, $(\text{covariate})_n$-adjusted %iles
- Replaces analyte cutoff values
  - With a condition-specific degree of overlap
- Enhances the clinical utility of individual markers
  - With all possible permutation of ratios
- Replaces sequential algorithms (“AND”)
  - With tool-based parallel algorithms (“OR”)

Covariate-Adjusted Disease Ranges of TSH in False Positive Cases (Site 1, N = 92)



55% reduction of FP before even making tools

TSH Unadjusted	TSH Adjusted for Age	TSH Adjusted for Age & BW	TSH Adjusted for BW
Overlap: 0%	Overlap: 30%	Overlap: 55%	Overlap: 1%

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