Newborn drug testing

Laboratory testing options, and what to expect from results

Gwen McMillin, PhD, DABCC(CC,TC), FAACC

Professor, Clinical Pathology, University of Utah Health

Medical Director, Clinical Toxicology, ARUP Laboratories

NOVEMBER 2022

Outline

Drug exposure during pregnancy

Biological specimens to collect and/or test

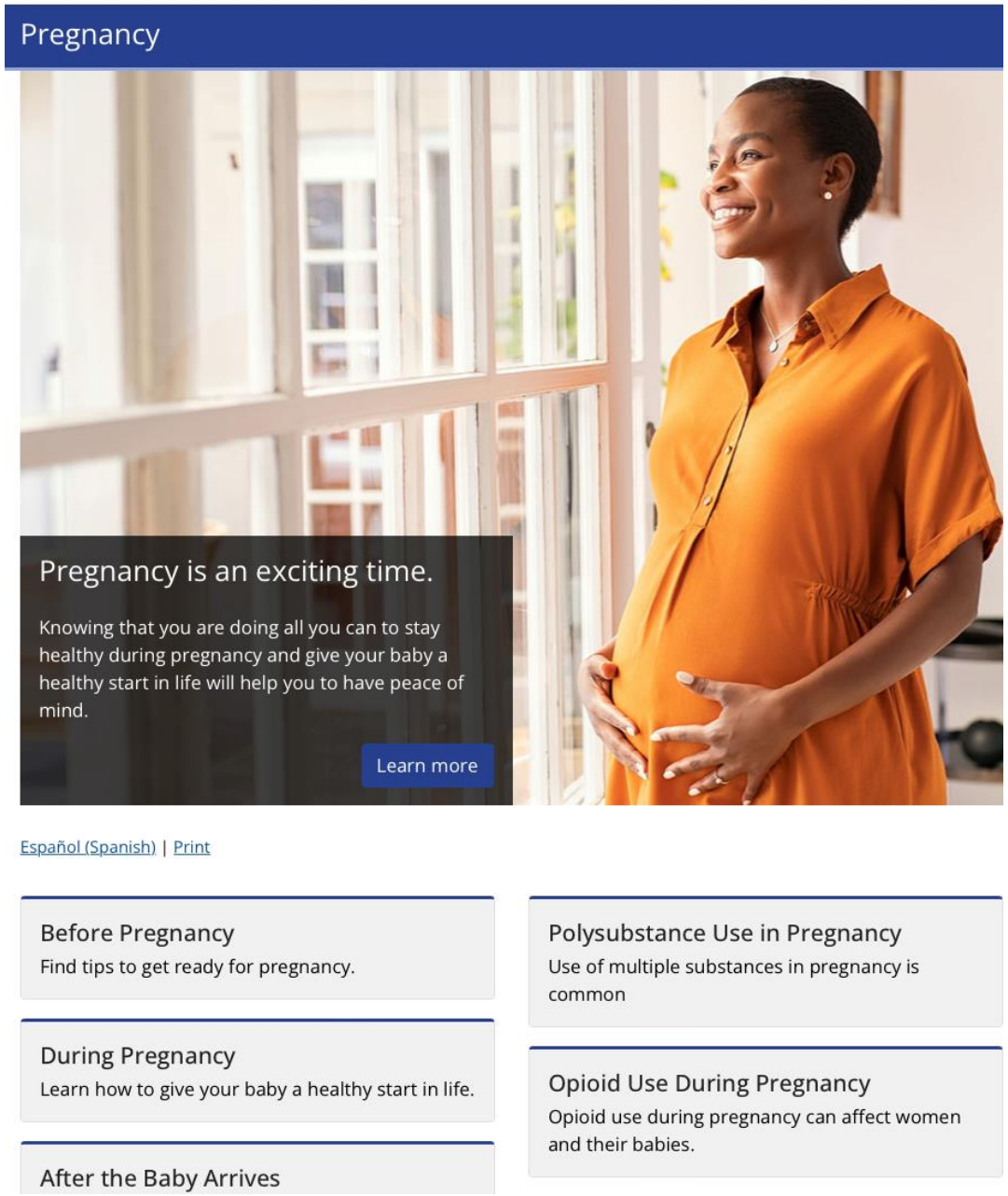
Approaches to testing

Interpretation of results

Investigating unexpected results

Objectives

- Compare and contrast specimen types used to detect drug-exposed newborns.
- List challenges associated with comparing cutoffs for meconium and umbilical cord drug tests.
- Describe how unexpected newborn drug testing results should be investigated.



Most pregnant people take drugs/supplements

- Drugs of most concern are those associated with adverse outcomes, including many illicit, prescription, non-prescription, and social drugs.
- Drug use patterns?
- Polysubstance use?
- Impact on breastfeeding?

https://www.cdc.gov/pregnancy/index.html

Drugs and Lactation Database (LactMed)

< Prev Next >

Bethesda (MD): National Library of Medicine (US); 2006-.

Copyright and Permissions

Search this book

The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency.

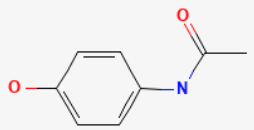
Contents

Acetaminophen

Last Revision: March 21, 2022.

Estimated reading time: 3 minutes

CASRN: 103-90-2



Drug Levels and Effects

Go to:

Summary of Use during Lactation

Acetaminophen is a good choice for analgesia, and fever reduction in nursing mothers. Amounts in milk are much less than doses usually given to infants. Adverse effects in breastfed infants appear to be rare.

Drug Levels

Maternal Levels. A single oral dose of 650 mg of acetaminophen was given to 12 nursing mothers who were 2 to 22 months postpartum. Peak milk levels of 10 to 15 mg/L occurred between 1 and 2 hours after the dose in all patients. Acetaminophen was undetectable (<0.5 mg/L) in all mothers 12 hours after the dose. The authors calculated that an infant who ingested 90 mL of breastmilk every 3 hours would receive an average of 0.88 mg of acetaminophen or 0.14% (range 0.04 to 0.23%) of the mother's absolute dosage.[1] Using data from this study, an infant would receive a maximum of about 2% of the maternal weight-adjusted dosage.

Three women took a single 500 mg dose of acetaminophen. Peak milk levels averaging 4.2 mg/L occurred within 2 hours after the dose.[2] Using data from this study, an infant would receive a maximum of about 3.6% of the maternal weight-adjusted dosage.

Four women who were 2 to 8 months postpartum were given a single 1 gram dose of acetaminophen. Milk was completely emptied from one breast every 30 minutes for 3 to 3.5 hours, with a final sample from the opposite breast. Peak milk levels occurred between 1 and 2.5 hours after the dose. The acetaminophen level in the breast that was sampled only once had a lower level than the breast sampled at half-hour intervals. The authors estimated that a breastfed infant would receive an average of 1.1% and a maximum of 1.8% of the maternal weight-adjusted dosage. This dose is about 0.5% of the lowest recommended infant dose of acetaminophen.[3]

Infant Levels. No acetaminophen was detected in the urine of 12 breastfed infants aged 2 to 22 months after maternal ingestion of 650 mg of acetaminophen.[4]

https://www.ncbi.nlm.nih.gov/books/NBK501922/

Drugs and Lactation Database (LactMed)

< Prev Next >

Bethesda (MD): National Library of Medicine (US); 2006-.

Copyright and Permissions

Search this book

The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency.

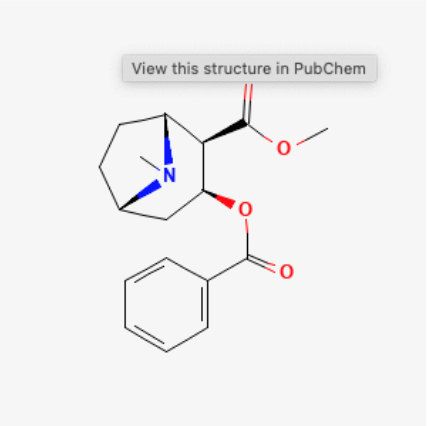
Contents

Cocaine

Last Revision: July 20, 2020.

Estimated reading time: 6 minutes

CASRN: 50-36-2



Great resource!

However, breast milk is not recommended as a routine specimen for drug testing.

Drug Levels and Effects

Go to:

Summary of Use during Lactation

No data are available on the medical use of **cocaine** in nursing mothers. However, because of its chemical nature, high concentrations of **cocaine** are expected in milk.[1,2] **Cocaine** and its metabolites are detectable in breastmilk, although data are from random breastmilk screening of mothers who used **cocaine** recreationally rather than controlled studies. **Cocaine** breastmilk concentrations have varied over 100-fold in these reports. Newborn infants are extremely sensitive to **cocaine** because they have not yet developed the enzyme that inactivates it and serious adverse reactions have been reported in a newborn infant exposed to **cocaine** via breastmilk.

Cocaine should not be used by nursing mothers or smoked (such as with "crack") by anyone in the vicinity of infants because the infants can be exposed by inhaling the smoke.[3,4] Other factors to consider are the possibility of positive urine tests in breastfed infants which might have legal implications, and the possibility of other harmful contaminants in street drugs. A breastfeeding abstinence period of 24 hours has been suggested for women who occasionally use **cocaine** while breastfeeding, based on the rapid elimination of **cocaine** by the mother.[5] Some authors have proposed that breastfeeding be discontinued only for those infants who test positive for **cocaine** exposure.[6] However, the Academy of Breastfeeding Medicine suggests that women who have abused **cocaine** generally should not breastfeed unless they have a negative maternal urine toxicology at delivery, have been abstinent for at least 90 days, are in a substance abuse treatment program and plan to continue it in the postpartum period, have the approval of their substance abuse counselor, have been engaged and compliant in their prenatal care, and have no other contraindications to breastfeeding.[7]

https://www.ncbi.nlm.nih.gov/books/NBK501922/

Pregnancy is a unique opportunity for care.

May represent the only time a person seeks medical care and is forthcoming about substance use, misuse, and addiction.

Pregnancy is a unique opportunity for care.

All pregnant people should be screened for drug use.

- American Society of Addiction Medicine, 2012
- American College of Obstetricians and Gynecologists, 2017

Examples of drug screening tools

- Self-report

- Questionnaire
  - » NIDA quick screen
  - » SURP-P (substance use risk profile – pregnancy)
  - » CRAFFT (items related to car, relax, alone, forget, friends, trouble)
  - » 5P's (parents, peers, partner, pregnancy, past)
  - » WIDUS (Wayne indirect drug use screener)

- Biological testing

Ondersma et al, *Addiction* 114:1683-93, 2019

Biological testing vs self-report in pregnancy

Marijuana use in Colorado, a state with legalization

Enrollment at delivery

- Singleton pregnancies presenting for delivery at 24 weeks of gestation or greater were enrolled at two urban medical centers in Colorado (n=116).

- Self-report of marijuana use over the previous 30 days, was collected two ways:
  - » Healthcare provider: 2.6% (n=3) reported use
  - » Anonymous survey: 6.0% (n=7) reported use

- Newborn drug testing (umbilical cord tissue)
  - » 22.4% (n=26) of samples were positive

Metz et al, *Obstet Gynecol*, 133:98-104, 2019

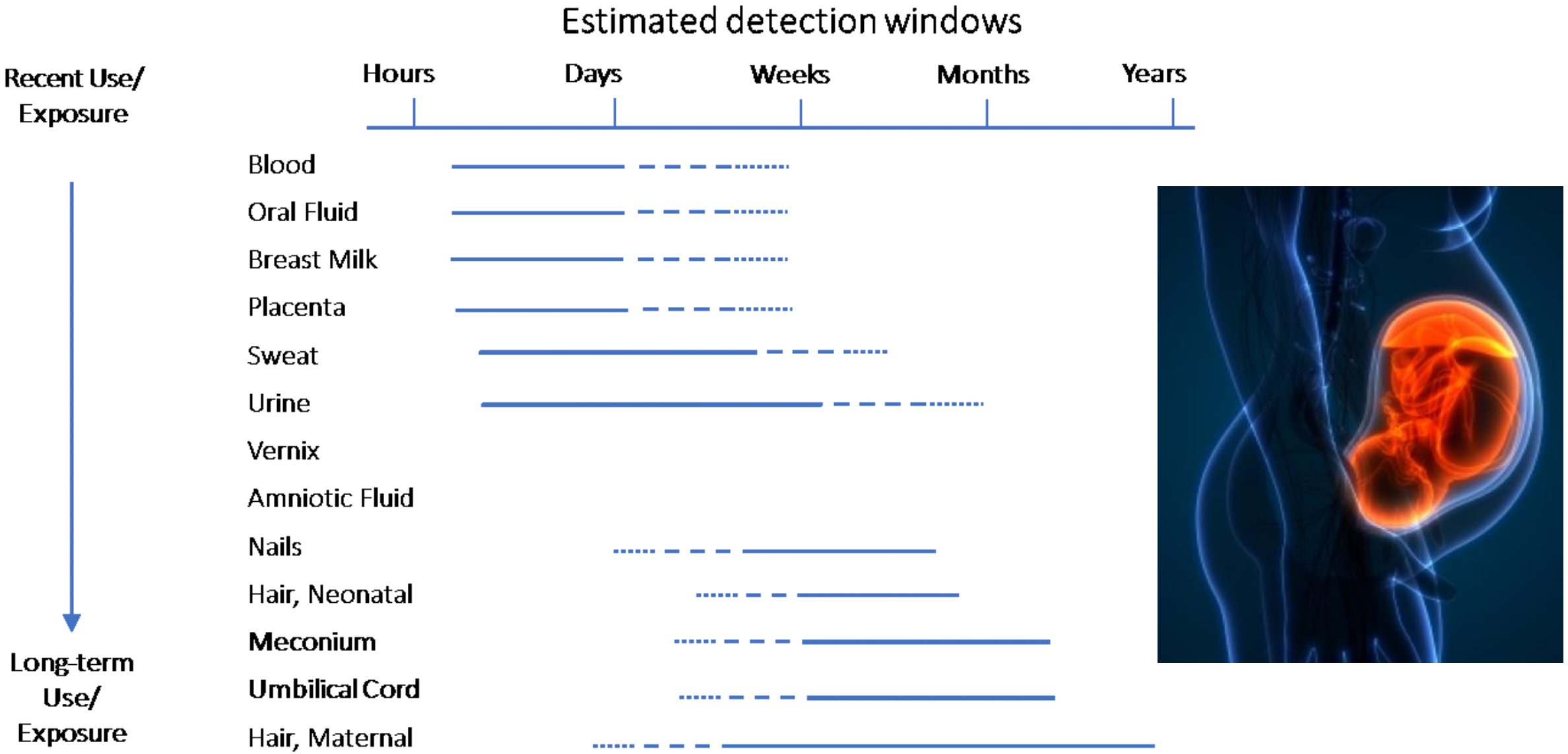
Longitudinal study

- Enrolled pregnant people (n=51) who self-reported marijuana use at first pre-natal visit (<16 wks gestation).
- Study visits included survey, collection of urine and blood.
  - » Enrollment (<16 wks)
  - » 18-22 wks
  - » 32-36 wks
  - » Delivery – umbilical cord collected and tested

Metz et al, *Addiction*, 117:172-84, 2021

- 87% agreement between self-report and maternal urine and/or blood testing.
- 44% demonstrated evidence of ongoing use at delivery.
- 94% of cords were positive when ongoing use was reported at delivery.

Conclusion: biological testing and self-report in combination is best



Wabuyele et al, *Ther Drug Monti* 40:166-85, 2018

Common biological specimens

	Maternal urine or blood	Newborn urine
Ease of collection	Yes	No (1^{st} void often missed)
Quantity of specimen	Good	Varies
Temporal representation	Short	Short
Detects medications administered in the hospital	No (if collected prior to meds)	Maybe (timing is important)
Detects drug exposure after birth	No	Maybe
Testing widely available	Yes	Yes

Common biological specimens

	Maternal urine or blood	Newborn urine	Cord tissue	Meconium
Ease of collection	Yes	No (1st void often missed)	Yes	No (laborious, unpredictable)
Quantity of specimen	Good	Varies	Yes	Varies
Temporal representation	Short	Short	~3rd trimester (less than meconium?)	~3rd trimester
Detects medications administered in the hospital	No (if collected prior to meds)	Maybe (timing is important)	Maybe (blood in cord increases risk)	Maybe (timing is important)
Detects drug exposure after birth	No	Maybe	No	Maybe
Testing widely available	Yes	Yes	No	Maybe

Testing for twins or triplets?

- Meconium
  - » 2,394 twins and 60 triplets
  - » Mismatched results were observed for 13% of twins, 10% of triplets
  - » Chart review identified two common reasons
    - Medications administered directly to one newborn but not the other, before meconium was collected
    - Results that straddled the cutoff (one above, one below)
- Umbilical cord
  - » 3,550 twins and 66 triplets
  - » Mismatched results: 3% of twins, 0% of triplets
  - » All mismatches straddled the cutoff

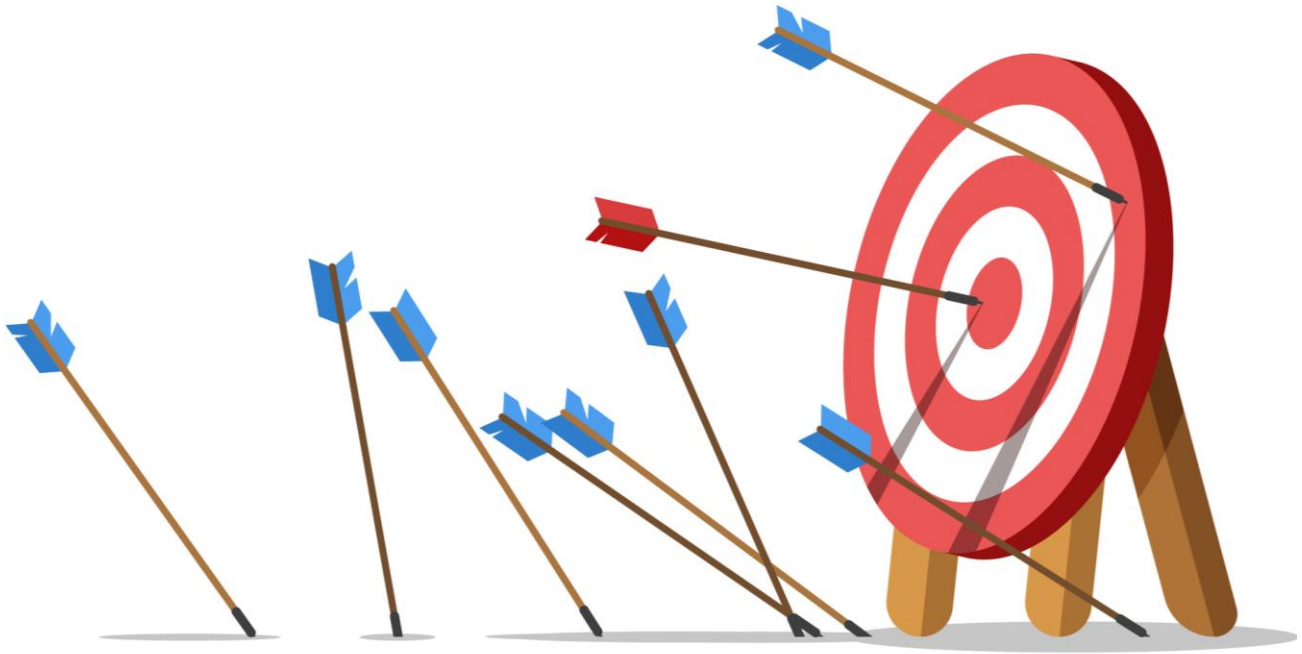
Wood et al, *JAT* 38:397-403, 2014
Nelson et al, *JAT* 46:611-8, 2022

Analytical sensitivity and specificity

Approach matters

Goal of clinical drug testing?

Separate and detect targeted drug analyte(s), at clinically relevant concentrations with accuracy and precision.



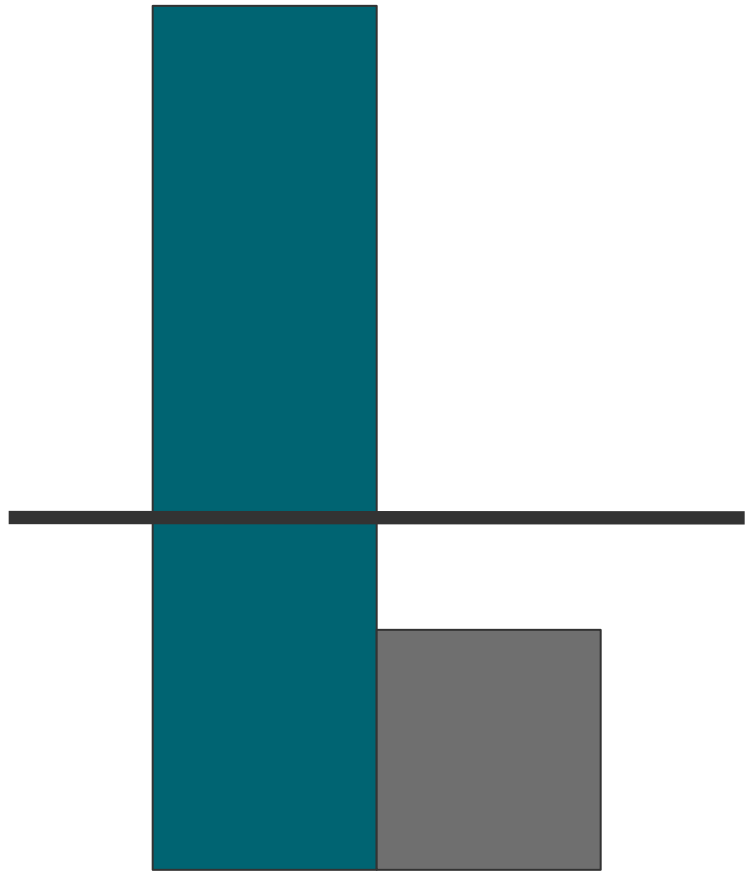
Common drug testing methods

- Immunoassay (IA) *separation and detection*
  - » Many platforms and formats
  - » Monoclonal or polyclonal antibodies (Ab)
- Chromatographic *separation*
  - » Liquid (LC)
  - » Gas (GC)
- Mass spectrometric *detection*
  - » Single stage (MS)
  - » Tandem (MS/MS)
  - » Time-of-flight (TOF)

- *False negative and false positive results are possible with any method*

Detection of drugs depends on

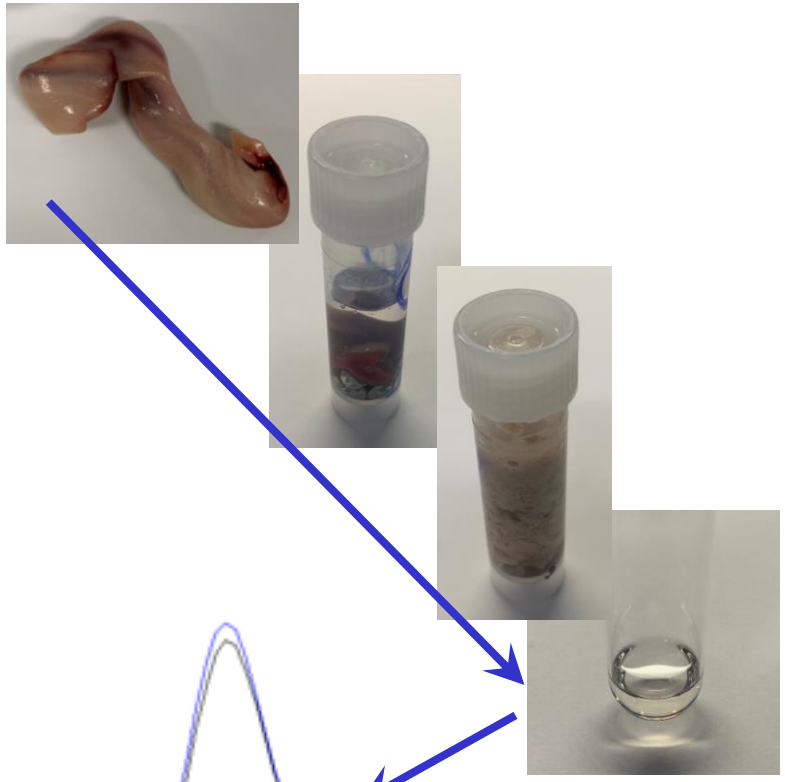
- Specimen quality, handling, and timing of collection relative to last drug use
- Drugs involved, drug use patterns, individual pharmacokinetics, individual patient characteristics, and stability of target analytes
- Analytical methods
  - » Technology applied
  - » Assay design

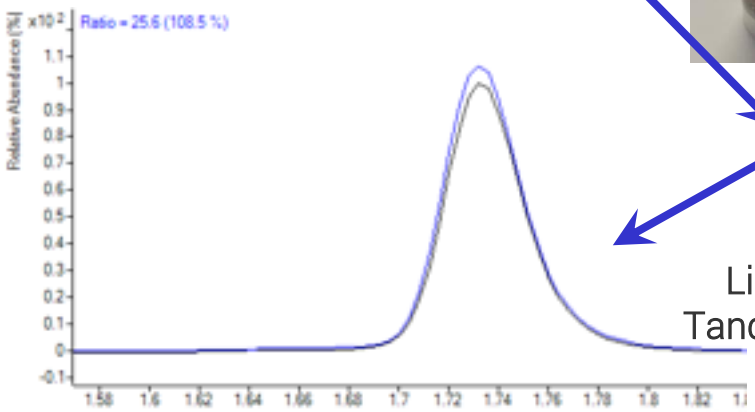


McMillin et al, *J Pain Palliat Care Pharmacother 27*:322-39, 2013

Considerations

- Collection: universal, risk-based, for cause
- Sample handling and preparation
- Testing variables:
    - Targeted analytes
    - Methods for compound identification
    - Performance characteristics
    - Qualitative vs quantitative
    - Interferences
    - Cutoff concentration vs LOQ
    - Quality assurance

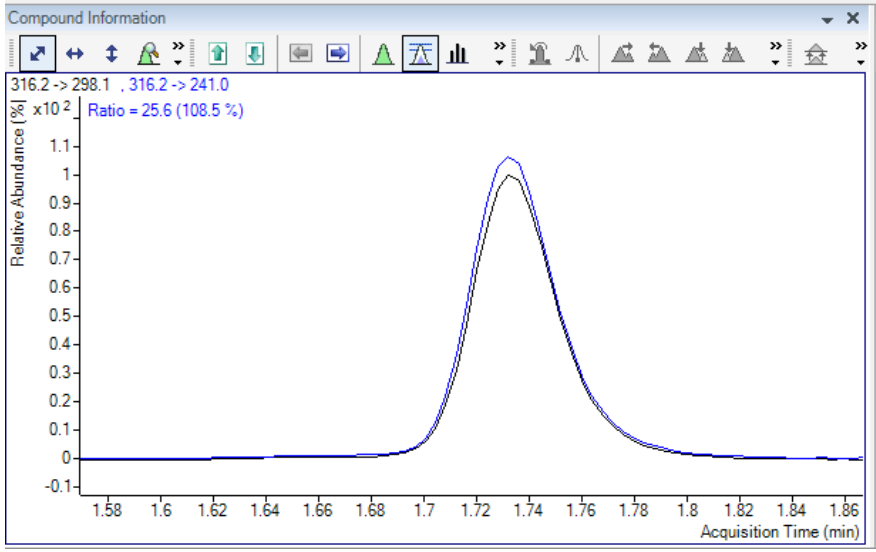


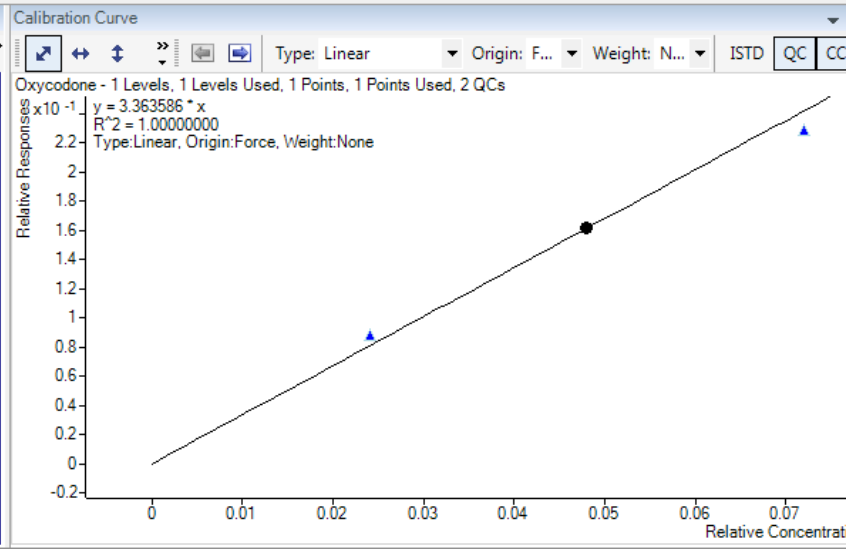


Liquid chromatography
Tandem mass spectrometry
(LC-MS/MS)

Example data for oxycodone in a panel

Name	Transition	RT	Resp.	MI	Calc. Conc.	Final Conc.	Accuracy	Transition	Ratio	MI	Name	Transition	RT	Resp.	Transition	Ratio	MI
Oxycodone	316.2 -> 298.1	1.732	580853		3.7760	3.7760		316.2 -> 241.0	25.6		6-acetylmorphine-d6	334.2 -> 165.1	1.724	2286674	334.2 -> 211.0	52.5	
Noroxycodone	302.1 -> 284.1	1.661	35322		2.0824	2.0824		302.1 -> 187.0	62.1		6-acetylmorphine-d6	334.2 -> 165.1	1.724	2286674	334.2 -> 211.0	52.5	
Noroxymorphone	288.1 -> 270.1	0.963	3437		0.5990	0.5990		288.1 -> 213.0	73.9		Morphine-d3	289.2 -> 152.1	1.006	3984654	289.2 -> 153.1	77.6	
Oxazepam	287.1 -> 241.0	3.151	2325		0.1687	0.1687		287.1 -> 269.0			a-OH-alprazolam-d5	330.1 -> 302.0	3.180	2854766	330.1 -> 210.1	51.1	
Norbuprenorphine	414.3 -> 101.1	2.512	563		0.0963	0.0963		414.3 -> 83.2	114.8		Meperidine-d4	252.2 -> 178.1	2.302	23303175	252.2 -> 224.1	95.9	
Phentermine	150.1 -> 133.1	1.862	355		0.0087	0.0087		150.1 -> 105.1	27.1		Methamphetamine-d5	155.2 -> 92.1	1.696	48115404	155.2 -> 121.1	78.8	
Benzoylecgonine	290.1 -> 168.1	2.143	2202		0.0085	0.0085		290.1 -> 77.2	49.9		Meperidine-d4	252.2 -> 178.1	2.302	23303175	252.2 -> 224.1	95.9	
N-Desmethyl-Tapentadol	208.2 -> 107.1	2.169	2892		0.0067	0.0067		208.2 -> 77.1	74.1		Meperidine-d4	252.2 -> 178.1	2.302	23303175	252.2 -> 224.1	95.9	
A-Hydroxymidazolam	342.1 -> 324.0	3.215	296		0.0062	0.0062		342.1 -> 203.0	51.5		a-OH-alprazolam-d5	330.1 -> 302.0	3.180	2854766	330.1 -> 210.1	51.1	
Tapentadol	222.2 -> 107.1	2.105	1191		0.0018	0.0018		222.2 -> 77.2	11.8		Meperidine-d4	252.2 -> 178.1	2.302	23303175	252.2 -> 224.1	95.9	
Phenobarbital	231.1 -> 42.2	2.531	1		0.0011	0.0011		231.1 -> 85.0	213...		Phenobarbital-d5	236.1 -> 42.2	2.507	270268	236.1 -> 193.0	8.9	
Propoxyphene	340.2 -> 58.2	2.960	37		0.0002	0.0002		340.2 -> 266.1	926.3		a-OH-alprazolam-d5	330.1 -> 302.0	3.180	2854766	330.1 -> 210.1	51.1	
MDMA	194.1 -> 163.0	1.786	15		0.0001	0.0001		194.1 -> 105.1	187...		Methamphetamine-d5	155.2 -> 92.1	1.696	48115404	155.2 -> 121.1	78.8	
Cocaethylene	318.2 -> 196.1	2.512	4		0.0000	0.0000		318.2 -> 82.2	167...		Meperidine-d4	252.2 -> 178.1	2.302	23303175	252.2 -> 224.1	95.9	
6-acetylmorphine	328.2 -> 165.0							328.2 -> 211.0			6-acetylmorphine-d6	334.2 -> 165.1	1.724	2286674	334.2 -> 211.0	52.5	
7-aminoclonazepam	286.1 -> 121.1							286.1 -> 222.1			Meperidine-d4	252.2 -> 178.1	2.302	23303175	252.2 -> 224.1	95.9	

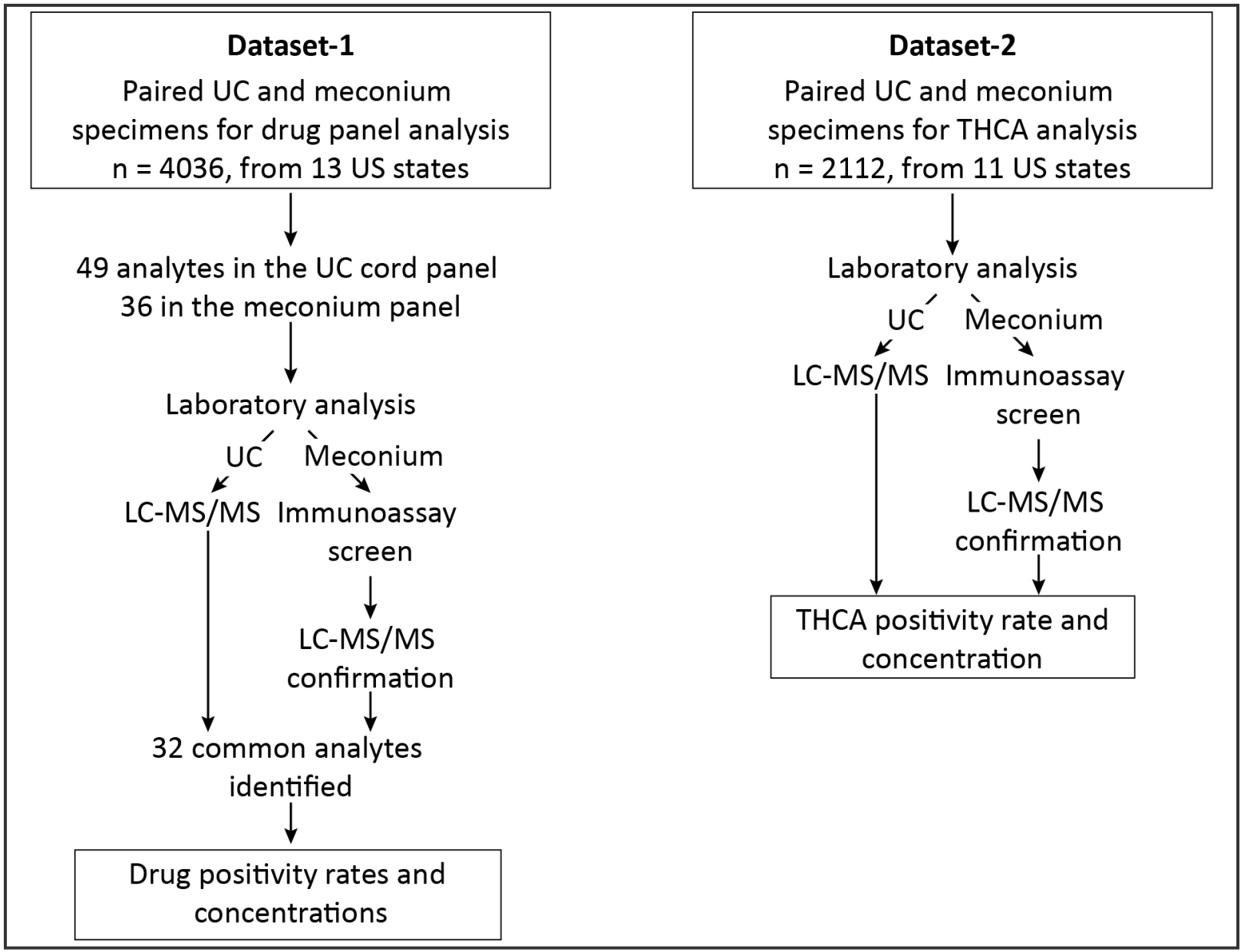




Cord vs meconium?

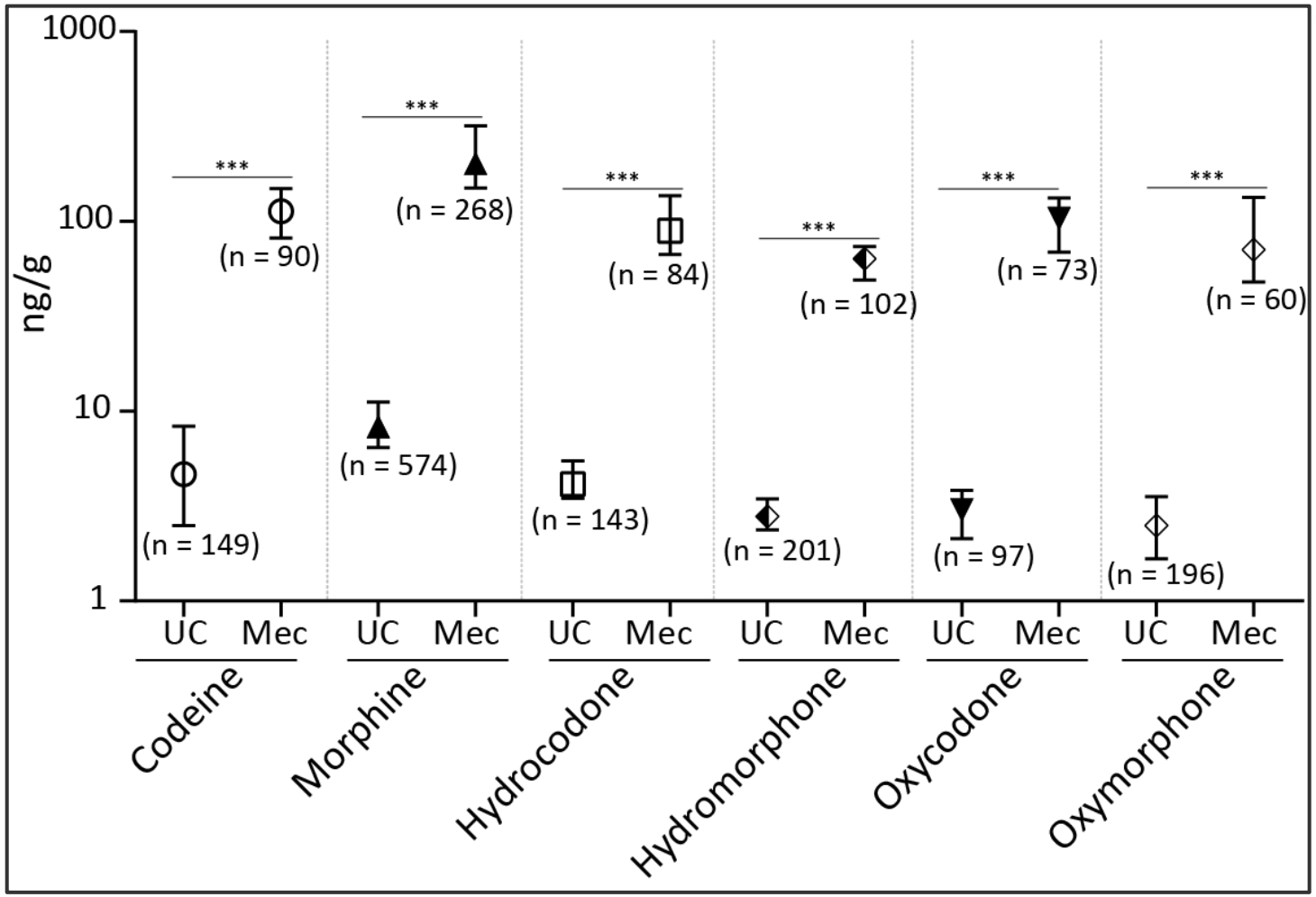
Is one specimen better at detecting drug exposures than the other?

2020 ARUP retrospective study of paired cord (UC) and meconium results



Pandya et al, *JAT*, 2022 (E-Pub)

Example concentrations of opioids



Positivity rates for most drug analytes were higher in cord tissue than in meconium.

	Umbilical cord Positive (%)	Meconium Positive (%)
6-acetylmorphine	1.0	0
Codeine	3.7	2.2
Hydrocodone	3.5	2.1
Hydromorphone	5.0	2.5
Morphine	14.2	6.6
Oxycodone	2.4	1.8
Oxymorphone	4.8	1.5
Methadone or EDDP	6.7	2.8
Buprenorphine or norbuprenorphine	15.6	9.1
THCA (COOH metabolite)	25.3	35.0
Amphetamine	6.7	7.7
Methamphetamine	6.8	7.8
Cocaine, benzoylecgonine, MOH, or cocaethylene	4.0	5.6
Alprazolam or α-hydroxyalprazolam	1.0	0.3
Clonazepam or 7-amino clonazepam	1.0	0.5
Butalbital	1.9	1.0

Data reflect ≥1% positivity rate in at least one specimen type with higher positivity rate indicated by red color font

Data combined for known drug/metabolites, organized by drug class (color coded)

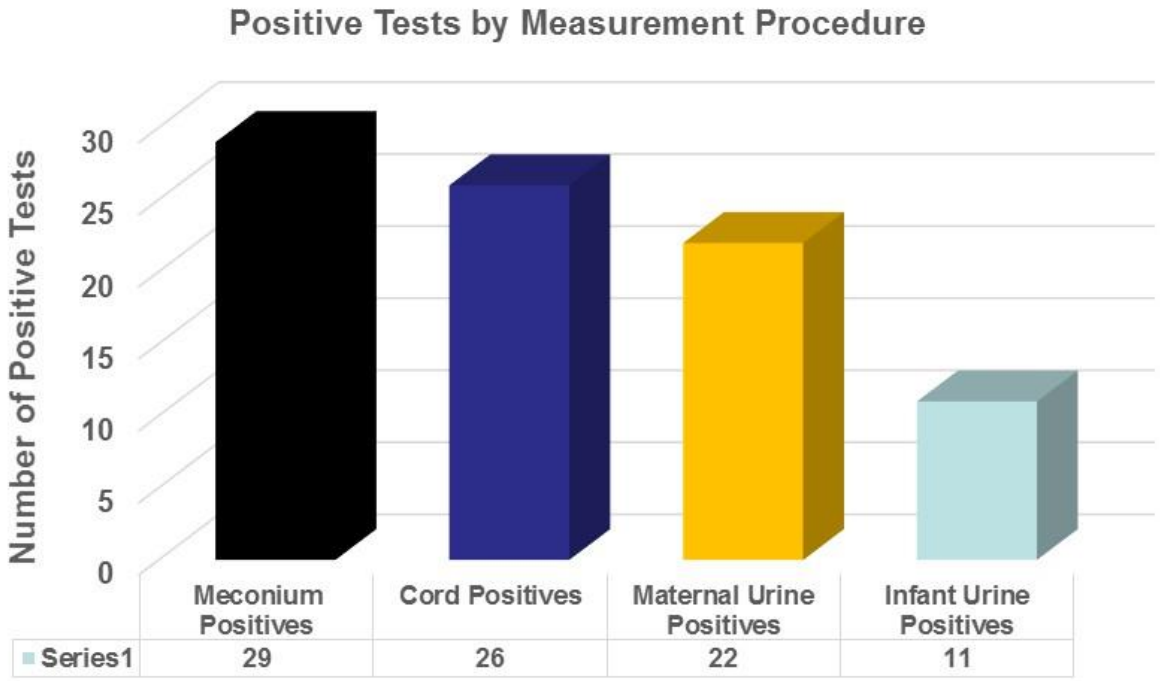
Cutoff comparisons for select drug analytes

- Cutoffs were lower in cord for all analytes, to help offset the differences in concentrations observed.
- Findings led to changes in the approach to testing for meconium.
- How does this apply to the 'real' world?

	Umbilical cord Cutoff (ng/g)	Meconium Cutoff (ng/g) screen (confirmation)
6-acetylmorphine	1	30 (20)
Codeine	0.5	
Hydrocodone	0.5	
Hydromorphone	0.5	
Morphine	0.5	
Oxycodone	0.5	
Oxymorphone	0.5	
Methadone or EDDP	1	40 (10)
Buprenorphine or norbuprenorphine	0.5	40 (20)
THCA (COOH metabolite)	0.2	30 (5)
Amphetamine	5	30 (20)
Methamphetamine	5	
Cocaine, benzoylecgonine, MOH, or cocaethylene	1	30 (20)
Alprazolam or α-hydroxyalprazolam	1	75 (20)
Clonazepam or 7-amino clonazepam	1	
Butalbital	25	75 (50)

University of Minnesota example

- Tested 80 births; paired samples
- Positivity rates were slightly higher in meconium.
- 41% positive; 89% agreement
- Discrepancies
  - » Meconium was more sensitive to cannabis.
  - » Cord more sensitive to opioids.
- Urine added no value.
- Chose cord as primary specimen.



University of Iowa example

- n=2072 newborns, independent births
- Positivity rates were slightly higher in cord.
  - » Cord, 29.2% positive for at least one analyte, 10.3% non-medical
  - » Meconium, 21.3% positive for at least one analyte, 8.2% non-medical
- Iatrogenic medications were often detected in meconium (codeine, morphine, lorazepam, phenobarbital), but not cord.
- Chose cord as primary specimen.

Palmer et al, *Clin Biochem* 50:255-61, 2017

Vanderbilt University example

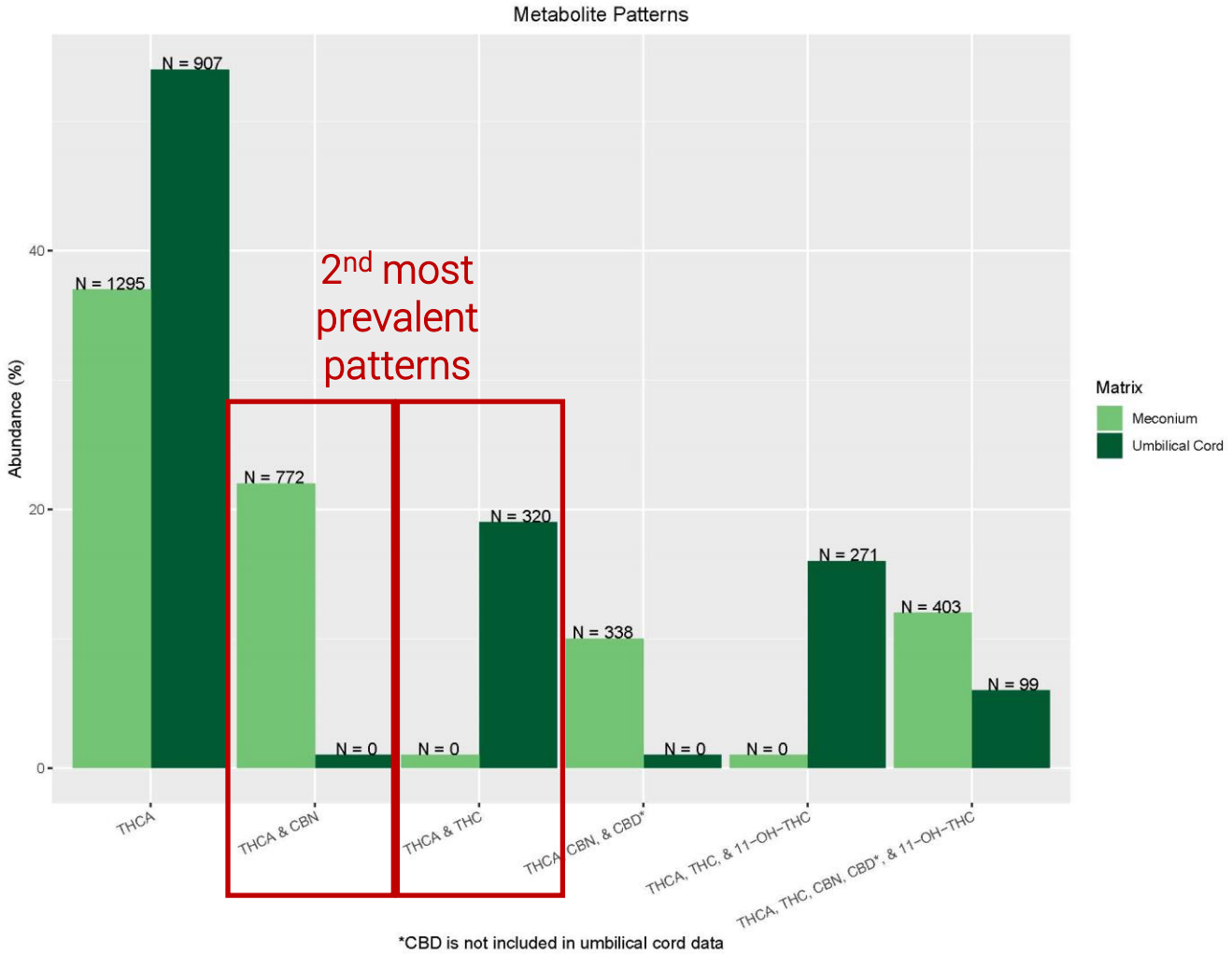
- n=501 newborns, paired specimens
- Agreement based on drug class varied from 80 - 100%
  - » Cord, higher positivity for amphetamines, barbiturates and benzodiazepines
  - » Meconium, higher positivity for cannabis and opioids
- Drugs were not detected in either specimen for some newborns that were diagnosed with NAS.
- Chose to collect both (paired) for most births.

Colby et al, *J Pediatr* 205:277-80, 2019

Analyte patterns matter

- Cannabis: THCA is the primary analyte analyte in both specimens, but average concentrations differ:
  - » Cord = 5 ng/g
  - » Meconium = 192 ng/g

- Cocaine: meta-hydroxy benzoylecgonine is most common in meconium, not cord.



Jensen et al, *Clin Mass Spec* 14:115-23, 2019
Pandya et al, *JAT*, 2022 (Epub)

Clinical sensitivity and specificity?

- Will all maternal drug use be detected?
- Are quantitative results necessary for interpretation?
- Will drug testing results predict outcomes?
- Will results agree for all specimens tested?
- What if results don't agree with maternal admissions/history?

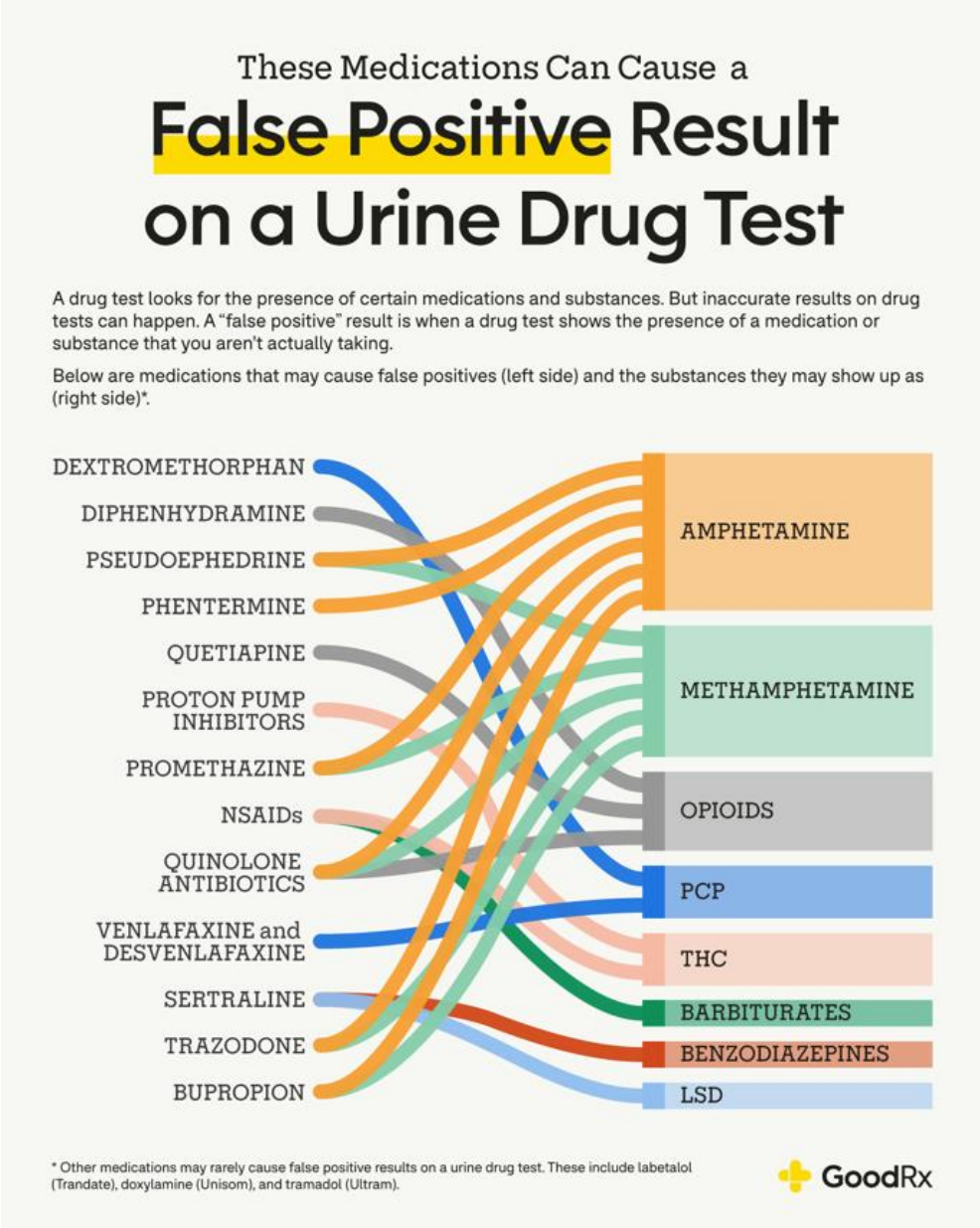
Example case scenario

- 22 yr old pregnant individual
- Late prenatal care, presents with pre-eclampsia
- History of smoking and polysubstance abuse
- Delivery at 36 wks
- Maternal urine positive for amphetamines and THC at delivery by immunoassay

- Multiple risk factors – newborn drug testing requested

Example case scenario

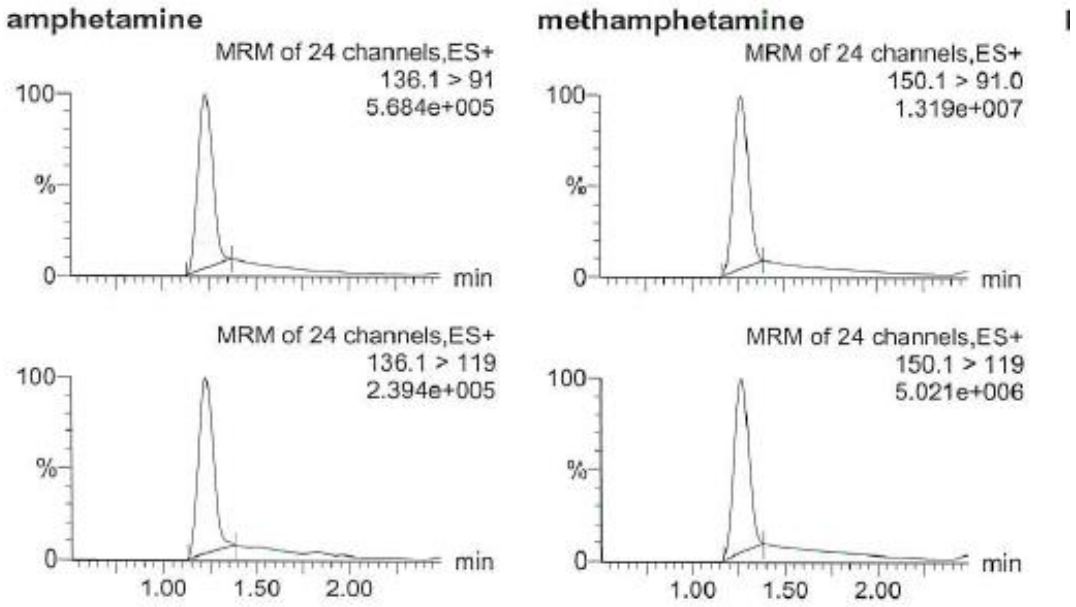
- Newborn admitted to NICU in respiratory distress; amphetamines and THC detected in urine by immunoassay.
- Meconium positive for methamphetamine, amphetamine and THC metabolite by LC-MS/MS.
- Amphetamine result was argued to be a false positive, due to cold medication.

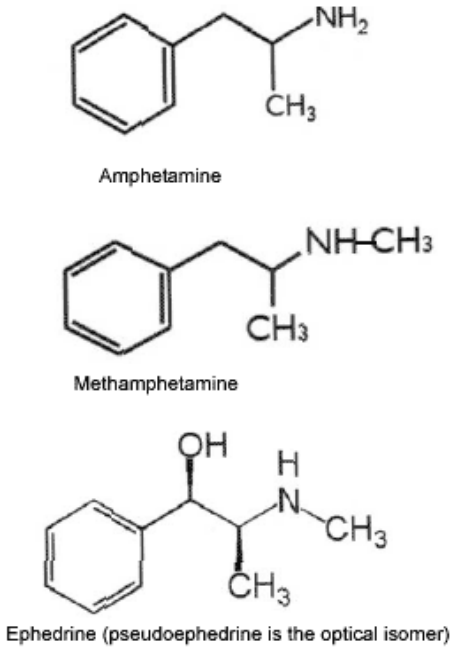


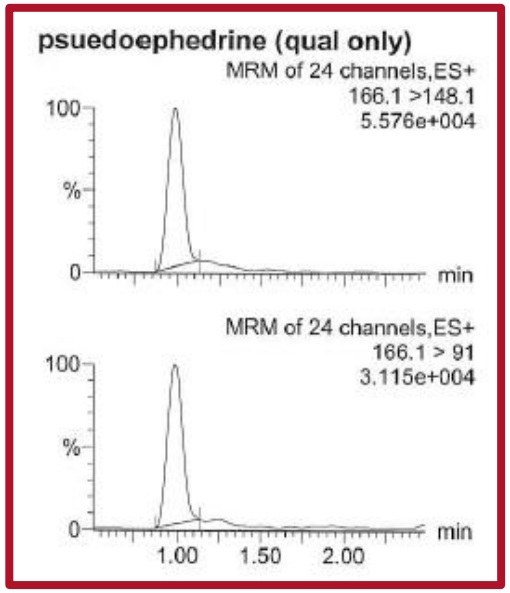
https://www.goodrx.com/drugs/side-effects/these-medications-can-cause-a-false-positive-on-drug-tests

The "Sudafed" Defense

- LC-MS/MS results
  - » Methamphetamine: 4762 ng/g
  - » Amphetamine: 498 ng/g
  - » Pseudoephedrine: 391 ng/g







Would reporting concentrations change the interpretation?

Can all "false positive" results be resolved by LC-MS/MS?

Other potential "false positives"

Possible source	Strategy
• Prescription methamphetamine and amphetamine directly or through metabolism • Isomers (e.g.Vick's inhalant that contains levometamfetamine) • Other structurally similar compounds (e.g. labetalol)	• Consult with the lab! • Consider concentration relative to the cutoff? • Alternate specimen(s) to test? • Alternate method(s)? • Literature search • Initiate research to study…

Example MAT case

- 31 yr old pregnant individual
- Limited prenatal care
- History of medication assisted therapy (MAT, buprenorphine)
- Delivery at 34 wks
- Maternal urine was positive for buprenorphine by immunoassay.
- Umbilical cord collected

- Newborn admitted to NICU, with significant symptoms of withdrawal requiring treatment.
- Cord positive for buprenorphine and gabapentin.

Retrospective evaluation of cord (n=7,054) showed ~8% positivity of gabapentin, for which 73% were positive for other drugs, largely buprenorphine and other opioids.

Okoye and McMillin, *JAT* 45:506-12, 2021

Other potential "false negatives"

Example scenario

- Drug(s) not included in test
  - » Synthetic drugs, drug analogs
  - » "Supplements" such as Kratom, and cannabidiol (CBD)
- Result fell below cutoff
- Change in drug maternal drug use patterns
- Limitations of the specimen and/or testing

Investigative options

- Review data for evidence of expected drug(s) below the cutoff? Relative concentrations?
- Alternate specimen(s) to test?
- Alternate method(s)?
- Literature search
- Testing in matrix

Investigate when results are unexpected

- What is the test designed to detect?
- How do results compare to the cutoff?
- Is an alternate specimen available?
- Is an alternate method available?
- Accuracy of maternal admissions/history?
- Adequacy of specimen?
- Risk of specimen mix-up? Contamination of specimen?

Summary of variables

- Pre-analytical
  - » Logistics for specimen collection
  - » Pharmacy history (adult and newborn)
- Analytical approach
  - » Technology
  - » Sample preparation
  - » Assay content
  - » Cutoffs
- Post-analytical
  - » Time to result
  - » Interpretation

- Non-laboratory variables
  - » Maternal social history
  - » Maternal medical history
  - » Maternal specimens tested
  - » Clinical presentation and course of birth
  - » Newborn specimens tested
  - » Newborn course after birth
  - » Breastfeeding status
  - » Home environment
  - » Other…

Conclusion

- Biological testing can detect and document drug exposures during pregnancy.
- Selection of specimen type(s) to test, and analytical approach should align with pre-test expectations.
- Results may inform short- and long-term medical and social management decisions.

ARUP® LABORATORIES | HEALTH UNIVERSITY OF UTAH

ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.