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One of These Tests is Not Like the Other:

Comparative effectiveness, cost-effectiveness and utilization guidance in pain management testing

Speaker

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Learning Objectives

- Discuss the various approaches to test design to support pain management.
- Compare and contrast several available strategies for determining pain management compliance testing.
- Determine the best approach to testing for a typical pain management patient population.

Speaker Financial Disclosure Information

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- Honorarium/Expenses: **None**
- Intellectual Property/Royalty Income: **None**

Important Points to Consider

- Client/patient demographics
- Available platforms
- Reimbursement challenges
- Technical competency
- Clinical competency
- IT competency

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The Clinical Goal for Testing
Pain Management Context

- Minimizing risk to maximize patient benefit
  - Monitoring Compliance
  - Detecting illicit use

Risk Category	Recommended Frequency of Testing (per year) - UDT
Low	≥ 1
Moderate	≥ 2
High	≥ 3 or 4
Aberrant Behavior	At visit

The Laboratory's Goal for Testing

Pain Management Context

- High quality testing
  - AMRs; Cross-reactivity (IA); TAT; QC; cutoffs; etc.
- Well-designed testing menu
  - Metabolites; Free vs. Conjugated vs. Total
- Easy to interpret reports
  - Data overload; Physicians are not pharmacologists
- Development of a test that actually gets ordered
  - Welcome to clinical mass spectrometry!

Dose and Time
Helpful or not?

- **Serum/Plasma**
  - Dose compliance can be determined
    - Absorption
    - $t_{1/2}$
  - Shorter window of detection
- **Urine**
  - Drug compliance
    - Yes or No
  - Longer window of detection
    - 1 to 3 days

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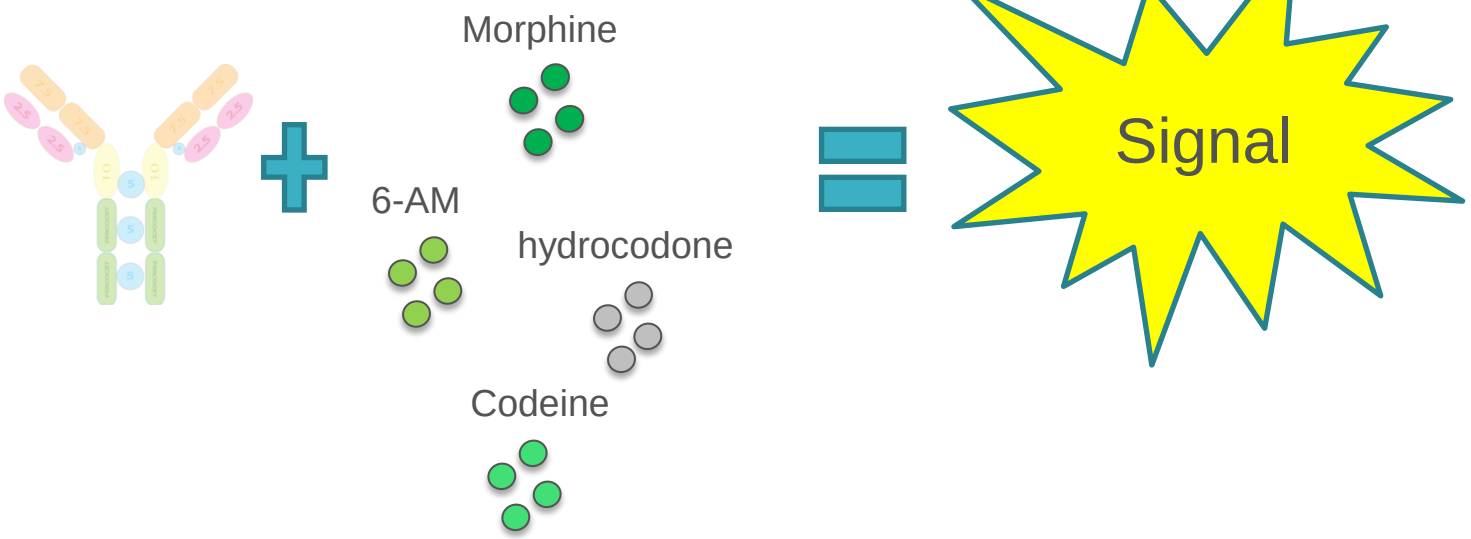
What is the difference between identification, quantitation and confirmation?

Confirmation Testing
Yes, no, maybe?

- True confirmation testing means that the identity of a drug has been determined by two different methods
  - e.g., an immunoassay "screen" and then a mass spectrometry "confirm"
  - *Two independent sample preps are key*
- For routine clinical testing, absolute identification is needed – *but not usually by two different methods!*

Confirmation Testing
When?

- Non-specific screening method used
  - e.g., immunoassay for opiates

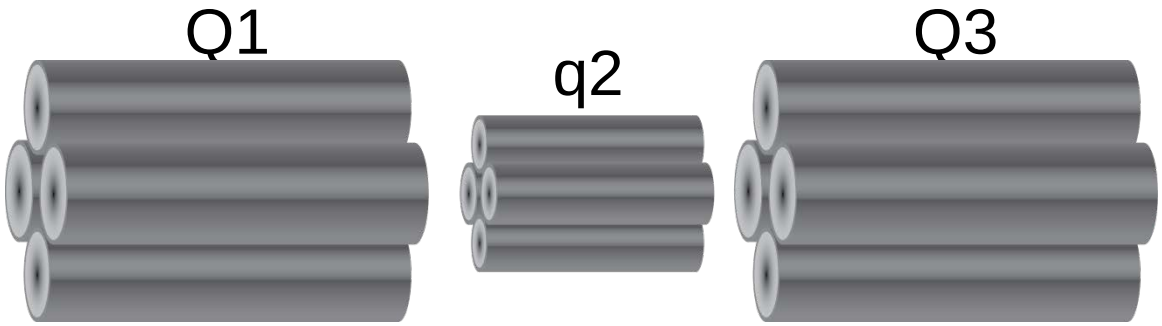


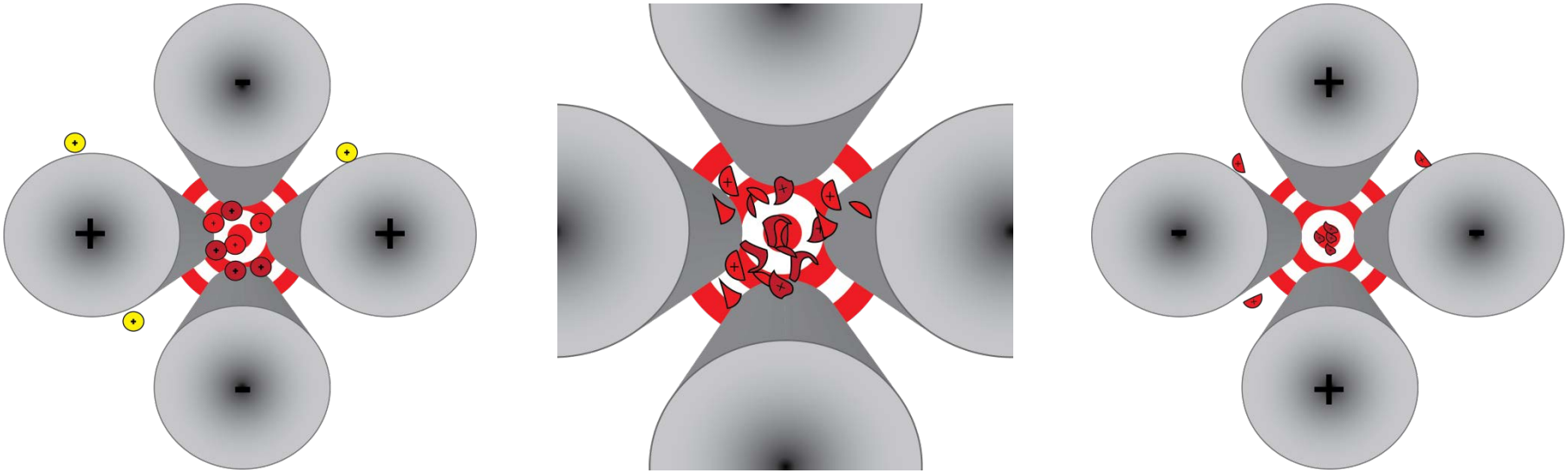
Interpretation:
Morphine only?
6-AM?
All of them?
None of them?

"You need this reflexed to confirmation."

Mass Spectrometry
Triple Quadrupoles

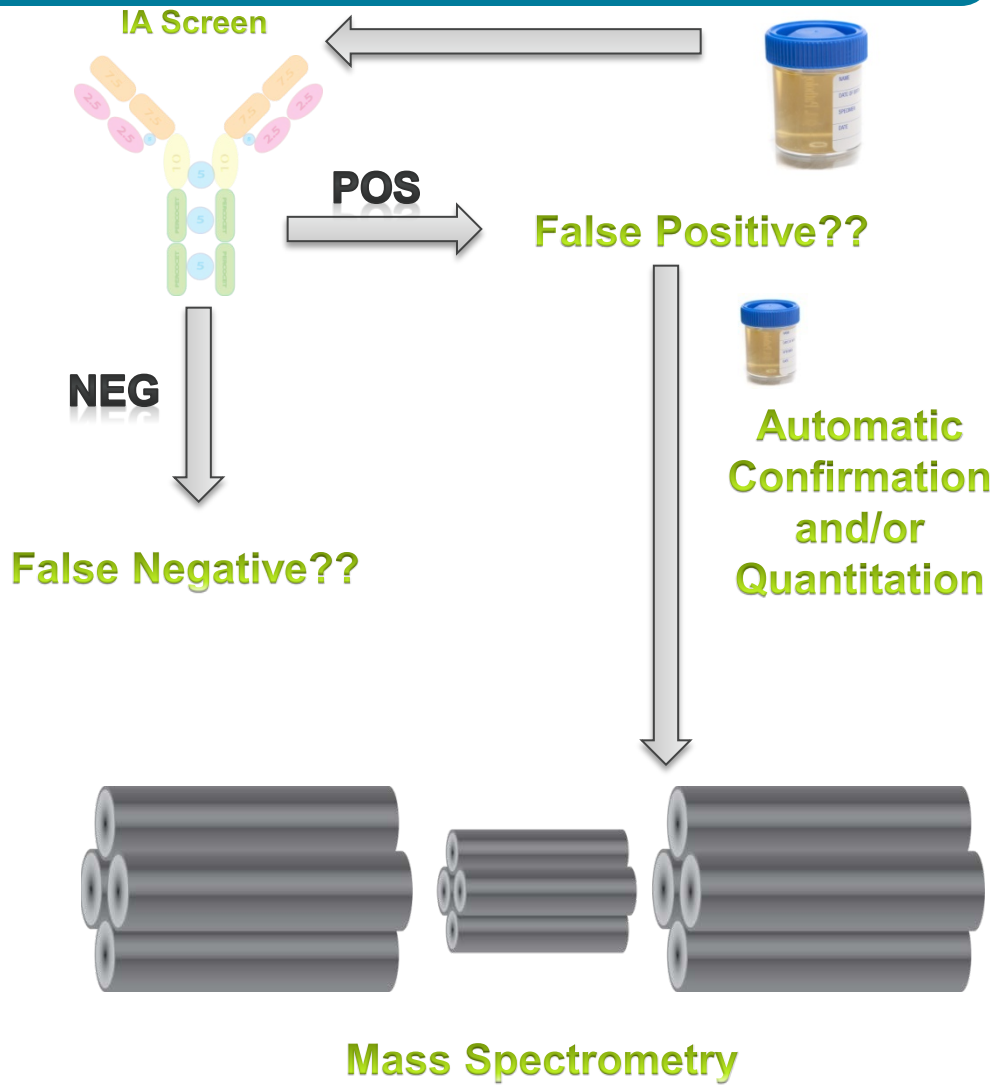
- Gas phase ions
- Mass-to-charge ratio (*m/z*)
- Flight stabilization
- **Fragmentation**





Rethinking Past Strategies

- Screen w/ reflex to confirmation
  - Forensic concept
    - Prep and measure by Method 1
    - Prep and measure by Method 2
- What are we after for compliance testing?
  - Yes or No
  - Absolute identification
  - Quantitation?



The Laboratory's Role: Identification, Quantitation, Confirmation

- Decide what is needed for the clinical context
- Think absolute identification
- Definitive methods can be used for "screening" purposes
- Break free of the forensic workflow if possible

When, if ever, does quantitation make sense for pain management?

Quantitative vs. Qualitative
When? Why?

- Will the amount of drug detected in the urine change management?
  - Remember to take urine concentration into account!
  - Quantitative value adds little when testing for compliance

Case Study #1

Mass Spectrometry Screen
Mass Spectrometry Quantitation

1. 55 y/o male prescribed 5mg hydrocodone and clonazepam.

Hydrocodone	PRESENT	262 ng/mL
Norhydrocodone	PRESENT	254 ng/mL
Clonazepam	PRESENT	42 ng/mL
7-aminoclonazepam	PRESENT	652 ng/mL

Creatinine	286 mg/dL

2. 48 y/o male prescribed 15mg hydrocodone and clonazepam.

Hydrocodone	PRESENT	32 ng/mL
Norhydrocodone	PRESENT	29 ng/mL
Clonazepam	NOT DETECTED	
7-aminoclonazepam	PRESENT	59 ng/mL

Creatinine	16 mg/dL

Case Study #2

- 39 y/o female prescribed oxycodone and lorazepam.
- Visit #1
  - Amphetamine
  - THC
- Visit #2
  - 3 weeks later

Oxycodone	PRESENT	657ng/mL
Noroxycodone	PRESENT	698 ng/mL
Lorazepam	PRESENT	58 ng/mL
Amphetamine	PRESENT	886 ng/mL
THC	PRESENT	432 ng/mL

Visit #1

Creatinine	154 mg/dL

Oxycodone	PRESENT	432 ng/mL
Noroxycodone	PRESENT	329 ng/mL
Lorazepam	PRESENT	43 ng/mL
Amphetamine	NOT DETECTED	
THC	PRESENT	59 ng/mL

Visit #2

Creatinine	156 mg/dL

Benefits of a Qualitative Assay

- Simpler testing strategy for multi-analyte tests
  - 67 drugs/metabolites with 67 calibration curves??
  - Negative, 1 @ cutoff, 1 @ 50% control, 1 @ 150% control
  - Analog ISTDs possible **if you can prove it**
- Reduced costs
- Addition of new analytes can be rapid

Limitations of a Qualitative Assay

- Quantitative results can be useful
- Accurate ratios may be lost
  - Methamp/amp
  - Pharmaceutical tolerances for impurities
- Makes many physicians nervous
- Platform can cause reimbursement challenges

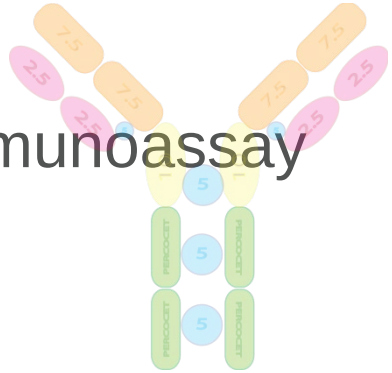
Recommendations: Quantitation

- Quantitation should be available (in-house or Send Out)
- Eliminate it when it isn't useful
  - Reduces cost, complexity and time
- Use AND report numbers wisely!
  - Always with creatinine

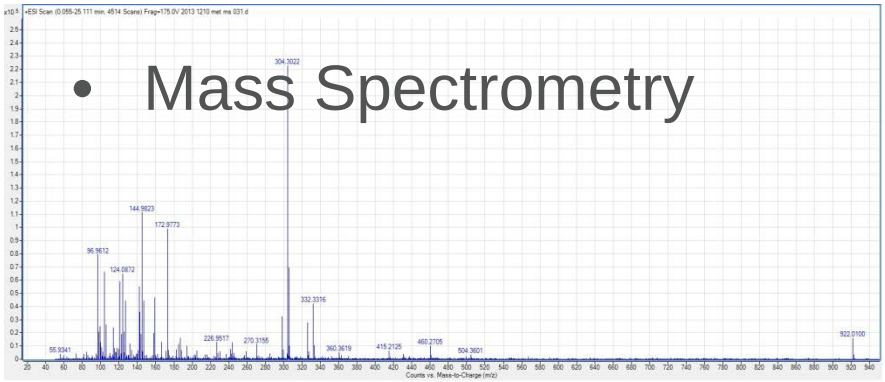
What is the best workflow for pain management testing?

Which Method is Best?

- Immunoassay

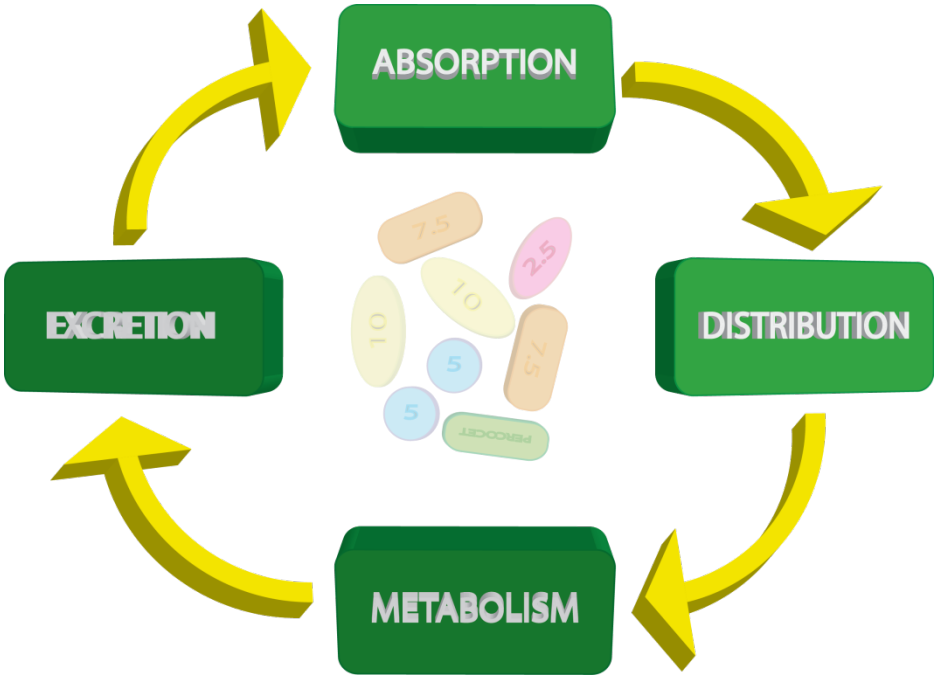


- Mass Spectrometry



- Situation dependent
- Expecting negatives
  - IAs work well
  - Think “workplace drug testing”
- Expecting positives
  - Depends on the class
  - Mass spectrometry more specific
- Immunoassays do have a role
  - POC
  - ER
  - Rapid screening

Metabolites are Key



Metabolites:
Accurate compliance determination

- 46 y/o male patient with Hx of diversion. Current medications include oxycodone and alprazolam.

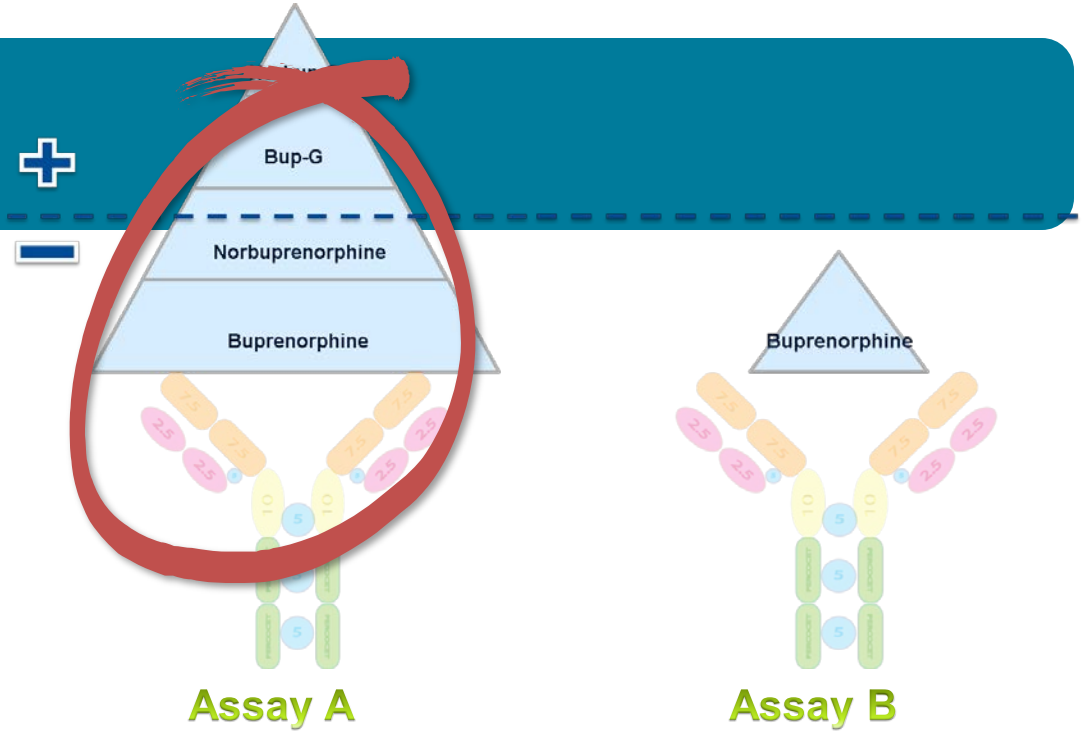
Result A

Oxycodone	PRESENT
Alprazolam	PRESENT

Result B

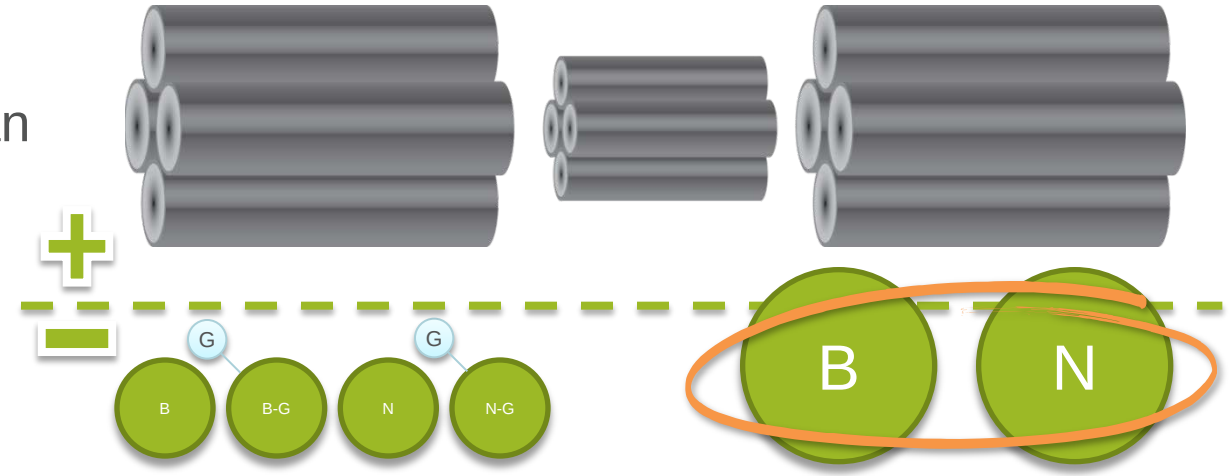
Oxycodone	PRESENT
- Noroxycodone	PRESENT
Alprazolam	PRESENT
- Alpha-OH-alprazolam	PRESENT

Metabolites:
Enhancing sensitivity



- 36 y/o female prescribed buprenorphine.
  - Buprenorphine
    - Norbuprenorphine
    - Buprenorphine-G
    - Norbuprenorphine-G

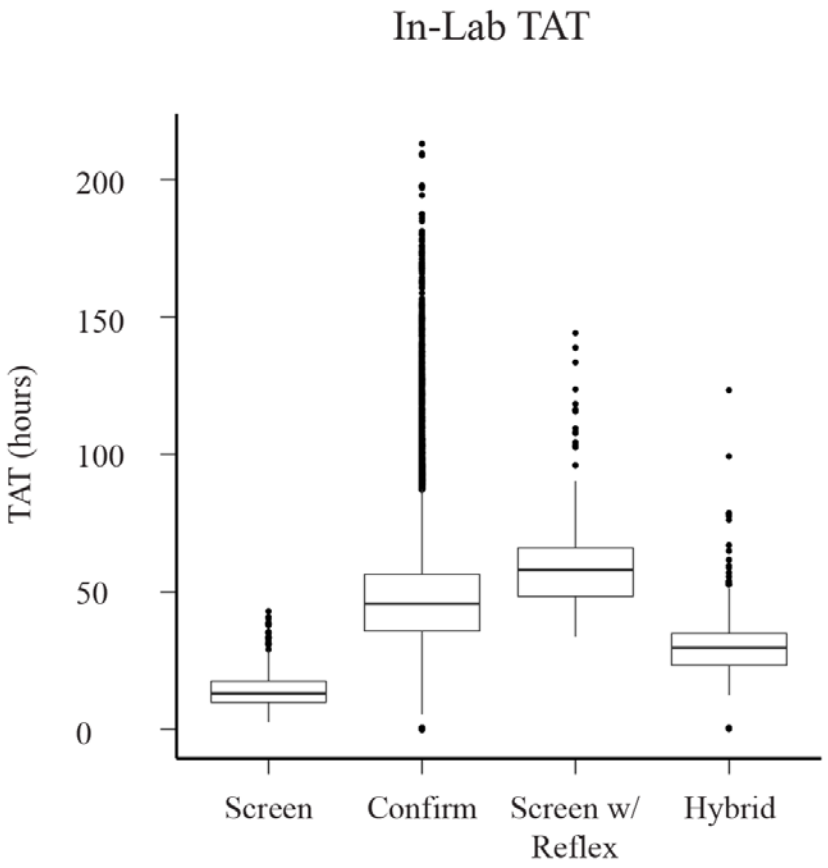
- Cross-reactivity in an immunoassay
- Hydrolysis for mass spectrometry

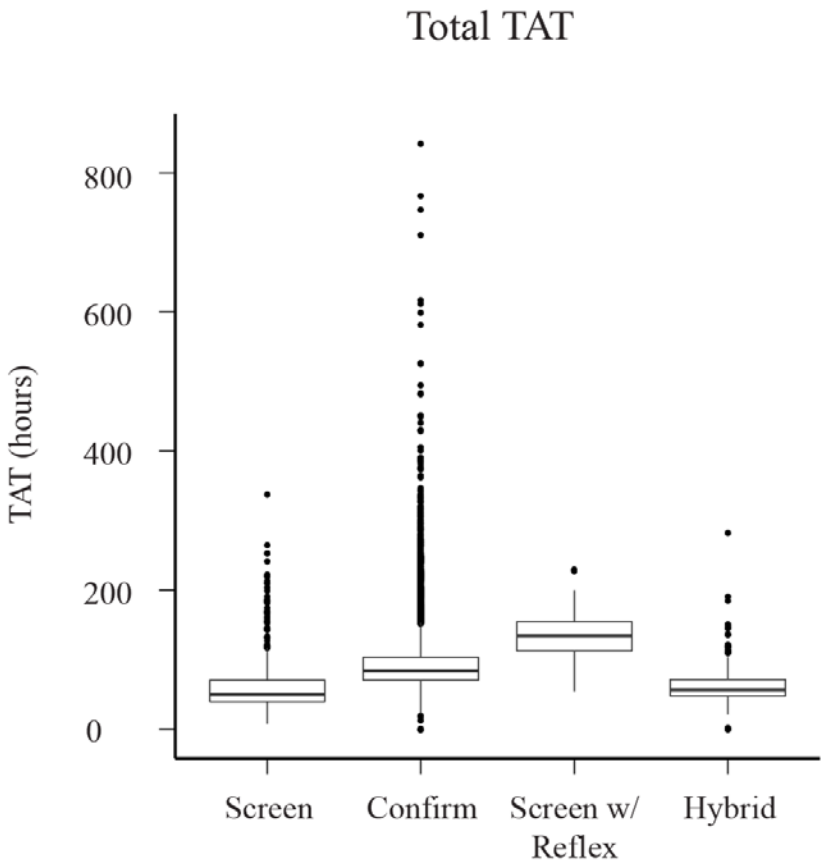


Benefits of a MS Screen

- Sensitivity & Specificity on par with classic “confirmatory” methods
- Individual compound/metabolite identification
- Elimination of cross-reactivity complications
- Drug/metabolite pairs for interpretations
- Drug abuse testing conducted concurrently for high risk populations
- Relatively easy integration of new targets
- “Reflex to Quantitation” still possible when needed

Reduction in TAT with a MS Screen





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Recommendations: Assay Design & Workflow

- Use the platform you know and have
- Keep things as simple as possible
- Know your client base and needs
- Flexibility
  - Reimbursement, new drugs
- Design an assay for what is needed – no more, no less

What level of interpretation should we offer and why?

Physicians are not pharmacologists!
Common calls

- “My patient is taking Klonopin but repeatedly screens negative for benzos.”
  - 7-aminoclonazepam vs. clonazepam
- “My patient is taking oxycodone but is negative for opiates. Is he diverting?”
  - Opiate IA vs. Oxycodone IA
- “My patient is taking Valium but is positive for 4 other drugs.”
  - Benzo metabolism

Interpreting Results
Easier said than done…

2013 DMPM Cap Survey Results

Dry Lab Challenge

Case Summary and Interpretation

A 41-year-old male with chronic low back pain came for a follow-up visit. The patient has a known right L5-S1 disc extrusion osteophyte complex and is being prescribed *Roxicet* (oxycodone + acetaminophen) and *Percocet* (oxycodone + acetaminophen).

Medication List

- LYRICA 150 mg p.o. b.i.d
- ROXICET/PERCOCET 5 per day p.r.n. pain
- VIAGRA p.r.n.

Test Results

Screen Results	Confirmation Results
Opiate screen NEGATIVE	Oxycodone 2500 ng/mL, oxymorphone 1500 ng/mL
Amphetamine screen POSITIVE	Amphetamine 2500 ng/mL
Benzo screen NEGATIVE	Lorazepam 4000 ng/mL

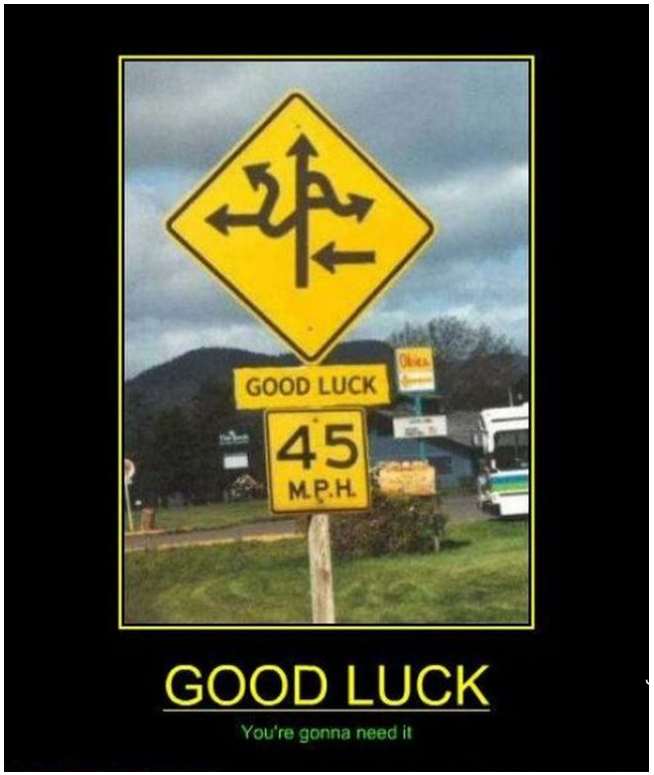
DMPM-04

Interpretation (Educational)

Result	No. of Respondents	%
Toxicology results are **inconsistent** with prescribed medication	49	59.8
Toxicology results are **consistent** with prescribed medication	33	40.2
Additional prescription drugs present	74	90.2
Additional prescription drugs absent	8	9.8
Illicit drugs present	40	48.2
Illicit drugs absent	43	51.8

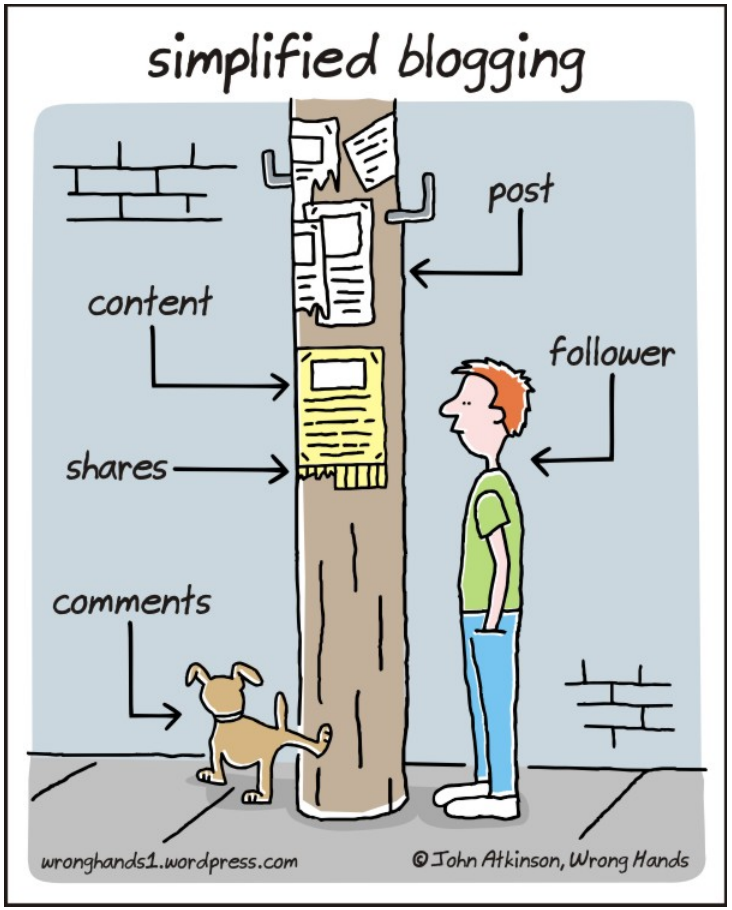
Two Paths for Supporting Interpretations

- Path 1
  - Provide all information to the *physician*
    - Results (qual and/or quant)
    - Guides (see appendix at the end)
  - Hope for the best
  - Wait for a call



Two Paths for Supporting Interpretations

- Path 2
  - Provide all information to the *Lab*
  - Provide interpretation to physician
  - Wait for a call



Example Interpretation: High Volume Test

Submitted with order

Drugs Provided:
NORCO
ALPRAZOLAM

Provided by Lab

Interpretation:
CONSISTENT with medications provided:
NORCO: based on hydrocodone, norhydrocodone, dihydrocodeine, hydromorphone
ALPRAZOLAM: based on alprazolam, alpha-OH-alprazolam

Tells physician what and why

INCONSISTENT with medications provided:
THC: based on immunoassay detection

Indicates detection method if not definitive

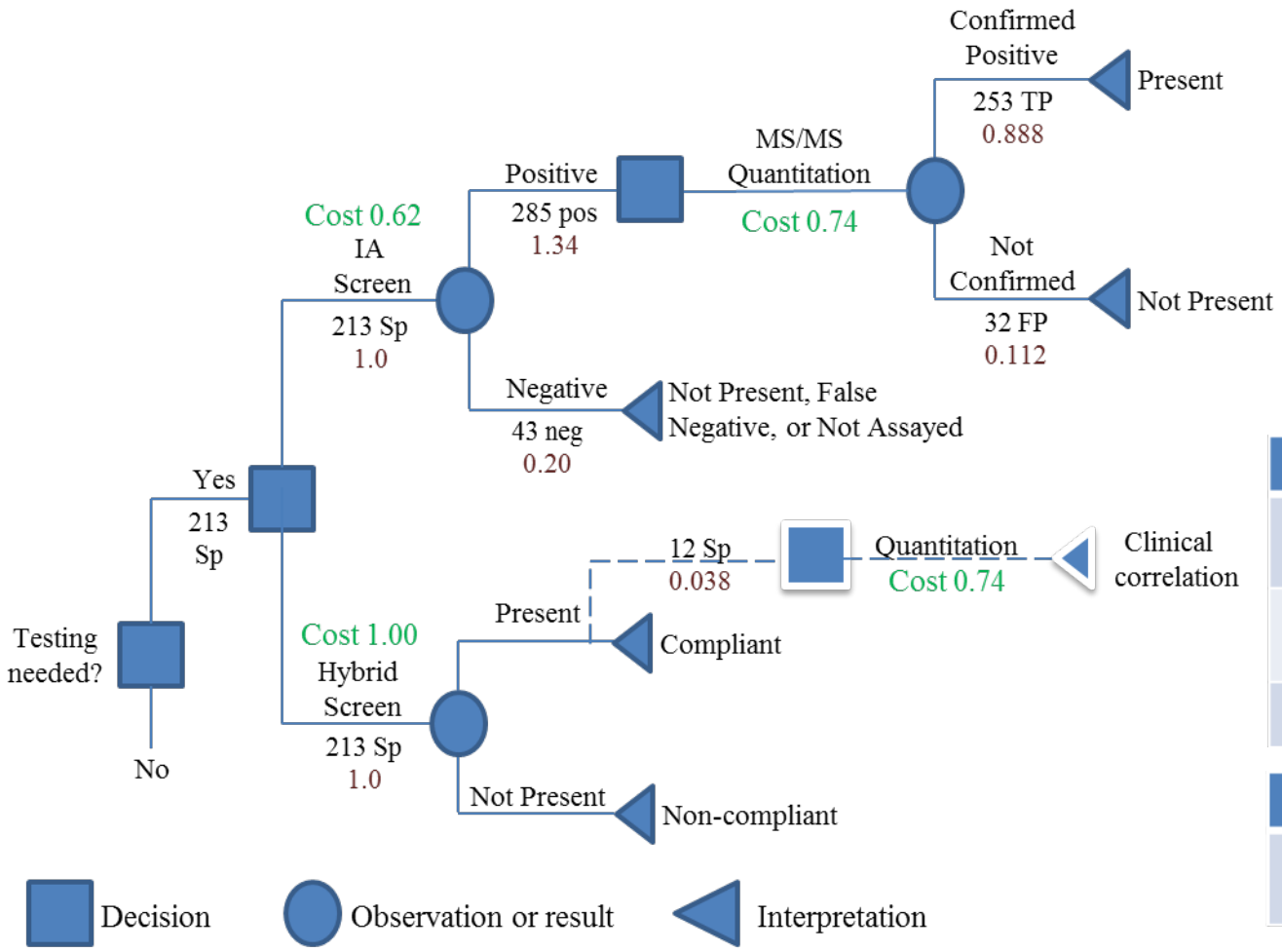
Drugs not included in this assay:
Acetaminophen

Helpful co-formulation information

Recommendations: Providing Interpretations

- Prepare for future volumes
- Decide on a level of detail and standardize
- Understand IT limitations
- Educate physicians if interest exists
- Provide tools customized to your assay

Relative Cost Effectiveness



IA to Confirmation Workflow
IA w/ Confirm (0.74*1.34) + (0.65*1.0) = 1.61
IA w/o Confirm (0.52*0.2) = 0.12
Total workflow = 1.74

TOF Hybrid Workflow
Total Worflow (1.0*1.0) + (0.74*0.04) = 1.03

*All costs are normalized the average hybrid screen cost

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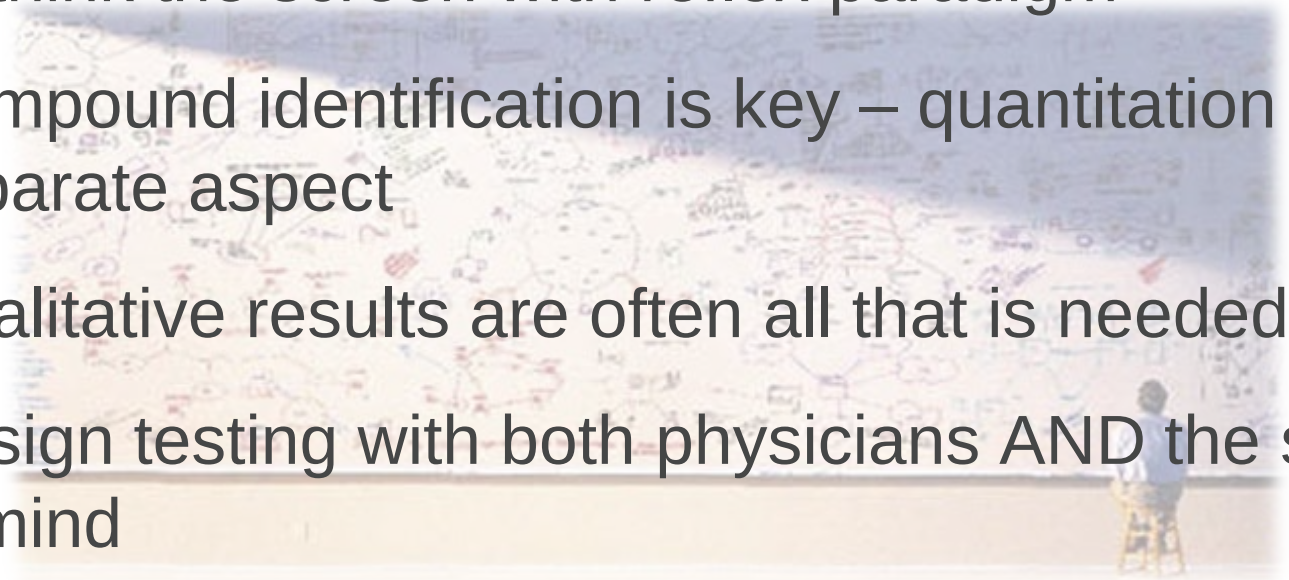
Summary & Key Points



- Rethink the screen with reflex paradigm
- Compound identification is key – quantitation is a separate aspect
- Qualitative results are often all that is needed
- Design testing with both physicians AND the staff in mind

Contact Information

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