The Scoop on Biological Testing for Detecting or Confirming Drug-Exposed Newborns – What, When and How?

Gwen McMillin, PhD, DABCC

University of Utah, ARUP Laboratories

Objectives

- Compare and contrast approaches to drug testing during and after pregnancy.
- Understand the strengths and weaknesses of meconium and umbilical cord tissue for drug testing.
- Discuss how to investigate an “unexpected” drug testing result.

Women are an important demographic in the opioid epidemic

- Women receive more opioid prescriptions than men US Opioid Prescription Claims, 2015
- Heroin use increased 100% among women between 2002 and 2013, compared with a 50% increase among men National Survey on Drug Use and Health
- Every 3 minutes a woman seeks emergency care related to prescription opioid misuse *SAMSHA 2013*
- Deaths from prescription opioids among women increased more than 400% from 1999-2010, compared with a 237% increase among men *CDC, 2013*

Pregnancy is a unique opportunity to identify and manage drug use/misuse

May represent the only time a woman seeks medical care and is forthcoming about drug use and addiction

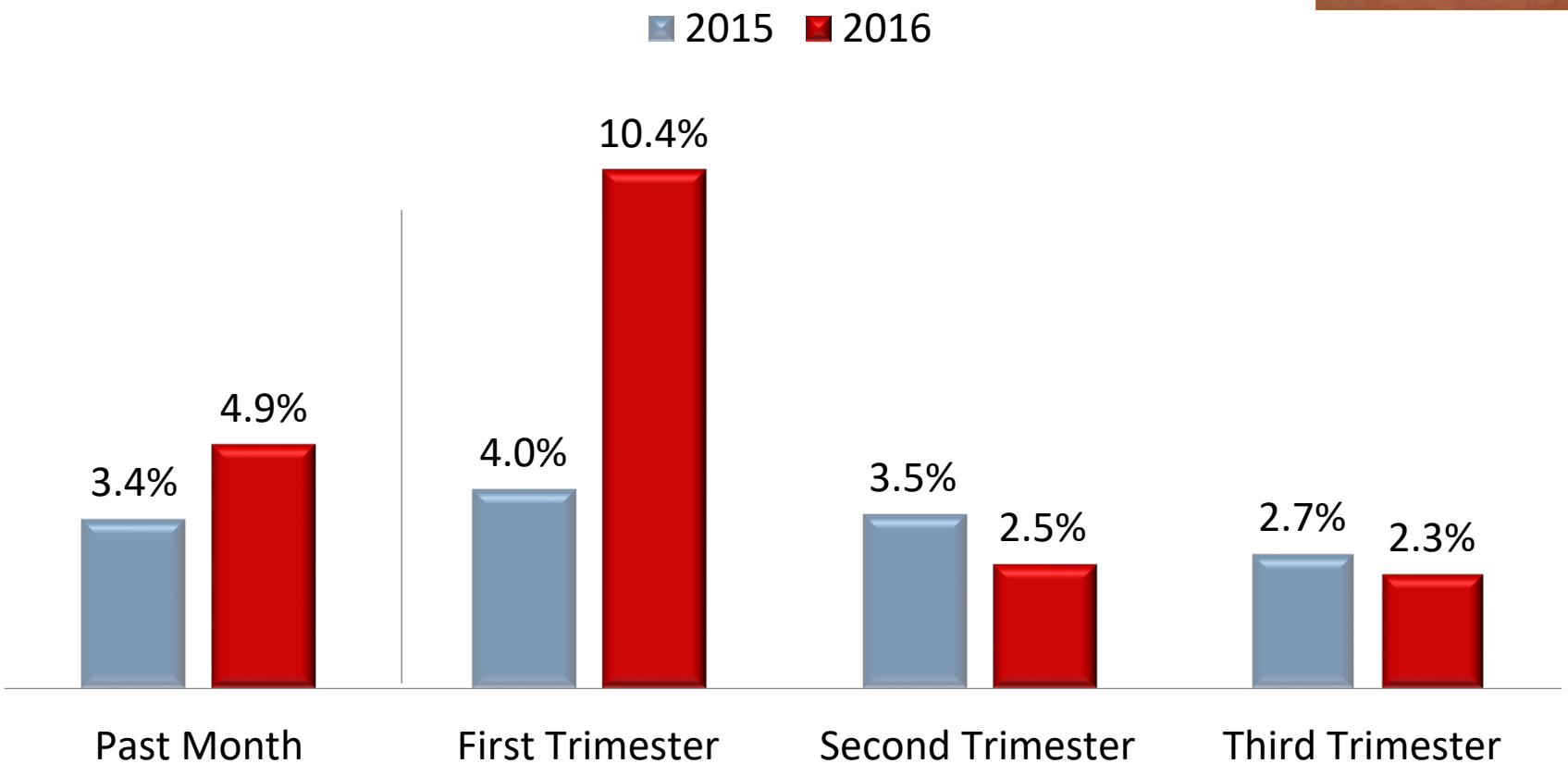
Non-prescribed drug use patterns in pregnancy

% that admitted to use within past month, aged 15-44 (NSDUH)

Drug	2015	2016
TOTAL	**21.7%**	**20.0%**
Nicotine	13.6%	10.0%
Alcohol	9.3%	8.3%
Marijuana	3.4%	4.9%
Psychotherapeutics	1.0%	1.4%
Opioids (heroin)	0.8%	1.2%
Inhalants	0.1%	0.3%
Methamphetamine	Data not available	0.3%
Cocaine	0%	0.1%

https://www.samhsa.gov

Marijuana use during pregnancy, by trimester (self-report)



https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf

Colorado study (Metz et al, *Obstet Gynecol*, Dec 4, 2018 Epub)

- Cross-sectional study of all deliveries at two urban medical centers in Colorado over a two-week period; 116 women completed the study
- Data collected
  - Self-report of cannabis use to the healthcare provider at the time of admission was collected.
  - Anonymous survey detailing cannabis use during pregnancy.
  - Biological drug testing for cannabis exposure.

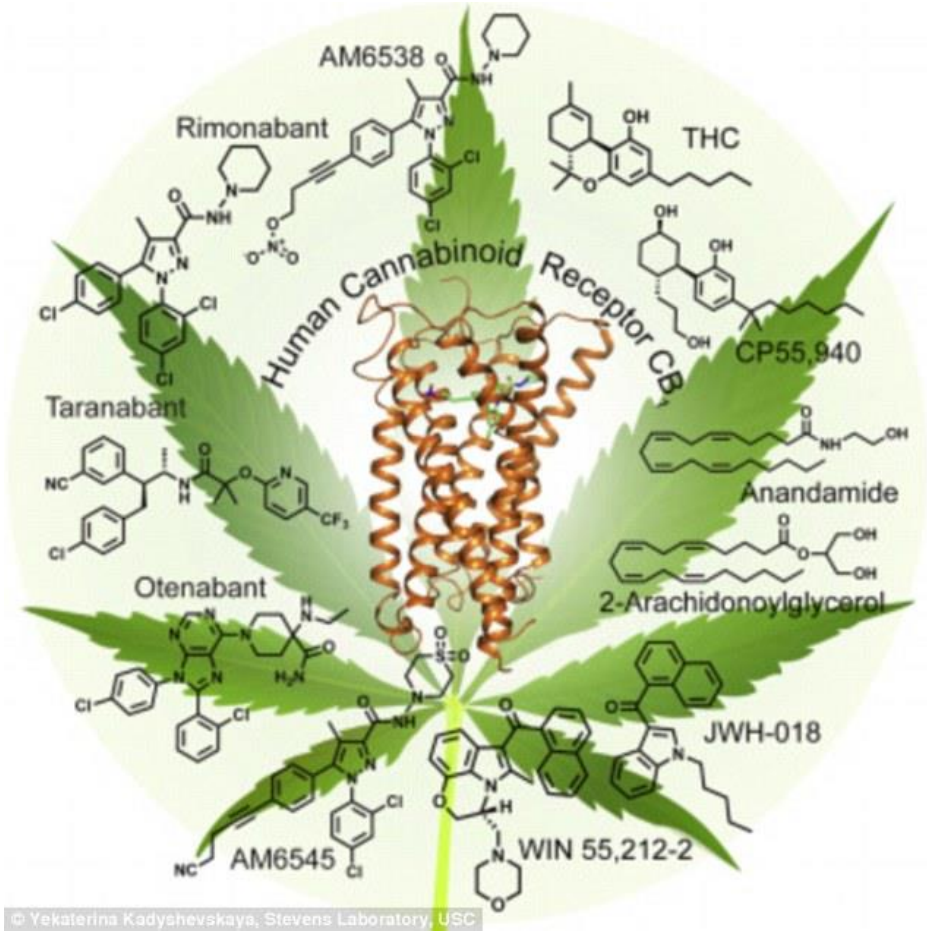
Does self-report accurately estimate use?

- Self-report
  - 2.6% reported marijuana use to healthcare providers at admission.
  - 6.0% reported use in the last 30 days on anonymous survey.

- Drug testing
  - 100% of cords were positive when the mother admitted to use over the past 30 days.
  - Overall, 22.4% of samples were positive.

Harmful effects of cannabis exposure *in utero*

- Decreased birth weight
- Reduced body length
- Smaller head circumference
- Increased likelihood of cannabis use during adolescence
- Behavioral and attention problems
- Reduced cognitive function



Gray et al. *Clin Chem* 56(9):1442-50, 2010

MARCH OF DIMES

Home > Pregnancy > Is it safe? > Marijuana and pregnancy

MARIJUANA AND PREGNANCY

KEY POINTS

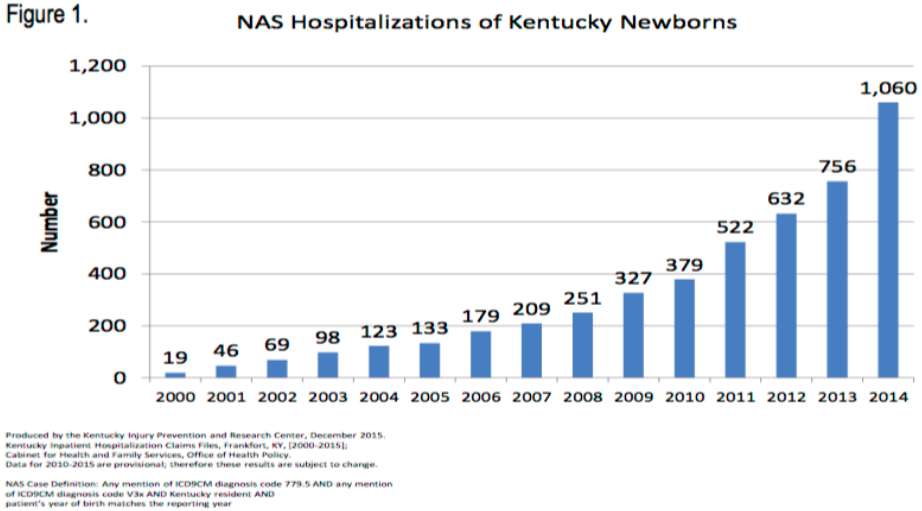
- No amount of marijuana has been proven safe to use during pregnancy.
- Using marijuana during pregnancy may cause problems for your baby, like premature birth, problems with brain development and stillbirth.
- It's not safe to use marijuana to treat morning sickness. Talk to your health care provider about treatments that are safer for your baby.
- If you use marijuana, don't breastfeed. You may pass chemicals from marijuana to your baby through breast milk.
- Talk to your provider if you need help to quit using marijuana or any other street drug.

https://www.marchofdimes.org/pregnancy/marijuana.aspx

Neonatal Abstinence Syndrome (NAS)

- Characteristic symptoms
  - Hyperirritability
  - Gastrointestinal dysfunction
  - Respiratory distress
  - Autonomic symptoms
- Occurs hours to days after birth; drug-dependent
- Rates have increased dramatically in the US
- Treated with supportive care (eat, sleep, console); pharmacological therapy if needed (opioids, sedatives, and tapering)

Figure 1.



https://www.awhonn.org
https://www.cdc.gov/grand-rounds/pp/2016/20160816-neonatal-addiction.html

Prescription drug use in pregnancy

- Opioid substitution reduces risk and severity of NAS
  - Methadone
  - Buprenorphine
- Polypharmacy is associated with higher risk of NAS and longer length of stay
  - Benzodiazepines
  - Gabapentin

Absolute risk of neonatal drug withdrawal (neonatal abstinence syndrome) after intrauterine exposure to both opioids and psychotropic medications versus opioids alone. Medicaid Analytic eXtract, 2000-10

	Opioids + psychotropic medications		Opioids alone	
	Cases/total	Risk (/100) (95% CI)	Cases/total	Risk (/100) (95% CI)
Antidepressants	495/14 183	3.49 (3.19 to 3.79)	1743/173 841	1.00 (0.96 to 1.05)
Antipsychotics	67/993	6.75 (5.19 to 8.31)	2481/199 151	1.25 (1.20 to 1.29)
Benzodiazepines	413/5361	7.70 (6.99 to 8.42)	1989/191 863	1.04 (0.99 to 1.08)
Gabapentin	57/501	11.38 (8.60 to 14.16)	2509/200 204	1.25 (1.20 to 1.30)
Z drugs	229/10 105	2.27 (1.98 to 2.56)	2286/188 216	1.21 (1.17 to 1.26)
1 psychotropic*	612/16 524	3.70 (3.42 to 4.00)	1423/168 086	0.85 (0.80 to 0.89)
≥2 psychotropics*	172/1737	9.90 (8.56 to 11.37)	1423/168 086	0.85 (0.80 to 0.89)

*Antidepressants, benzodiazepines, gabapentin.

Huybrechts et al, *BMJ* 358, 2017
Wachman et al, *Drug Alcohol Depend* 192:45-50, 2018

Consensus

All pregnant women should be screened by a validated test

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

Which births to test? Risk factors…

- Mothers who
  - History of drug use/abuse
  - Known at-risk home environment
  - <18 yrs
  - Had no or little pre-natal care (<5 visits)
  - History of hepatitis, AIDS, prostitution
  - Present with placental abruption
  - Present with unexplained premature labor
- Newborns with
  - Unexplained neurological complications
  - Unexplained intrauterine growth retardation
  - S/S of NAS

Kwong and Ryan, *Clin Chem* 43(1):235-42, 1997

Most common risk factors for drug-exposed newborns

THE UNIVERSITY OF IOWA

- 68.6% Maternal history of non-medical drugs
- 51.1% Maternal history of tobacco

- 90.8% Maternal history of tobacco and non-medical drugs
- 96.9% Maternal history of tobacco, non-medical drugs, poor prenatal care, and/or social risk factors (e.g., domestic violence, incarceration, history of prostitution, HIV, etc.)

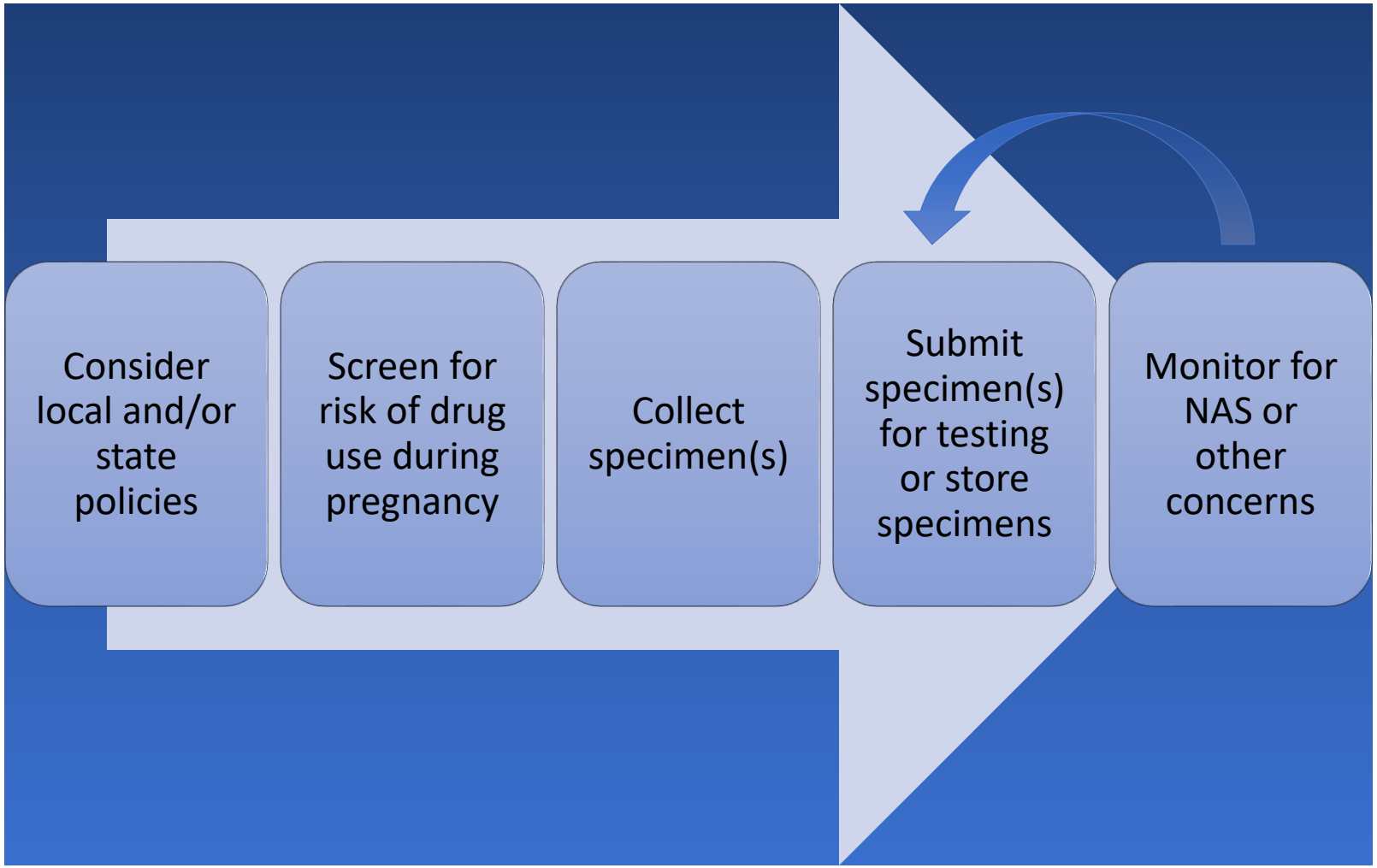
Wood et al., *BMC Pregnancy and Childbirth* 14:250, 2014

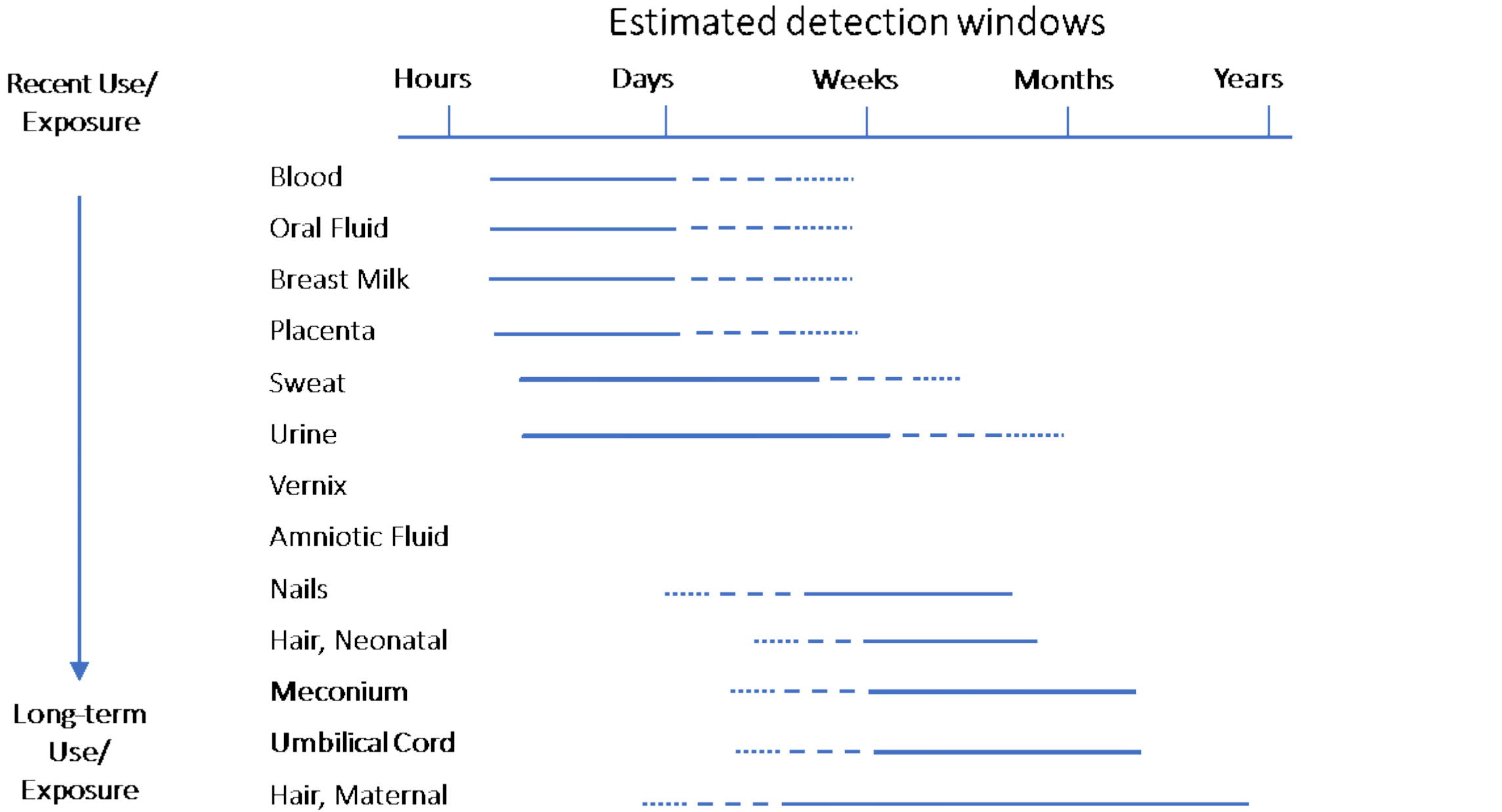
Universal maternal urine screening?

- Unbiased, by definition; will identify more drug use than not testing.
- Test performance characteristics and content must be understood to select the most appropriate test(s).
- When to test?
  - Before pregnancy?
  - First pre-natal visit? Other pre-natal visits?
  - At delivery?
- To be used in cooperation with psychosocial evaluations, physical exam, history, etc. with the overall goal to promote safety – should not be punitive.

Price et al, *Fronteirs in Pharmacol* 9, 2018
Wexelblatt et al, *J Pediat* 166:582-6, 2015

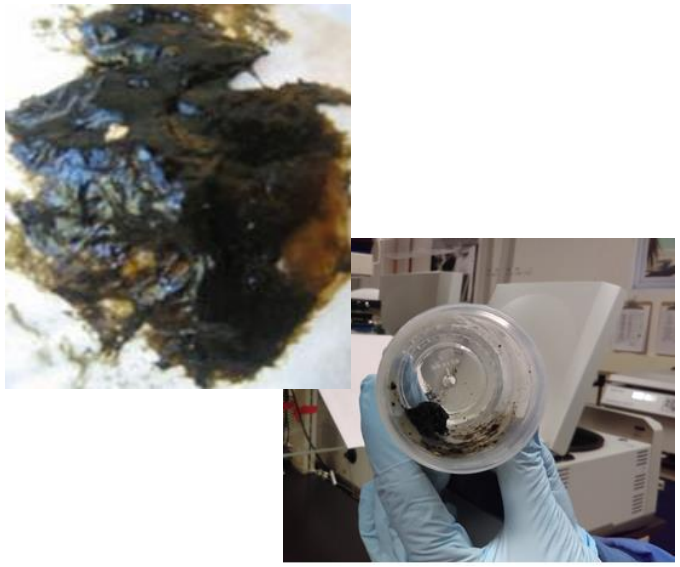
Typical approach to testing





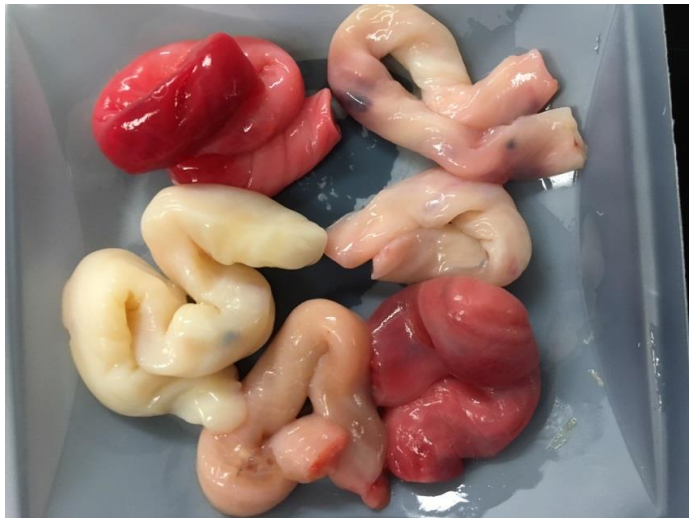
Wabuyele, et al.. *TDM* 40(2):166-85, 2018

Meconium



- First stool of the newborn.
- Used for drug testing for decades.
- Begins to form at ~12-16 wks gestation.
- Accumulates over remainder of pregnancy (a non-linear process).
- Usually passes within 48 hours of birth; sometimes before/during delivery.
- Collection laborious.

Umbilical cord tissue



- Forms ~5th week of gestation.
- Grows with fetus throughout pregnancy (non-linear process).
- Easy to collect at time of birth.
- Particularly useful for high-risk scenarios wherein time to result is critical.
- Concentrations of drug analytes are lower in cord than in meconium, but can be detected with appropriate methods.
- Drugs appear to deposit consistently across the length of cord.

Major advantages of these specimens:

Meconium

- Concentrations of drug analytes are much higher for most drugs, than in cord.
- No debate about specimen reflecting exposure to the infant versus the mother.
- Substantial research to support interpretation.

Cord

- Specimen is available at birth; time to result may be faster than meconium.
- Avoids detection of drugs that are administered directly to the infant after birth.
- Less likely to be discrepant in multiple births.

Major disadvantages of these specimens:

Meconium

- Specimen availability
- Collection process

Cord

- Not always as sensitive as meconium for many drugs

Specimen heterogeneity

Risk of contamination from other specimens

Negative results do not exclude possibility of exposure

No standardized methods or cutoff concentrations

Common technologies used for drug testing

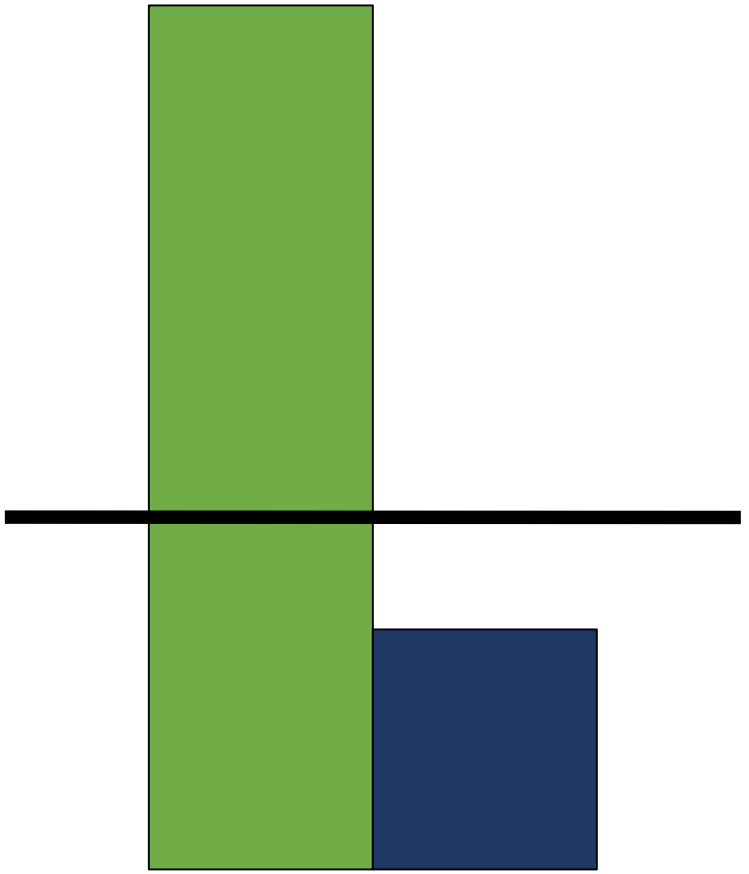
- Immunoassay
  - Many platforms
  - Monoclonal or polyclonal antibodies
- Chromatographic separation
  - Liquid (LC)
  - Gas (GC)
- Mass spectrometric (MS) detection
  - Single stage
  - Tandem (MS/MS)
  - Time-of-flight (TOF)

The “perfect” drug test

- Specific – detects the drugs of interest with low or no false positives (~accuracy)
- Sensitive – detects the drugs of interest with low or no false negatives (~cutoff)
- Precise (reproducible)
- Rapid
- Inexpensive
- Not vulnerable to adulteration
- Meets the needs of testing

Detection of drugs depends on

- Quality of specimen
- Drug use patterns
- Patient pharmacokinetics
- Technology used for testing
- Specimen cleanup
- Assay design and performance
- Cutoff concentrations



False positive?

- Relatively common for ***some*** (not all) tests
  - Amphetamine immunoassays
  - Tricyclic antidepressant immunoassays
- Rates vary with individual tests and drugs
- Some “false” positives are not, but rather, represent limitations of the testing.
  - Poppy seeds and codeine/morphine
  - Vick’s nasal inhaler and methamphetamine
  - Levorphanol and dextrorphan
- False positives can result from analytical challenges or specimen mixup
- The cause of the false positive may not be known.

Product Insert – Cross Reactivity

Key Points

- Cutoff is based on a "representative" compound/calibrator.
- Cross-reactivity allows for structurally related compound detection.
- Affinity of the antibody for a compound relative to the calibrator dictates "signal"

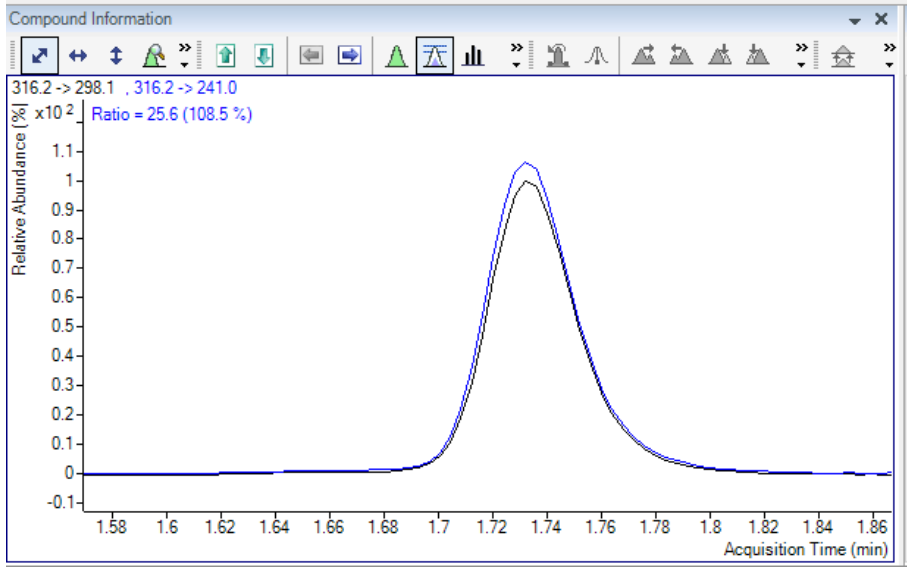
Table 7 — Concentrations (ng/mL) of Opiate Compounds That Produce a Result Approximately Equivalent to the 300 ng/mL Cutoff

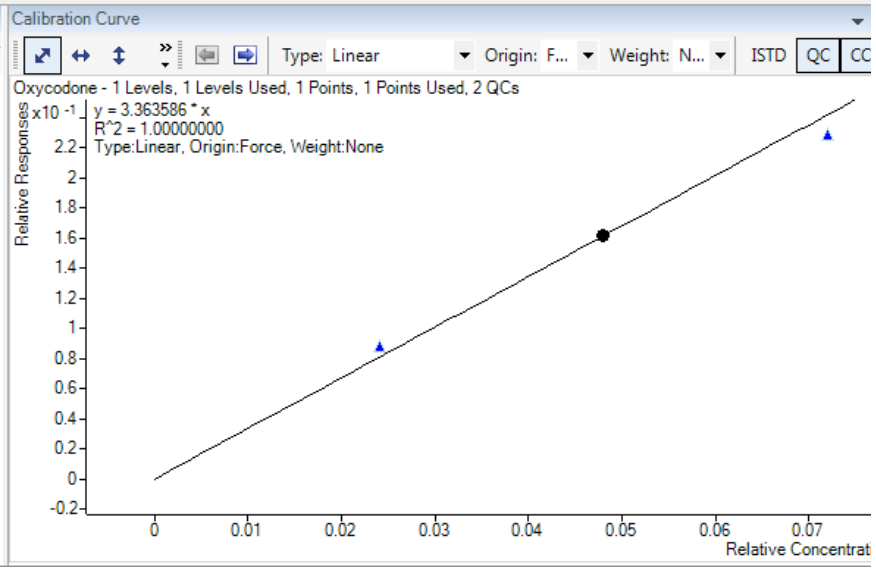
Compound	Concentration (ng/mL) at 300 ng/mL Cutoff
Codeine	102–306
Dihydrocodeine	291
Hydrocodone	247
Hydromorphone	498
Levallorphan	>7500*
▶ Levorphanol	1048
Meperidine	>50000†
6-Acetylmorphine	435
Morphine-3-Glucuronide	626
Nalorphine	9862*
Naloxone	828139
▶ Oxycodone	2550
Oxymorphone	>20000

Therapeutic doses of ofloxacin (Floxin) or levofloxacin (Levaquin), non-opiates, may produce positive results with this assay. A positive result from an individual taking ofloxacin or levofloxacin should be interpreted with caution and confirmed by another method.

Sample LC-MS/MS data

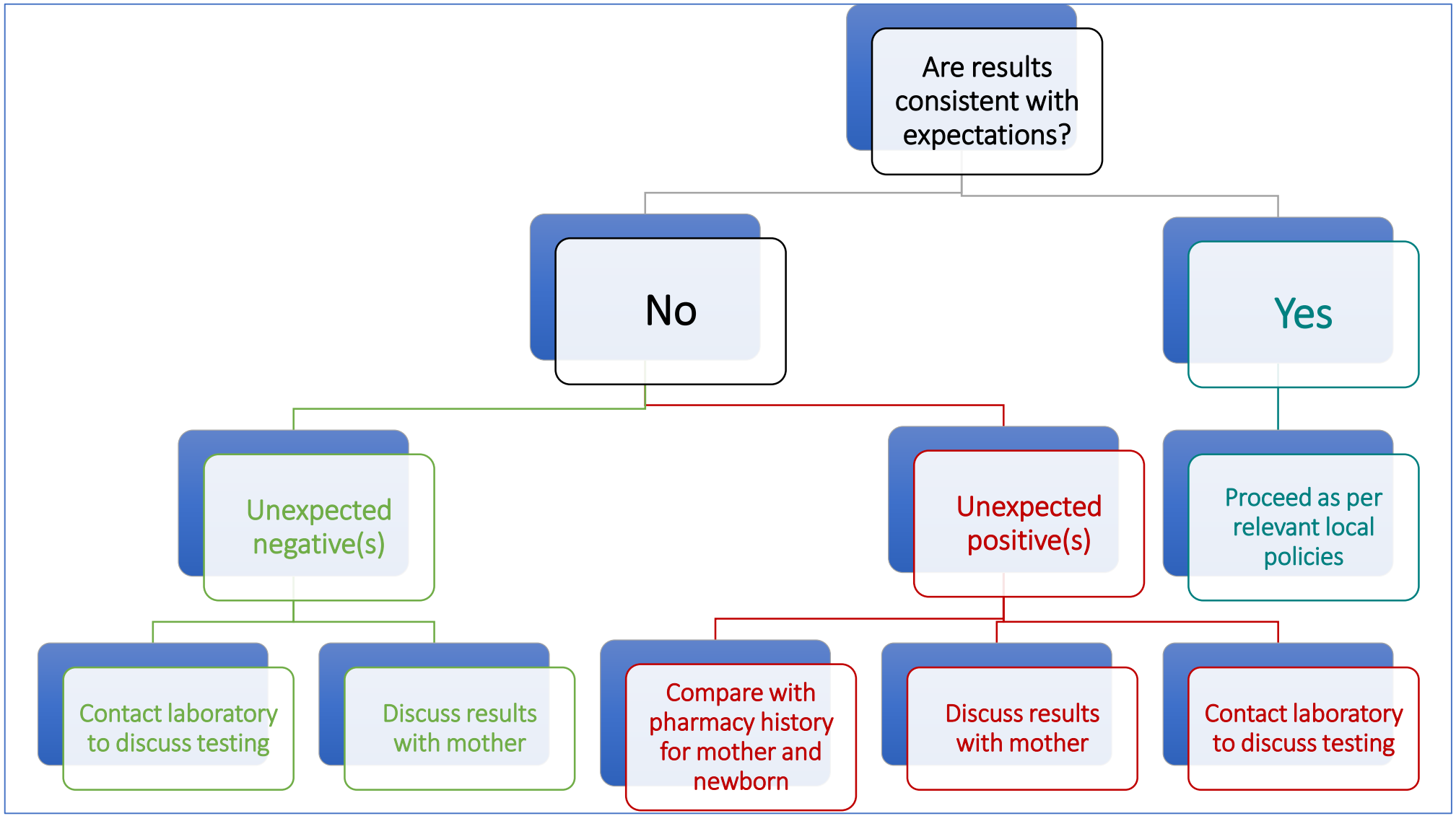
Name	Transition	RT	Resp.	MI	Calc. Conc.	Final Conc.	Accuracy	Transition	Ratio	MI	Name	Transition	RT	Resp.	Transition	Ratio	MI
Oxycodone	316.2 -> 298.1	1.732	580853		3.7760	3.7760		316.2 -> 241.0	25.6		6-acetylmorphine-d6	334.2 -> 165.1	1.724	2286674	334.2 -> 211.0	52.5	
Noroxycodone	302.1 -> 284.1	1.661	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	



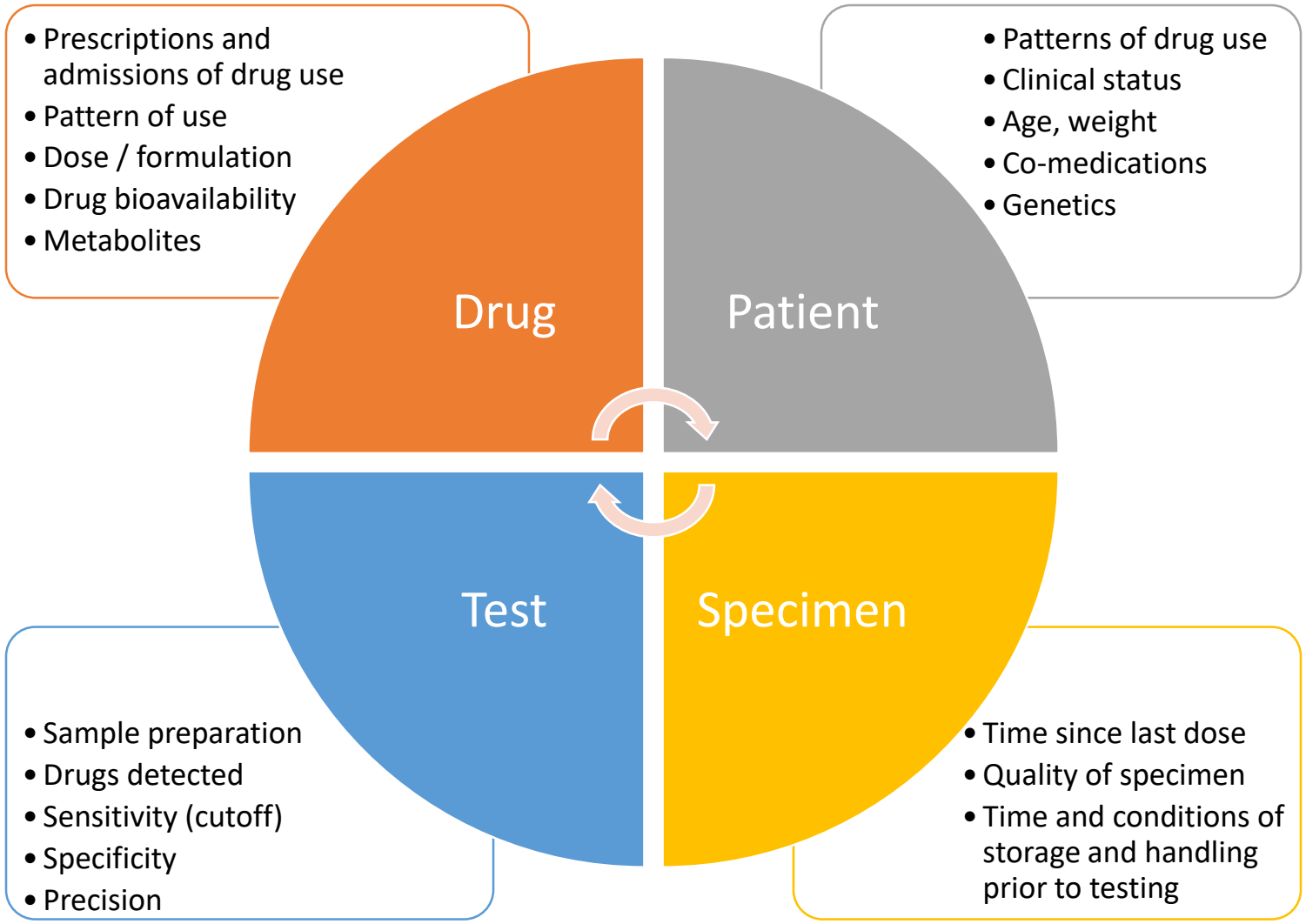


- Retention time
- Peak shape
- Mass of parent drug
- Mass of product ions
- Ion mass ratios, as compared to standards
- Internal standard performance
- Metabolite patterns

Algorithm for evaluation of results



Consider drug, patient, specimen, and test



McMillin et al, *J Pain & Palliative Care Pharmacotherapy*, 2013

Common questions about newborn drug testing

- Are first trimester exposures detected?

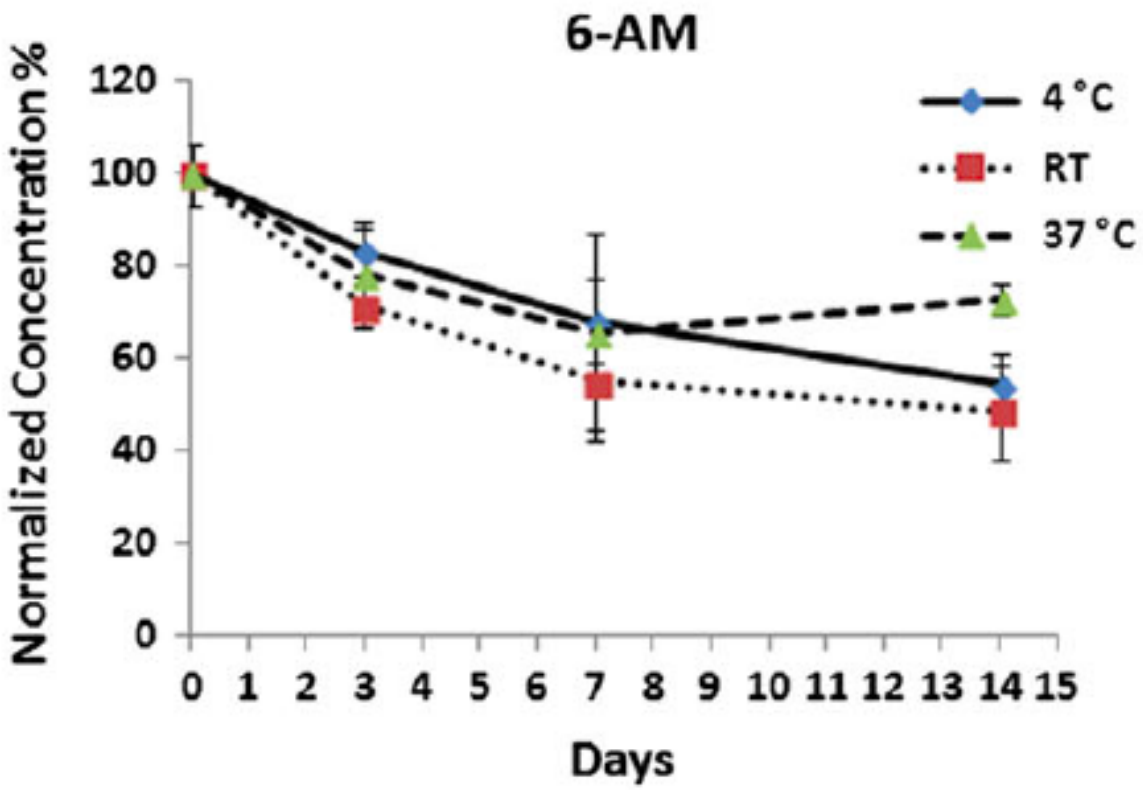
Considerations

- Size matters

- Samples are mixed/homogenized in lab
- Stability/metabolism of drugs in meconium

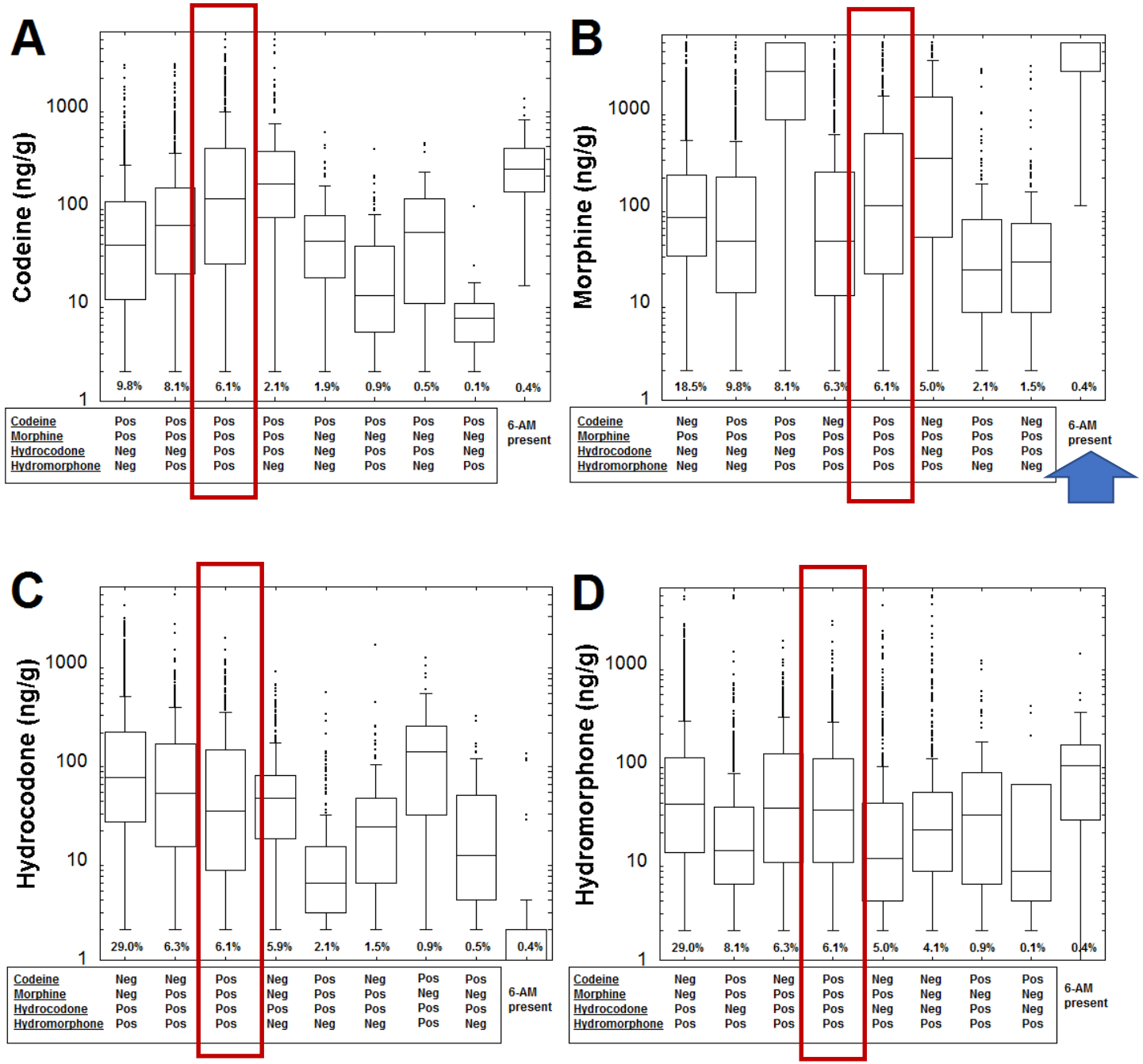
Observations of the heroin metabolite 6-monoacetylmorphine (6-AM)

- Rarely observed in most specimens
- Generally in low concentration
- Stability concerns



Wu et al., *JAT,* 41(3):196-204, 2017

Patterns of opiates



McMillin et al, *Ther Drug Monit* 37(5):568-80, 2015

Common questions about newborn drug testing

- Are first trimester exposures detected?
- Can we detect how frequently the mother used drugs, or how much?

ARUP/IHC nicotine study

- Consented mothers at delivery.
- Surveyed smoking history:
  - Smoked consistently (3-20 cigarettes/day) during pregnancy, n = 14.
  - Stopped smoking during pregnancy, n = 2.
  - Exposed to second-hand smoke only during pregnancy, n = 3.
- Determined nicotine and metabolites in paired cord and meconium samples.

Nic	Cot	3-OHCot	Smoked/day/trimester		
ng/g	mec	mec	1st	2nd	3rd
322	150	354	20	20	20
224	103	231	5-7	5-7	5-7
322	188	223	10	7	7
172	70	222	8-10	8-10	8-10
590	317	187	3-4	3-4	3-4
183	53	110	0	4-5	4-5
84	39	99	7	7	7
76	26	87	5-6	2-3	2
43	39	83	20	10	10
114	92	74	7	7	7
43	77	65	8	8	8
61	31	65	20	20	20
136	107	56	6	6	5
21	34	35	10	10	10
18	9	26	0	0	0
<4	<2	<4	3	1	0
<4	<2	<4	3-4	0	0
<4	<2	<4	0	0	0
<4	<2	<4	0	0	0

Marin et al, *TDM,* 33(1):80-5, 2011

Common questions about newborn drug testing

- Are first trimester exposures detected?
- Can we detect how frequently the mother used drugs, or how much?
- Can we detect drugs administered in the hospital?

History of morphine in hospital

	Morphine (ng/g)	Hydrocodone (ng/g)	Hydromorphone (ng/g)	Known Maternal Prescription	Known Infant Prescription
1	1014	Neg	34		**Morphine**
2	510	Neg	11		**Morphine**
5	390	34	Neg	Hydrocodone	**Morphine**
6	226	3	32		**Morphine**
7	42	9	Neg		**Morphine**
8	3159	Neg	1066	Hydromorphone	**Morphine**
3	41	26	Neg	**Morphine**	
4	23	Neg	11	**Morphine**	
9	41	2	Neg	**Morphine**	
10	31	Neg	Neg	**Morphine**	

McMillin et al, *TDM,* 37(5):568-80, 2015

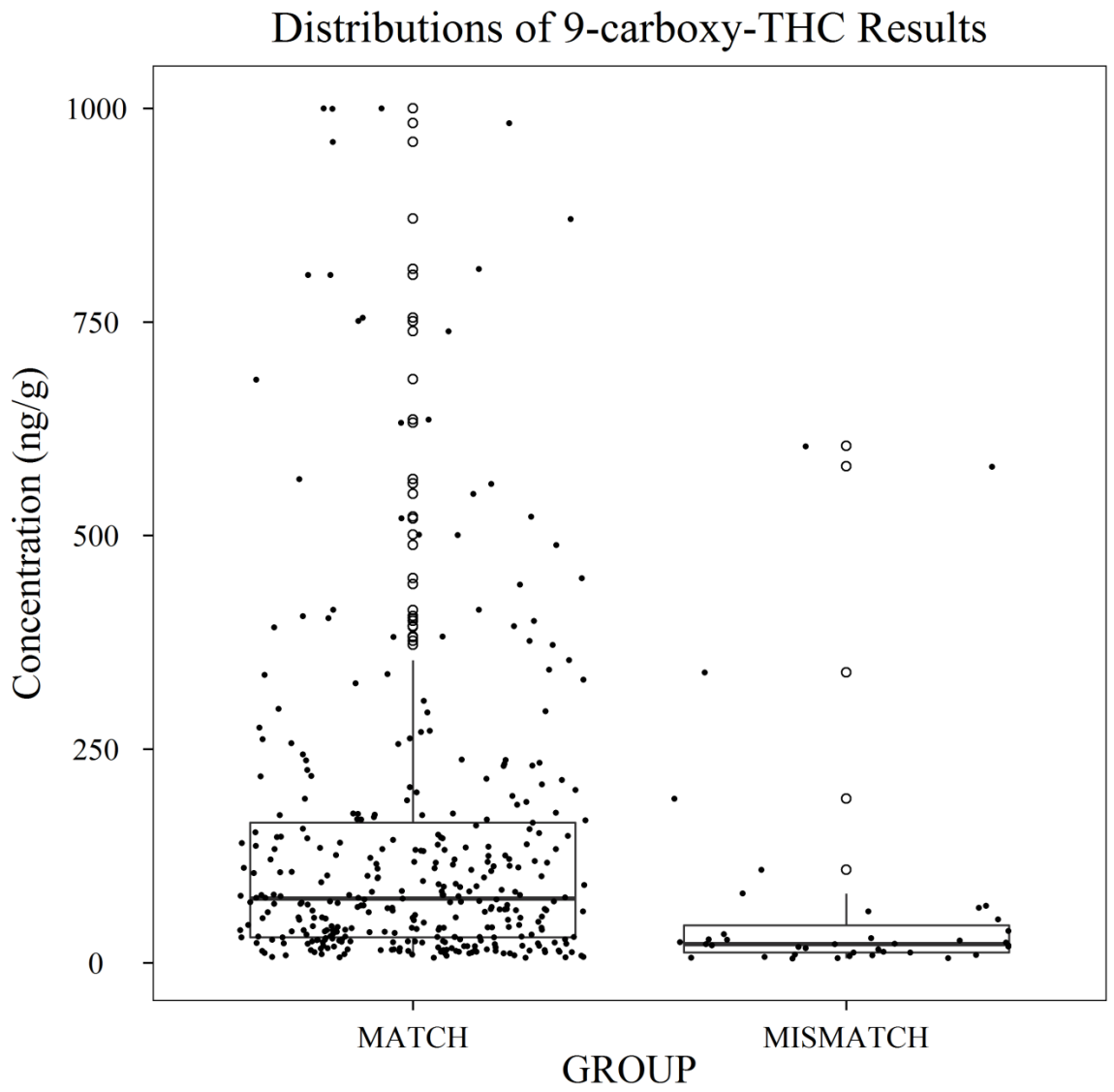
Common questions about newborn drug testing

- Are first trimester exposures detected?
- Can we detect how frequently the mother used drugs, or how much?
- Can we detect drugs administered in the hospital?
- What if results from multiple births (e.g. twins) don't agree?

Why would results be discrepant?

- Timing of meconium collection before drug administration for one infant, and after drug administration for the other
  - Barbiturates
  - Opiates
  - Benzodiazepines
- Timing of specimen collection after milk stool has started to form
- Specimen mixup
- Results are close to the reporting/detection limit for the test
  - Marijuana metabolite

9-carboxy-THC results for twins



Wood et al, *J Anal Toxicol* 38(7):397-403, 2014

Common questions about newborn drug testing

- Are first trimester exposures detected?
- Can we detect how frequently the mother used drugs, or how much?
- Can we detect drugs administered in the hospital?
- What if results from multiple births (e.g. twins) don't agree?
- Should breast milk be tested?

Care does not end after birth

The Academy of Breastfeeding Medicine Protocol #21, 2015 provides guidelines for breastfeeding when drug use is known.

- Concentrations of methadone and buprenorphine in breast milk are low and breastfeeding is encouraged.
- Concentrations of cannabis analytes are up to 8 times higher than in maternal plasma. Breastfeeding is discouraged.
- Breastfeeding after use of codeine is not recommended unless CYP2D6 status is known.
- Testing breast milk directly is not routinely recommended

Reece-Stremtan et al, *Breastfeeding Medicine* 10(3):135-41, 2015

U.S. National Library of Medicine

TOXNET TOXICOLOGY DATA NETWORK

Mobile | Help | FAQs | TOXNE

TOXNET Home > LactMed

LactMed

A TOXNET DATABASE

Drugs and Lactation Database (LactMed)

SEARCH LACTMED | BROWSE LACTMED | ADVANCED SEARCH

e.g. sertraline, SSRIs

Search

Search Term singular/plural

Records with all of the words

Include Synonyms and CAS Numbers in Search

Summary and conclusions

- Biological testing can detect drug use/exposure that can improve patient care decisions.
- Meconium and umbilical cord testing are useful tools for identification of *in utero* drug exposure during approximately the last trimester of a full term pregnancy.
- Interpretation of results depends on a good understanding of
  - Maternal history
  - Infant history
  - Specimen collection and handling
  - Limitations of testing (laboratory contacts)

Thank-you for your attention!!!

Gwen.mcmillin@aruplab.com

Clinicial Perspective

Shannon Miles BSN, RN

Manager Perinatal Outreach & Ambulatory Services

Centra Healthcare

Clinicial Perspective

Amy N. Sanborn, DNP, RN, C-EFM

Nurse Manager, OB Inpatient Services

University of Iowa Health Care