

Newborn Screening on New Disorders
Mucopolysaccharidosis I (MPS1) and other
Lysosomal Storage Disorders (LSDs)
– Illinois' experiences

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Why Illinois Decided To Initiate Screening for MPS1 and other LSDs

2007 - Legislative mandate for five LSDs,
including Pompe, Fabry, Niemann-Pick A/B, Krabbe and Gaucher

2011- MPS-I (Hurler) & MPS-II (Hunter), subsequently added
Senate Bill 1566 (revised 2011):

“Provide all newborns with expanded screening tests for the
presence of certain Lysosomal Storage Disorders known as
Krabbe, Pompe, Gaucher, Fabry, and Niemann-Pick.”



Implementing screening for MPS I and other LSDs:

Key decision points



1. Available test methodology/technology

- * should be fast, easy, and inexpensive
- * capable of multiplexing using single DBS high throughput (to handle 600 -1800 specimens / day)
- * provide consistent results

2. Availability of instrumentation / reagents

3. Ease of hiring / training laboratory personnel

4. Completion of validation studies and pilot testing

Changes to prepare for the screening

Purchase new instruments (4-5 UPLC/MS/MS)

Laboratory construction (electrical, gas, ventilation, temperature control and exhaust system).

Hire and train additional three technologists for the new test method.

Introduce Saturday shift due to 17 hours incubation

Integrate Lab information management system (LIMS) to receive data and generate reports



How did we set up cut-off range?

Establishment of the Cut-off Range

Analyzed de-identified random samples' (approx. 12,000), checked distribution of enzyme activities, and obtained percentile range

Analyzed confirmed positive samples and checked percentile range distribution in the normal pool

Initial cut-off range was established between 0.05 to 0.10 percentile of normal pool and 95-100 percentile of confirmed samples

Continue monitoring new confirmed or false positive cases and update the cut-off range

Enzyme activities were expressed as percentage of batch median.

Repeat test rate

The positive repeat rate is 0.05% for MPS I. Positive specimens are referred to a LSD geneticist.

The borderline repeat rate is 0.08%. After confirmation, a second specimen submission is requested.

Hit Rate/Provisional cut-offs (Pilot vs population screening)

Started with conservative cut-off due to low number of confirmed positive samples during validation studies.

During pilot study, compared the presumptive positives sample results (below initial cut-off) with CLIA certified lab to fine tune the cut-off value (conservative cut-off)

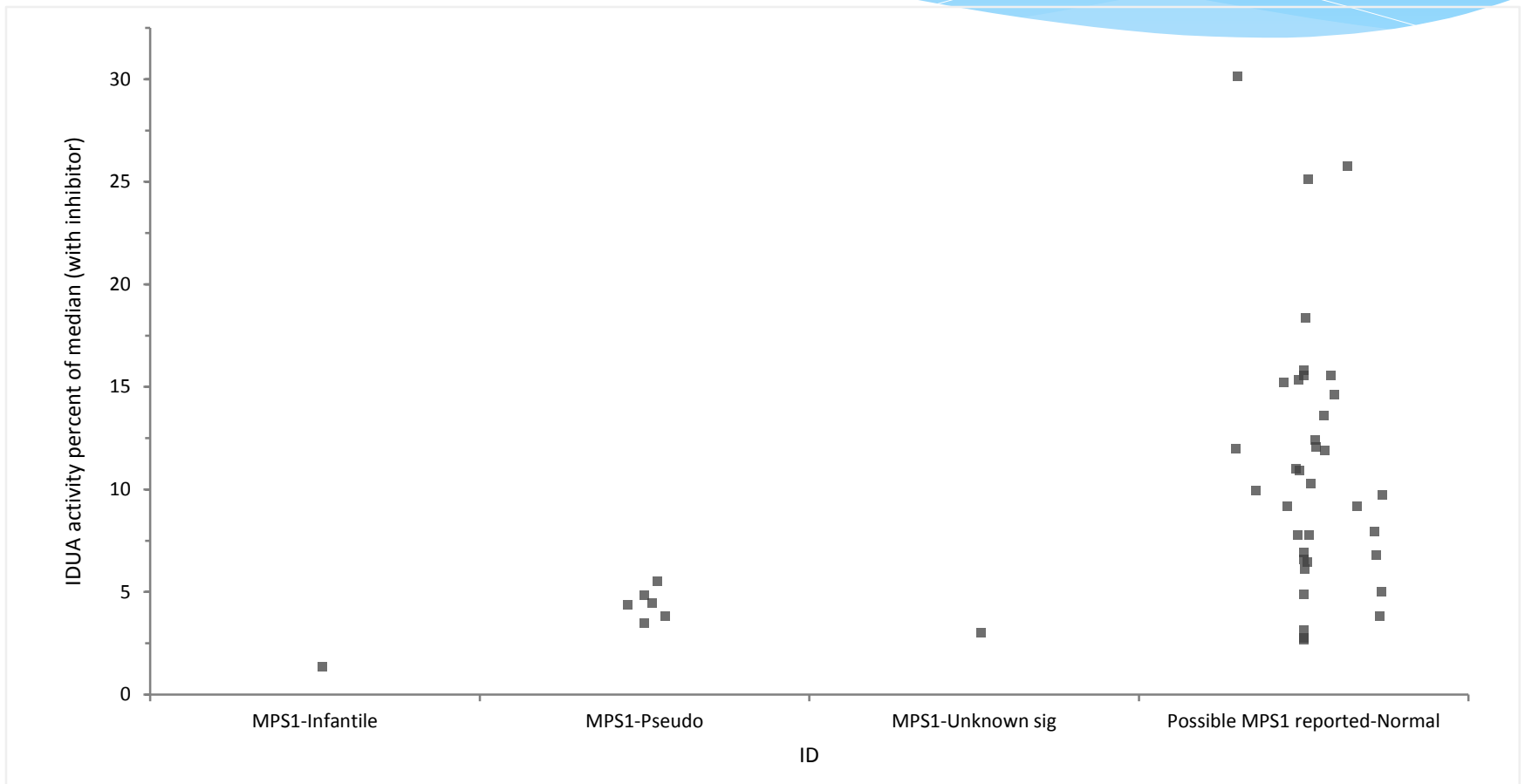
Improve test method and cut-offs by reviewing confirmed and false positive results as well as CDC PT specimens to reduce the false positive rate.

Six lysosomal enzymes normal and abnormal ranges (disorder logic)

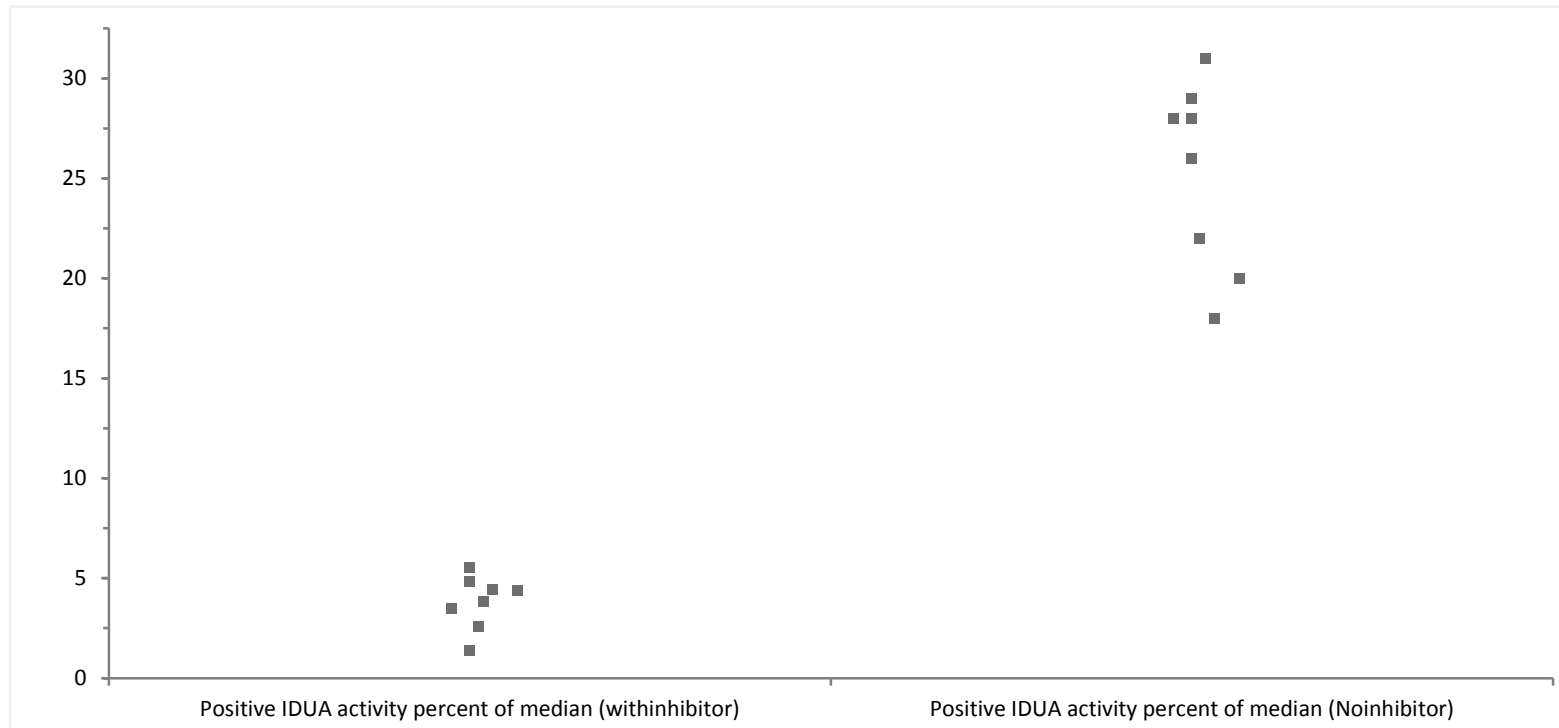
Unit: (% of batch median)

| Enzyme | Disorder | Borderline ¹ | Positive ¹ |
|-------------------|--------------|-------------------------|-----------------------|
| GLA | Fabry | >13 and ≤18 | ≤13 |
| GAA | Pompe | >18 and ≤22 | ≤18 |
| ASM | Niemann-Pick | >11 and ≤15 | ≤11 |
| GBA | Gaucher | >17 and ≤20 | ≤17 |
| IDUA ² | MPS1 | >14 and ≤18 | ≤14 |

IDUA activity percent of median (with inhibitor)



Positive IDUA activity percent of median (with inhibitor), Positive IDUA activity percent of median (no inhibitor)



Outcome of screening in 219,793 infants

| Disorder | Total # Abnormal (Include Borderline sand Positives)* (%) | # <37 weeks gestation ¹ (%) | Outcome | | | | | |
|----------|--|---|---------|----------|---------|----------------------|--------------|-------------|
| | | | Normal | Affected | Carrier | Pseudo deficiency | Undetermined | Unresolved* |
| MPS I | 151 (0.06%) | 55 (37%) | 87 | 1 | 5 | 30 | 4 | 24 |

* Total 84 positives call-outs (0.038%); False positive rate = 0.025% (exclude undetermined and Unresolved);
Estimate false positive rate /100,000 = 25

*Unresolved: infants who have expired, could not be located, or where DNA testing was refused or unable to be completed

IL State Newborn Screening for MPS1 Disease—Summary (update)

| | |
|--|--------------|
| Incidence | 1 in 369,572 |
| Abnormal call-out rate | 0.06% |
| Screening method | UPLC/MS/MS |
| Total samples screened (06/03/2017) | 369,572 |
| Total True MPS1 Cases | 1 |
| <i>Infantile-onset</i> | 1 |

Important points

The importance of making the buffer and reagents

UPLC/MS/MS instrument cleaning and trouble shooting

The variation between instruments and batches/plates

Multiple LSD enzymes below the cut-offs

Age related enzymes activities

Acknowledgments

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