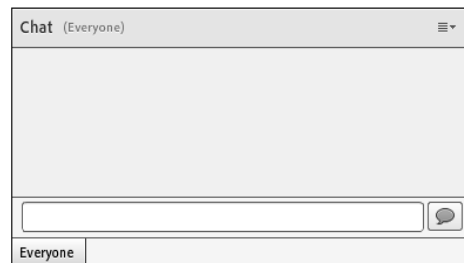


ICON Statewide Call

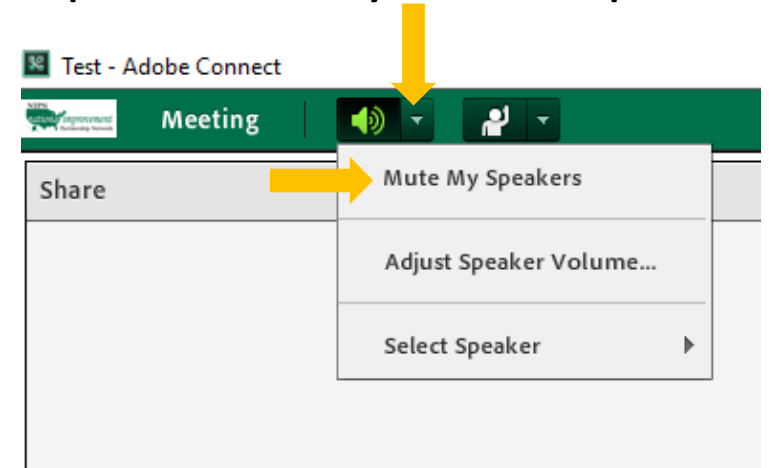
November 6, 2019

Fundamentals of Urine Drug Testing

- (1) Upon arrival, please use the **Chat** box to provide your first **and** last name **and** your phone number (if you called in using your phone).
- (2) Please provide first **and** last names for those with you on the call.
- (3) Please include your practice or organization name.



Please remember to mute the phone line by dialing *6 (#6 to unmute) and/or mute the speakers on your computer.



Fundamentals of Urine Drug Testing

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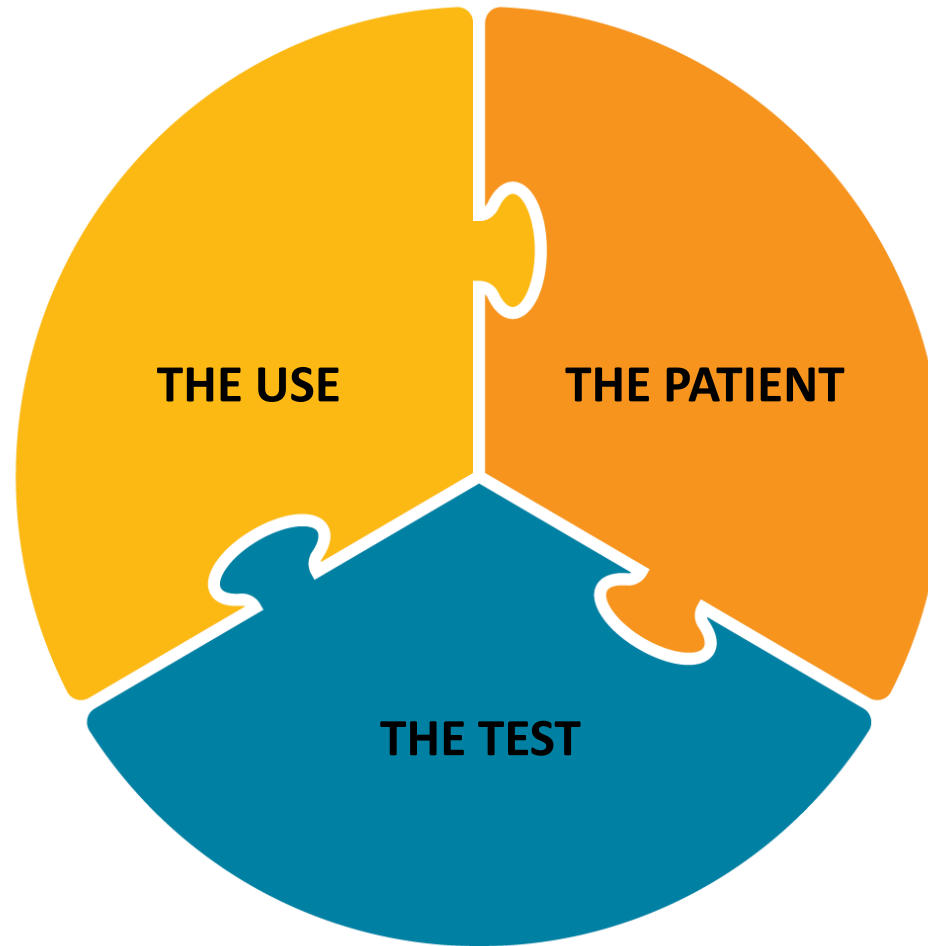
Chief Medical Officer, Aspent Health

Disclosures

- Clayton Wilburn: I have no relevant financial relationships to disclose or conflicts of interest to resolve
- Jill Warrington: I am on the Blue Cross Blue Shield Community Advisory Council in which I receive reimbursement for time/travel. I am employed solely by the University of Vermont Medical Center and the Larner College of Medicine.

For appropriate use of testing...

Know:



What is substance use testing?



It IS

- An objective measure of substance use
- A tool used by physicians to support patient care
- A mechanism to support treatment adherence

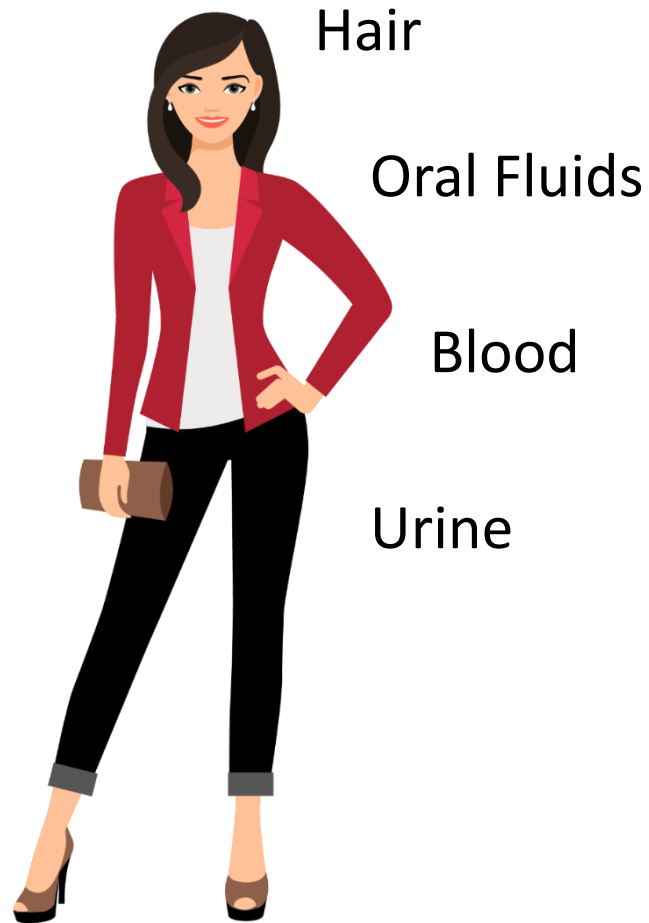


It is NOT

- A substitute for active therapy
- A strategy to punish or harm patients on their pathway to recovery

It does, however, require understanding the test to use this technique effectively.

Sources of samples for testing



Most common body fluid used: Urine

Pro's

- Easy access
- Long window of detection
- Broad test menus

Con's

- Difficult to establish time since last dose
- Tampering issues arise

Two types of testing

Screening

- Designed to provide fast, early diagnostic information
- Compare to other screening tests (e.g.: mammography)
 - Moderate sensitivity
 - Poor specificity
- Method used: Immunoassay

Definitive or confirmatory

- Designed to provide more diagnostic certain information
 - Excellent sensitivity
 - Excellent specificity
- Method used; Chromatography-Mass spectrometry

Screening

Point-of-Care



Lab-Based Immunoassays



Both rely on the ability of an antibody to detect a drug

Screening: Point of Care Testing

Point-of-Care



- Also known as POCT (Point-of-Care Testing)
- Used in the office
- Can be in the form of a cup or test strip
- Look often for the absence of a line to call a drug positive
- It's a yes or no answer
- Often 7-10 drugs per cup

Screening: Lab-Based Immunoassays

Laboratory – based immunoassays



- It's sent to the lab
- It's performed on lab instruments
- Report may be qualitative (yes or no) or quantitative
- Can detect ~10-25 drugs
- Usually 1-6 hour turnaround time

Screening immunoassays: How they work

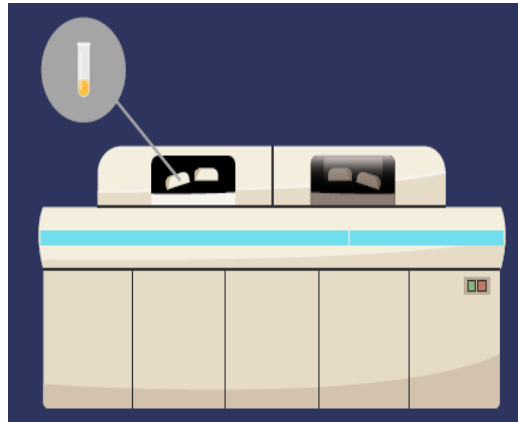
A simplified representation

Step 1



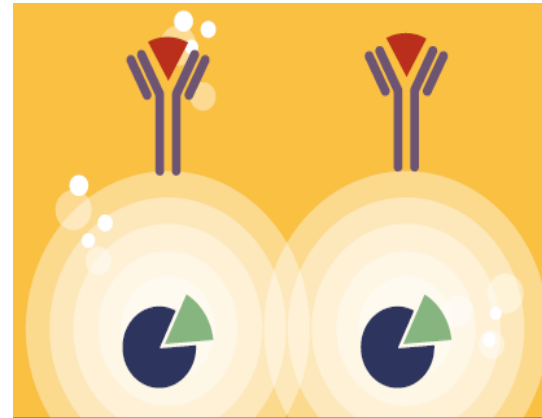
Pour urine into
test tube

Step 2



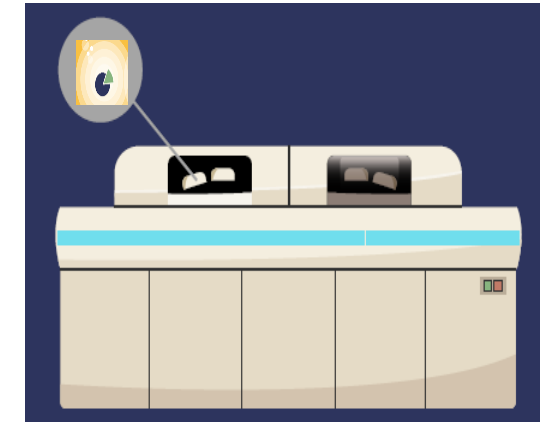
Add antibodies,
sample placed in analyzer

Step 3



If drug present, antibody binds
and emits light

Step 4

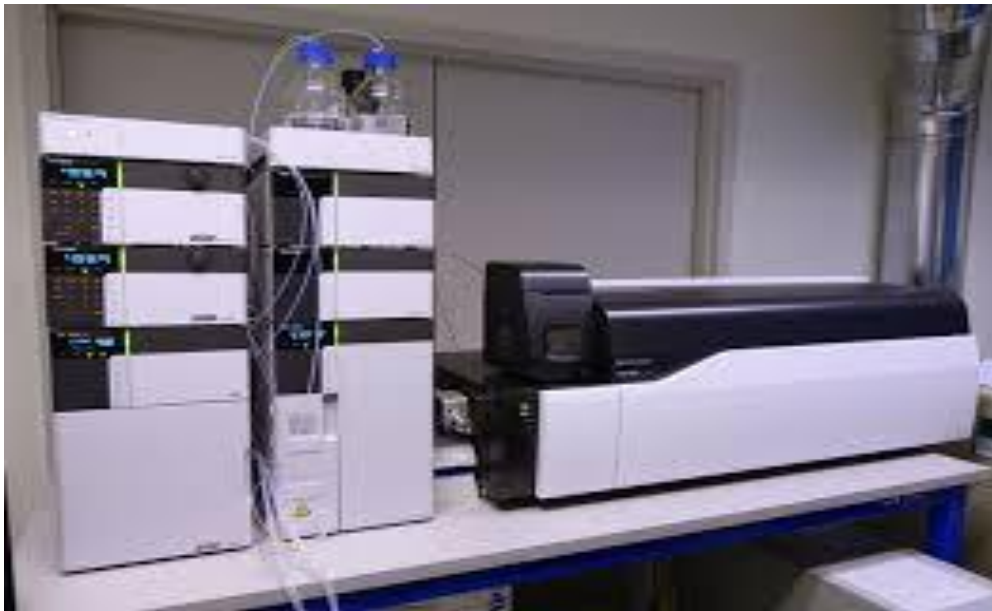


Detector measures
amount of light

The Lab-Based Immunoassay is shown here; similar process on a Point-of-Care Testing cup.

Confirmation (or Definitive) testing

Liquid-Chromatography Tandem Mass Spectrometry (LC-MS/MS)



Liquid
Chromatography

Tandem
Mass Spectrometry

- This is not a screening test
- This is used to definitively identify a drug
- The sample is sent to the laboratory
- The turnaround time can be 2-4 days
- It is run on an instrument known as a liquid chromatography tandem mass spectrometer
- It is a composite of two separate methods:
 - Liquid chromatography – separates the drugs
 - Mass spectrometry – fragments drugs with identification of drug by its fragments

LC-MS/MS: How they work

A simplified representation

Liquid Chromatography (LC)

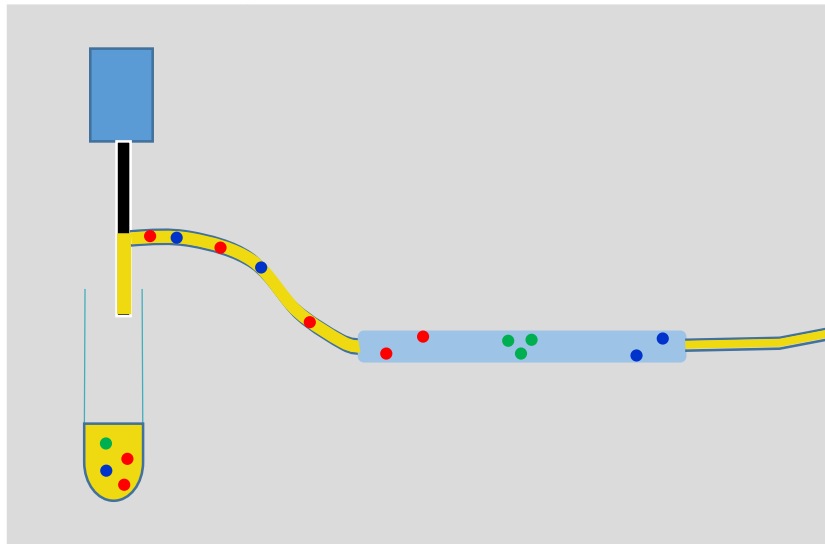
Chemical separation

Tandem Mass spectrometry (MS-MS)

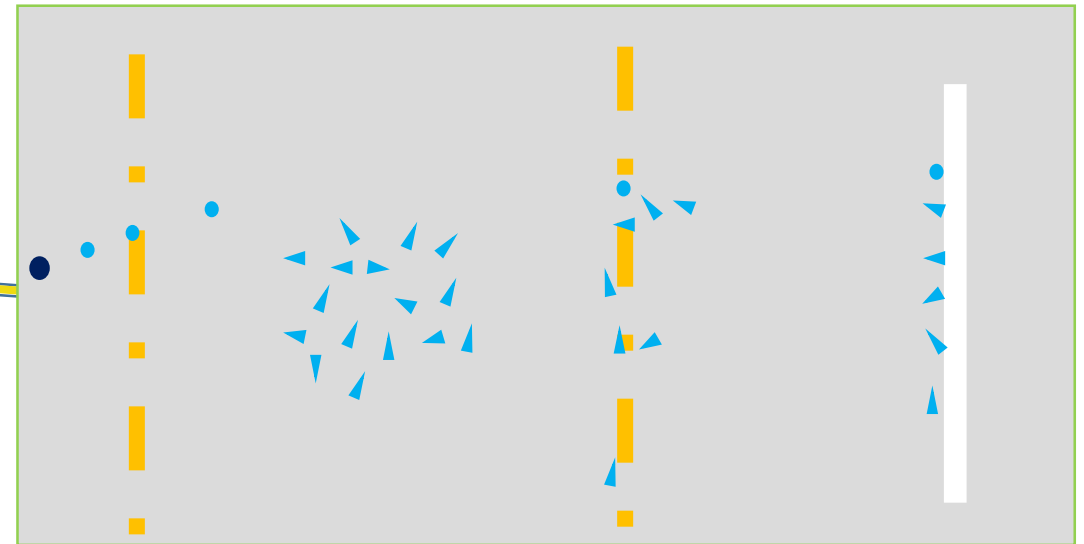
Fragments & Identifies drug by its fragments



Urine
containing
many drugs



Urine is run through a
column to separate drug



Drug is fragmented

Drug is
fragmented
again

Fragments identified
at detector

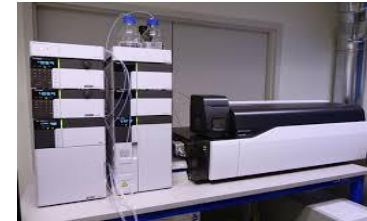
How accurate is the test?



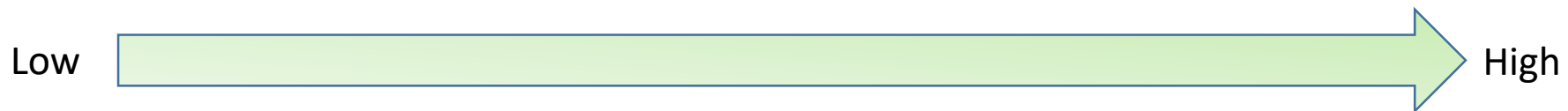
POCT



Lab immunoassays



Confirmation testing
LC-MS-MS



Diagnostic Certainty (or Result Reliability)

Diagnostic Certainty

Sensitivity

- Ability to detect drug taken
- How low can you detect
- How well you detect specific drug in a given class
i.e. Lorazepam in Benzodiazepines

Specificity

- Ability to detect just the drug(s) of interest
- Low specificity = more unwanted cross reactions
i.e. Bupropion in Amphetamines

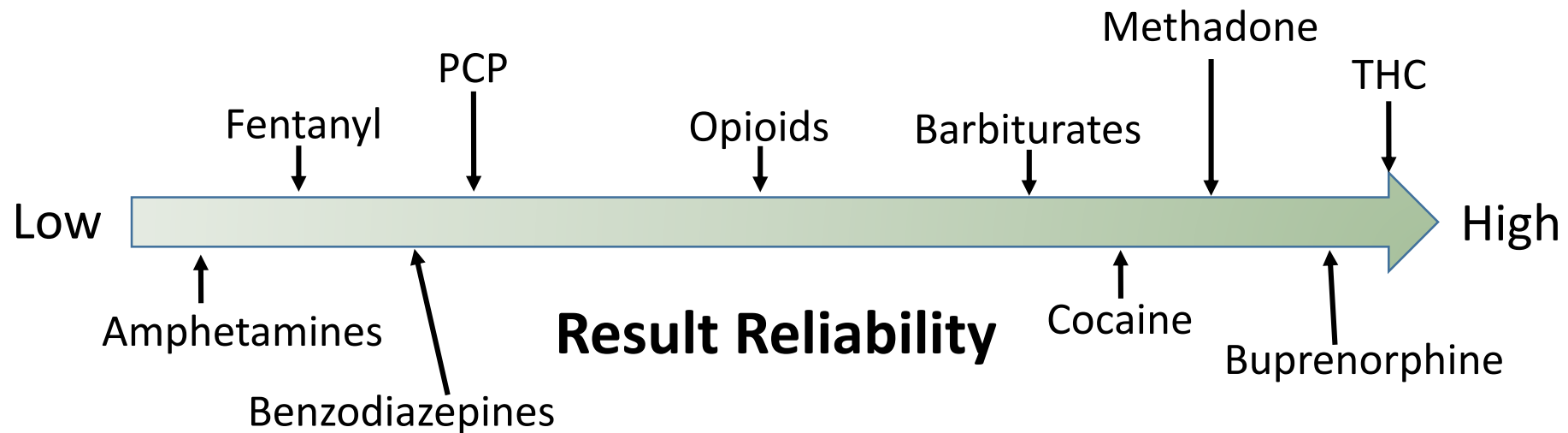
In screening assays there is always a balance between the two

Talking Positives and Negatives

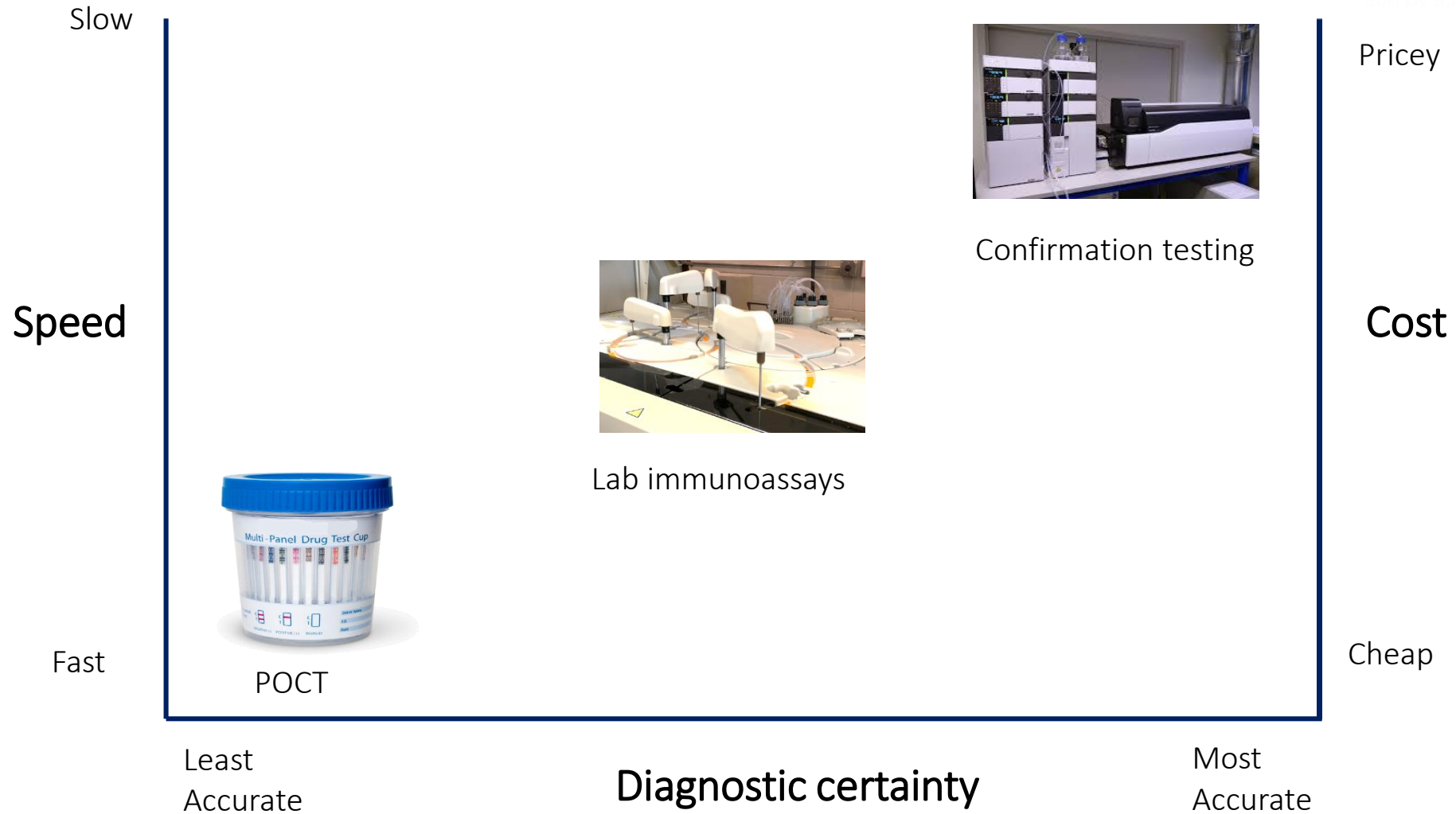
Possible Results	Drug Taken	Screen Positive	Confirmation Positive
True Positive (TP)	Yes	Yes	Yes
True Negative (TN)	No	No	No
False Positive (FP)	No	Yes	No
False Negative (FN)	Yes	No	Yes

Putting It All Together



















- A Test's Sensitivity and Specificity Drive its Reliability
- For Screening Immunoassays:



Comparison of strengths and weaknesses



Comparison of assays

Characteristic	POCT	Lab EIA	Confirmation
Speed			
Cost			
Accessibility			
Test menu			
Sensitivity 1. How low can you go?			
Specificity 1. Can you tell me the drug? 2. Are you sure it's that drug?			

Complexities of testing

Complicated by:

Tests

False positives and
negatives

Highly technical
language

Complex metabolic
pathways

Patients

Denied use or
nonadherence

Tampering

Lack of
standardization

Variable cutoffs and
methods

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Common causes of false positives



Cross-reactivity of immunoassay (most common)

- [Antibody
- Drug of interest
- Illicit drugs
- Over the Counter drugs
- Some foods/drinks
- Bacterial production (!)

Antibodies can
(incorrectly) pick up on
some/any of these

Interfering substance in confirmation testing (very rare)

Unlike in immunoassay, this will be identifiable and called out on the patient report

Common causes of false negatives



1) Too little drug to detect, due to:

- When drug consumed
- Dilutions
- Degradation (rare)

2) Can't detect, due to:

- Cutoff of the assay (below level of detection)
- Drug is masked by other materials in urine (e.g. adulterants).
- The incorrect test was ordered.
- Tampering with the specimen cup.
- Low cross reactivity in drug class

Specimen validities help work out whether dilution or adulteration has occurred.
Recognize some could be characterized as true positives depending upon clinical context

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Parent Drug	Metabolite
Heroin	6-acetylmorphine or 6-AM
Buprenorphine	Norbuprenorphine
Methadone	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)
Ethanol	Ethyl Glucuronide (EtG)/Ethyl Sulfate (EtS)
Cocaine	Benzoyllecgonine (BCE)
Methylphenidate	Ritalinic acid

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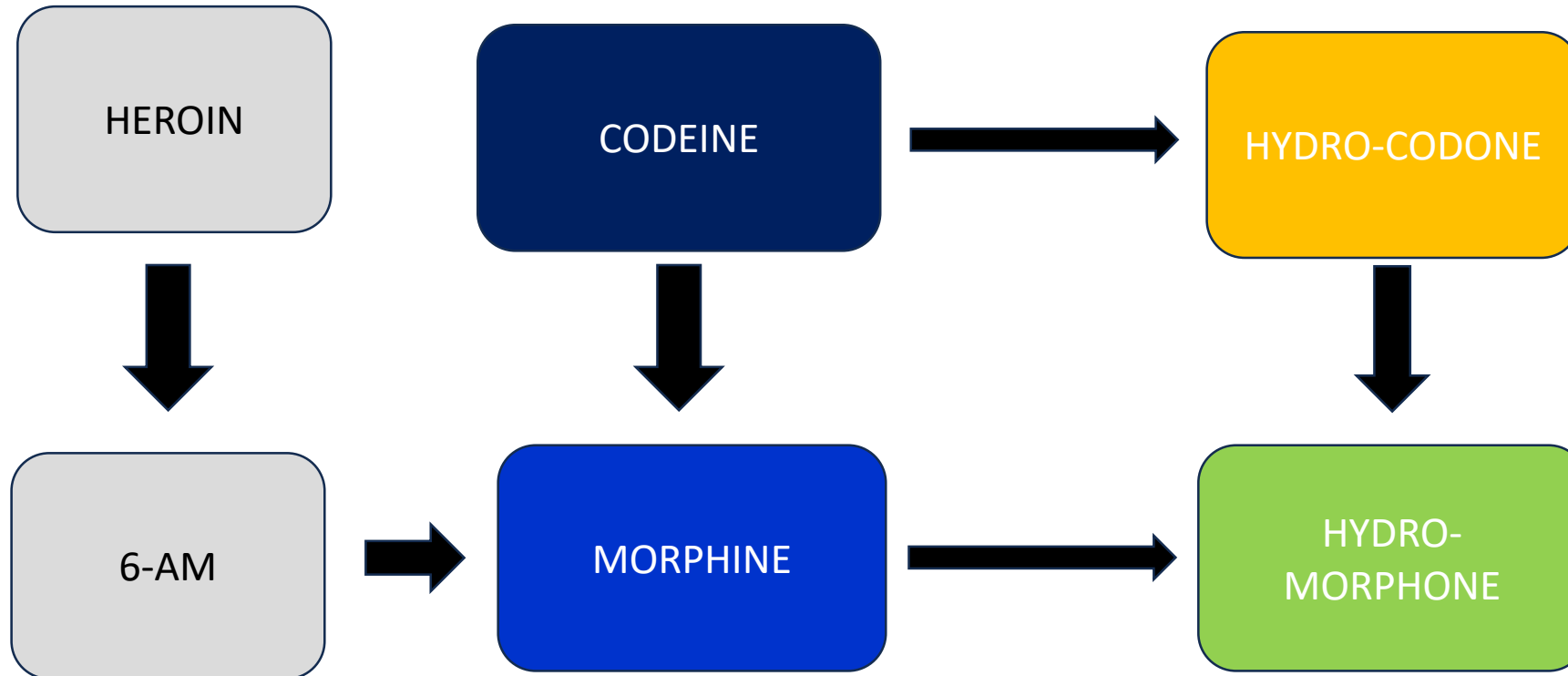
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Simplified metabolic pathway: Opioids

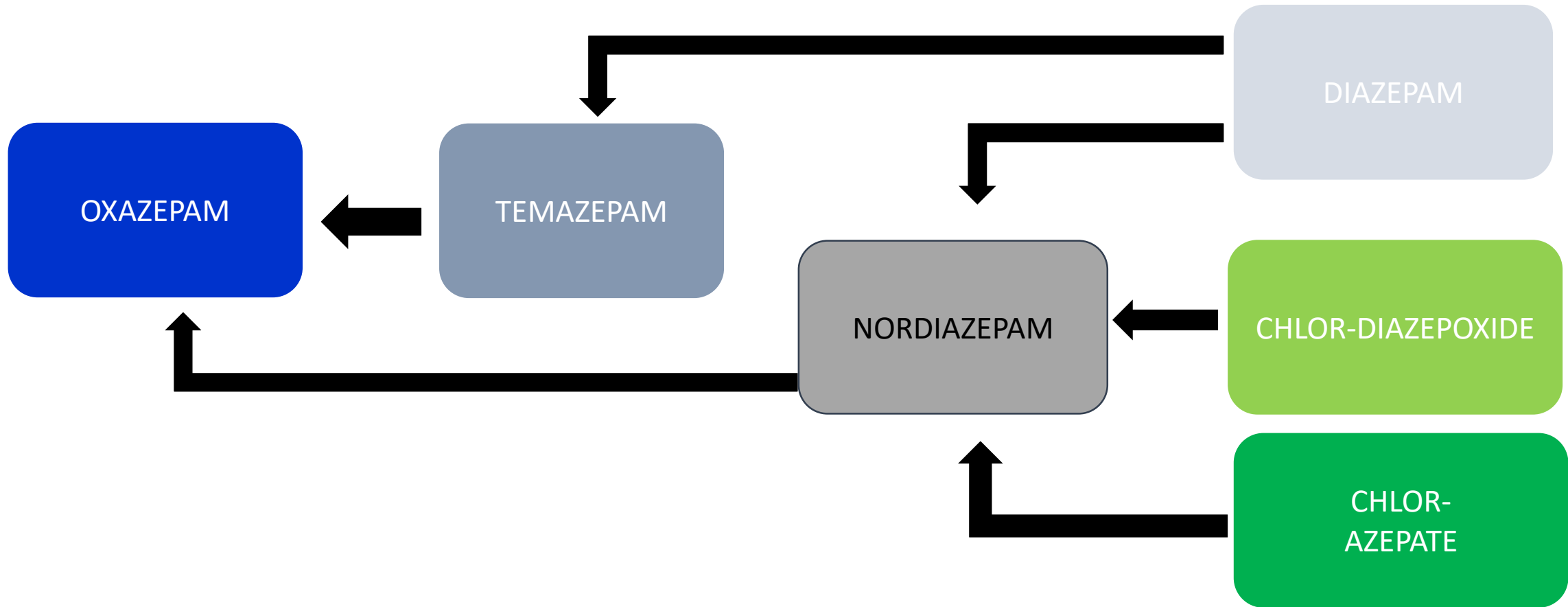


Opioids: A more comprehensive metabolite list

Opioids	Metabolites
Buprenorphine	Norbuprenorphine Norbuprenorphine-3-glucuronide Buprenorphine 3-glucuronide
Butorphanol	Hydroxybutorphanol Norbutorphanol
Codeine	Hydrocodone (minor) Norcodeine Morphine
Fentanyl	Norfentanyl
Heroin	Morphine Codeine (contaminant) 6-monoacetylmorphine (6-AM)
Hydrocodone	Hydromorphone Dihydrocodeine Normorphine Norhydrocodone Hydrocodol Hydromorphol

Opioids	Metabolites
Hydromorphone	Dihydromorphone Hydromorphone-3-glucuronide
Methadone	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) 2-ethyl-5-methyl-3,3-diphenylpyrrolidine
Morphine	Hydromorphone (minor) Morphine-3-glucuronide Morphine-6-glucuronide Normorphine
Oxycodone	Oxymorphone Noroxycodone Oxycodols and their oxides
Oxymorphone	Oxymorphone-3-glucuronide Oxymorphol
Propoxyphene	Norpropoxyphene
Tramadol	O-desmethyl-tramadol Nortramadol

Common metabolic pathways: Benzodiazepines



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A word about the patient's journey



“ They are willing to give up *everything they care for* in order to take a drug—it is not enough to say that addiction is a chronic brain disease. What we mean by that is something very specific and profound...and that healthy people take for granted, *free will.*”

- Nora Volkow, Director of National Institute on Drug Abuse (NIDA), 2015

Nonlinear pathway



Punctuated by:

- Relapse
- Remission
- Denial
- Recovery

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Types of Specimen Tampering

SUBSTITUTION

Replacing one's urine
with other urine or
substances

DILUTION

Intentionally "watering down" urine
through hydration or adding liquid to sample

ADULTERATION

Adding products to mask
appearance of drugs

Ways to identify/limit tampering

Types of Tampering	Counter-response (at collection or in laboratory)
Substitution	Collections: Observed and/or Randomization Laboratory: Innovative detection of synthetic urine
Dilution	Collections: Observed collections and/or Randomization Laboratory: Creatinine, specific gravity
Adulteration	Collections: Observed collections and/or Randomization Laboratory: pH, General oxidants

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A brief word about differences between labs



- Laboratories are heavily regulated but lack standardization
- Laboratories use different methods
 - Different antibodies in immunoassays
 - Prepare specimens differently for confirmation testing
 - Use different equipment
 - Multiple methods can be in one hospital system
- Reports vary and require orientation to use most effectively

Case 1

A 34 year old pregnant woman is 18 weeks into her pregnancy and comes to your office for an ultrasound. She has a history of a Stimulant Use Disorder and you periodically are monitoring her with Urine Drug Testing. At intake you perform a urine drug Point-of-Care test (POCT) and you see that her urine is positive for cocaine. Prior urine drug testing has been negative.

What do you do?

Case 1



After discussing this finding with the patient, she admits to recent use of cocaine.

What do you do?

Is any additional testing required?

Case 2



A 22 year old woman with a history of an Opioid Use Disorder is 32 weeks pregnant. You have been monitoring her with urine drug testing. To date, her urine drug testing has been negative. You have an in-house laboratory that you send the urine sample to and it comes back positive for fentanyl.

What do you do?

Case 2



Given the rate of false positives with fentanyl testing and she has been adherent to your treatment plan to date (negative prior urine drug testing), you suspect this is a false positive but send the laboratory to perform a confirmation test for fentanyl. The confirmation test is negative for norfentanyl and fentanyl.

What do you do?

Is any additional testing required?

Summary

- Intent was to provide a broad level overview
- We reviewed the three types of urine drug testing options including:
 - Point-of-Care testing – an in-office drug testing option, provides rapid, accessible answers, but least reliable test result
 - Lab-Based Immunoassay testing – a testing option that is sent to a laboratory, provides reasonable turnaround times, a more extensive selection of drugs but produces a moderate number of false positives and false negatives
 - Confirmation testing – a testing option that is sent to a laboratory, is slower and expensive, but provides the most accurate answer
- Discussed the complexities that influence result interpretation

Any test result must be considered in the context of the patient to provide the best care

Questions?



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