PAINWEEK®

KEY-09 - Urine Drug Testing: Meeting the Test of Medical Necessity Through Patient-Centered Care

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Disclosure

- No conflicts to disclose

Learning Objectives

- Describe the origins of Drug Testing in America
  - With emphasis on the differences between forensic and clinical
- Review the technology in current use in clinical drug testing
- Identify a Testing Strategy that: Meets the definition of “Medical Necessity” as it applies to Clinical Drug Testing and is based on the “Choosing Wisely” model of investigation
- Discuss the “Absence analyte” compliance scenario – with strategies to handle it

Drug Testing in America

- Drug testing in USA began in earnest in 1980s with Reagan-era goal of "a drug free America"
  - In 1986 Michael Walsh, PhD, of Bethesda, MD, and the Division of Applied Research were tasked with implementing Executive Order 12564, Drug-Free Federal Workplace
  - 1988 "The Drug-Free Workplace Act" required that all organizations that contract with or receive money from the federal government maintain a drug-free workplace
  - A key element of this program was forensic integrity: results had to withstand legal scrutiny in a court of law
    - Chain-of-Custody / screen and confirmatory testing by a "second scientific method"
    - Restricted to labs that maintained a high level of proficiency through blinded and random quality testing
  - Important to remember that testing was adversarial – often with serious consequences to those who tested positive for any of the "federal five" substances
  - Marijuana/cocaine/opioids*/amphetamines/phencyclidine – specifically for DOT testing

www.ecfr.gov/cgi-bin/text-idx?SID=44edbc0e557a4cc5ff03365810ee5b1c&mc=true&node=pt49.1.40&rgn=div5#se49.1.40_187

Regulated Drug Testing Strategy

- The widespread use of drug testing in America is predicated on several key points
  - The donor pool is made up largely of non-users, so, reporting thresholds are typically set relatively high
  - Test analytes are limited to the “federal five” (even though there are far more drugs of abuse used today)
  - All +ve results are confirmed by a “second scientific method”
    - Screens are often class-specific not drug specific while confirmations are definitive
  - “A negative result will never harm the donor”
    - This is a critical point when interpreting test results
  - The process is overseen by certified Medical Review Officers using SAMSHA certified labs*
  - *Heit. J Pain Symptom Manage. 2004;27(3):260-267.

Clinical Drug Testing

- Really the opposite
  - At least in the chronic pain population the donor pool is ***expected*** to be users
    - The difference is their use is legitimized by a lawful prescription for an appropriate therapeutic indication
    - A negative result (for the analyte of a prescribed drug) ***can*** call into question patient compliance and potentially, their honesty
    - All abnormal results ***do not need*** to be "confirmed"!
      - Only ***"contested"*** results need to go on to more definitive testing
  - The goals behind clinical testing are different (or should be!)
    - We want to avoid the "Gotcha Test Result"
    - Our goal is clinical – to open a dialog with the patient

Example 1

- A truck driver's urine drug test is reported as "opiates not detected"
  - What does that mean?
    - They are a non-user
    - They use, but not recently
    - The lab made a mistake and reported "not detected" instead of "detected"
    - **The test result was below the reporting threshold**
  - In this case, the donor gets a pass – the benefit of the doubt (if there was any) is given to the trucker
    - "Not Detected" does not say "Not There"

Example 2

- A 65-year-old grandmother, with chronic low back pain is being prescribed Acetaminophen with codeine (325mg/8mg) by mouth, 3 times per day
- She receives a 3-month supply
- In this case, the report indicates “Opiates not detected”
  - Again, what does that mean?
    - She’s not taking the drug!
    - She’s taking some just before the test and selling the bulk!!
    - Her grandson is stealing most of her oxycodone
    - Something else????

Examples:
Beware of the Peri-Threshold Result

- First, we need to know the reporting threshold or “Cutoff” for reporting
  - The opiate cutoff is 2000ng/ml
    - Prior to 1998, it was 300ng/ml
- When was the sample collected?
  - Early morning vs late afternoon
  - Alternatively, Creatinine as a measure of concentration would be useful
- Time, date of last use and quantity
  - Without this information, unexpected negatives can be difficult to assess

Examples - Discussion

- With the cut off set at 2000ng/ml, a value of 1999ng/ml would be reported as “not detected”
  - A value of 2001ng/ml would be reported as “detected”
  - There really is no difference scientifically between these two values
    - But there is a world of difference therapeutically
- What if you repeated the same, immunoassay test and got the same result? Have you assured yourself of the test results?
  - No, you’ve established repeatability NOT accuracy
  - In a forensic sense, this is where testing by “a second scientific method” makes sense….
  - Clinically, it suggests the need for more definitive testing!
    - If the result is contested!

Forensic and Clinical Testing Are at Crossed Purposes

- In many ways, forensic and clinical paradigms of testing are (should be?) at crossed purposes
  - One is trying to establish unauthorized use to a reasonable scientific certainty
  - And the other is trying to assess clinical compliance.
    - This is a much bigger challenge!
- Unfortunately, many who order clinical drug tests really don't know the strengths and limitations of the test(s) that they are ordering and worse
  - They're often making critical decisions based on misinterpretation of results

Urine Drug Test Interpretation: An Educational Program's Impact on Resident Knowledge and Comfort Level

- A study conducted at Beaumont Hospital; Royal Oak Campus, UM described the results of an educational program to improve resident knowledge related to urine drug testing
- Prior to the educational intervention
  - Of the 44/76 eligible trainees, 81.8% indicated they had no prior education in the ordering and interpretation of UDT yet 97.% indicated that they reviewed UDT results on a monthly basis
    - 22.7% had refused to refill requested medications based on UDT results in the previous month
  - Following a 30-minute PPT presentation by a clinical pharmacist, immediate and 2 month follow up showed both increased knowledge and comfort in ordering and interpreting UDT results ($p<.0001$ for both variables)

- Autman. MedEdPORTAL. 2018;14:10684.

"….a dry topic?"

UDT Methods 101

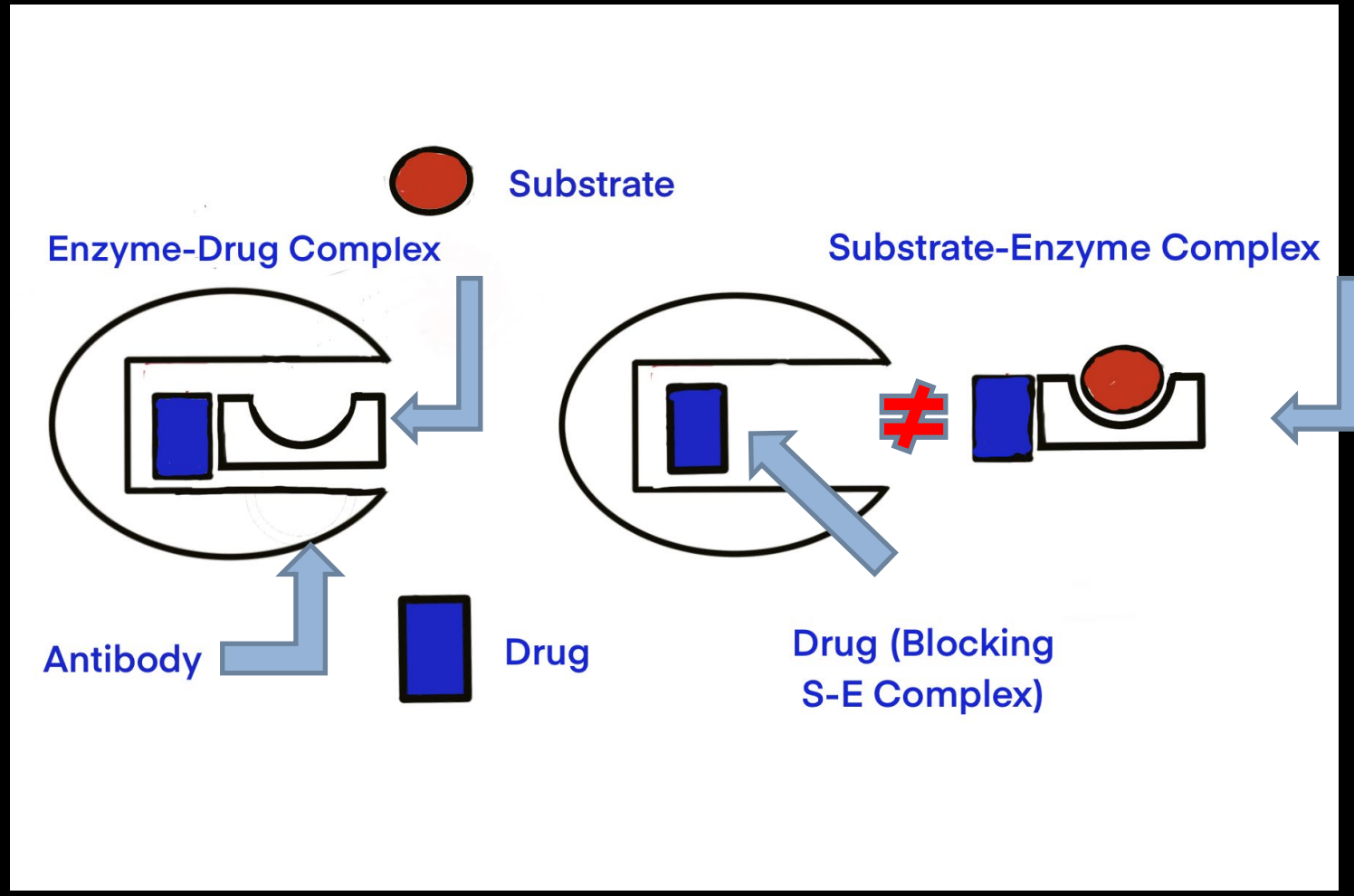
Testing Methods

- Most of the testing in the regulated and clinical testing world is based on preliminary screens (screen/presumptive testing)
  - These are often antibody/antigen tests that react to the presence of “classes” of certain drugs, ie, “benzodiazepines” or “amphetamines” or “opiates”
    - Which amphetamine (if any) contributes to the positive result is, at this point, unknown
      - It could be the agent you are prescribing or another member of that class of drug obtained from a different source (ie, “Vicks Nasal Inhaler”)
  - In order to establish the identity of the agent causing the positive result, a “Confirmatory Test” or “Definitive Test” must be performed
  - If a prohibited substance is identified by a second scientific method, such as GC/MS, the result is said to be valid (forensically)
    - If a patient acknowledges an abnormal result, you have “clinical confirmation”

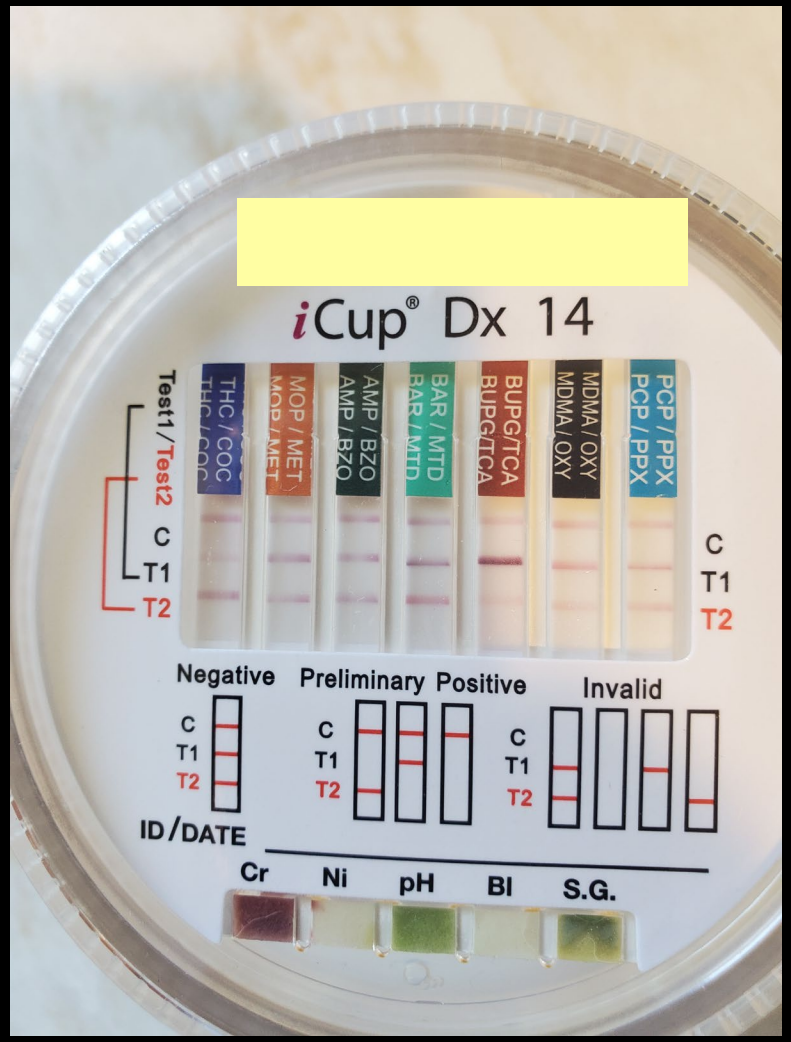
Clinical Drug Testing

- More recently, to redefine drug testing in a clinical, more patient-centered fashion, the terms Screen and Confirmation are being replaced by the terms “Presumptive” and “Definitive” testing
  - So, a positive immunoassay result for the benzodiazepine class of drugs may be specifically identified (by more sophisticated testing methods) as diazepam
- While these terms are often used interchangeably, sometimes within the same journal article, it’s helpful to maintain a clear distance between you, your patient, and the forensic world!

Immunoassay-Based Presumptive Tests



Reading the EMIT test



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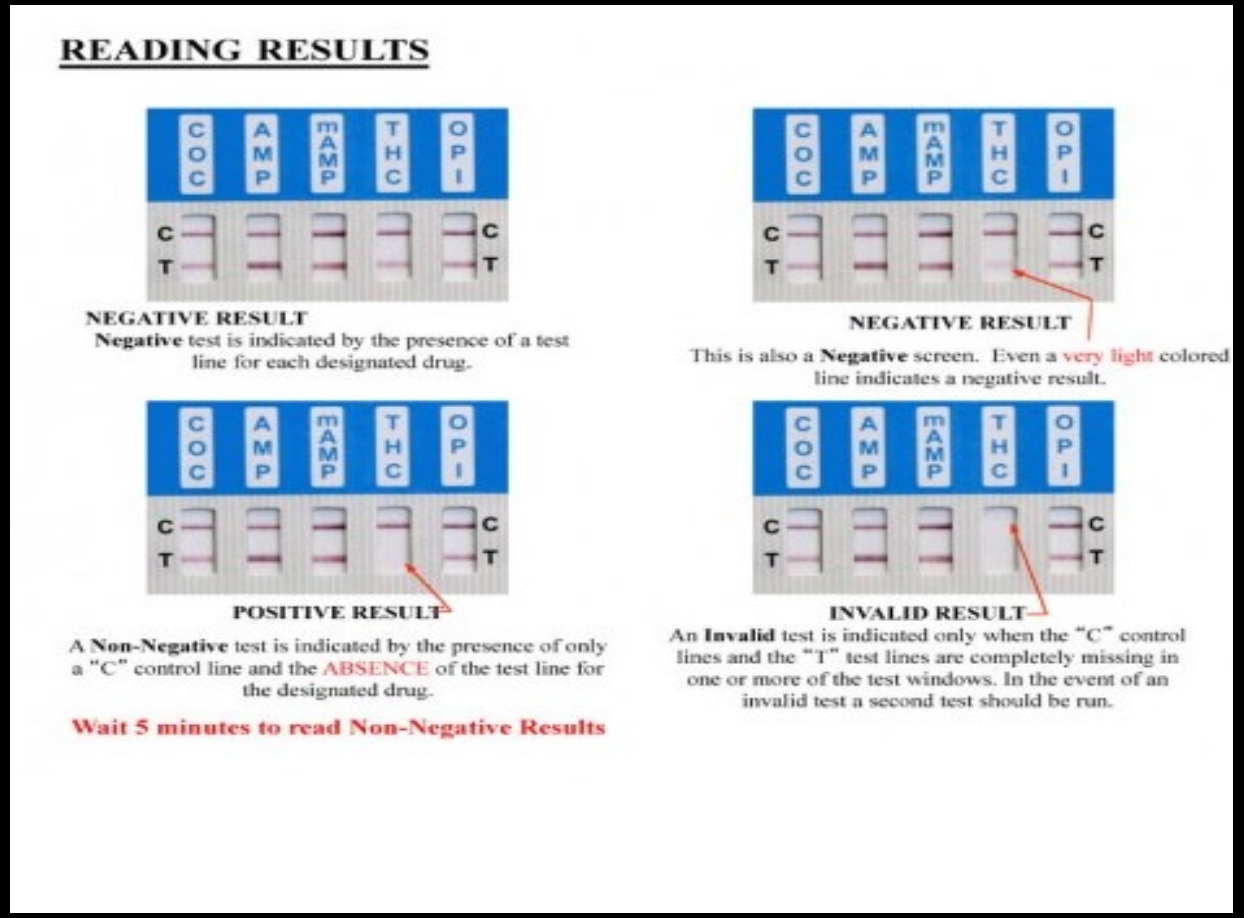
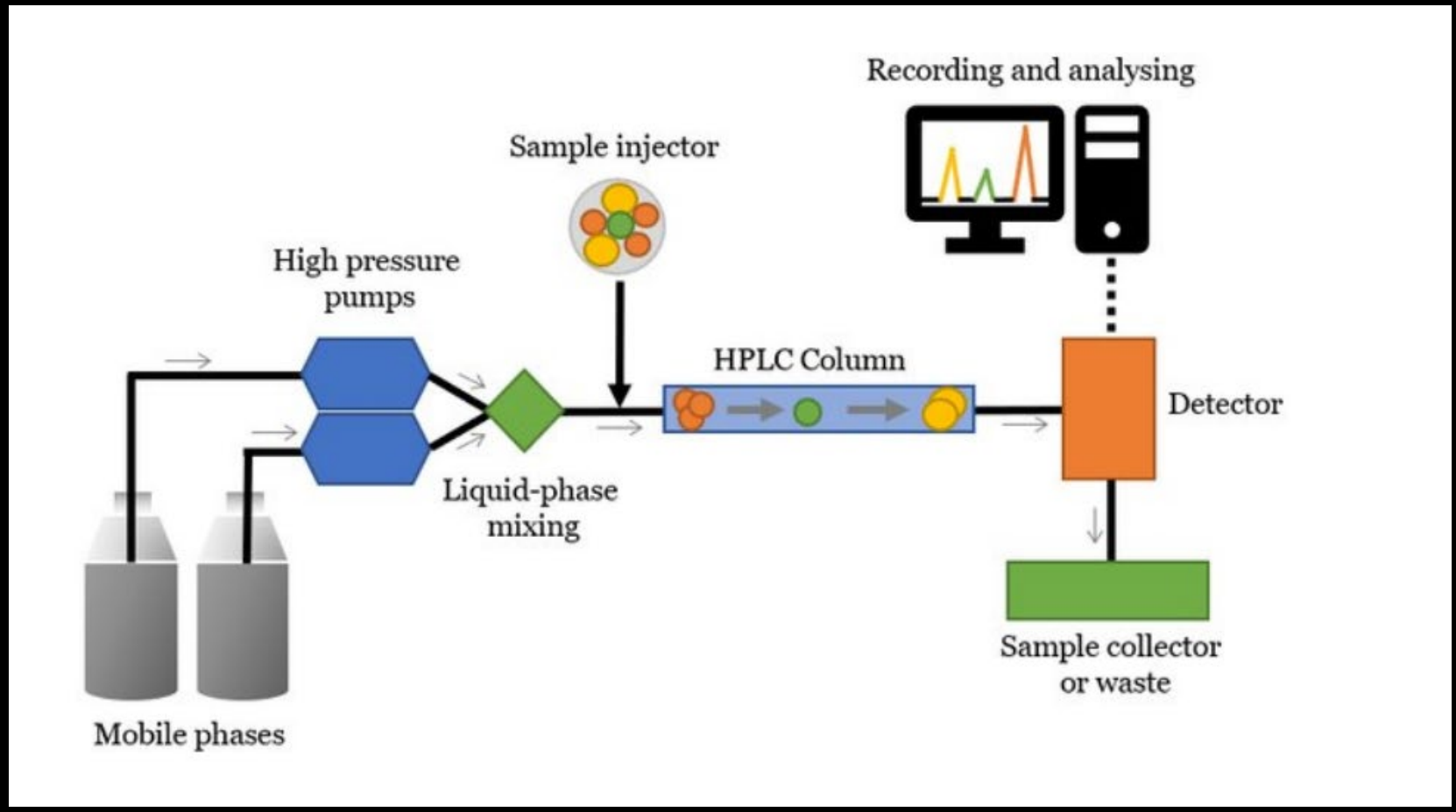


AccuTest Strip, Product Insert

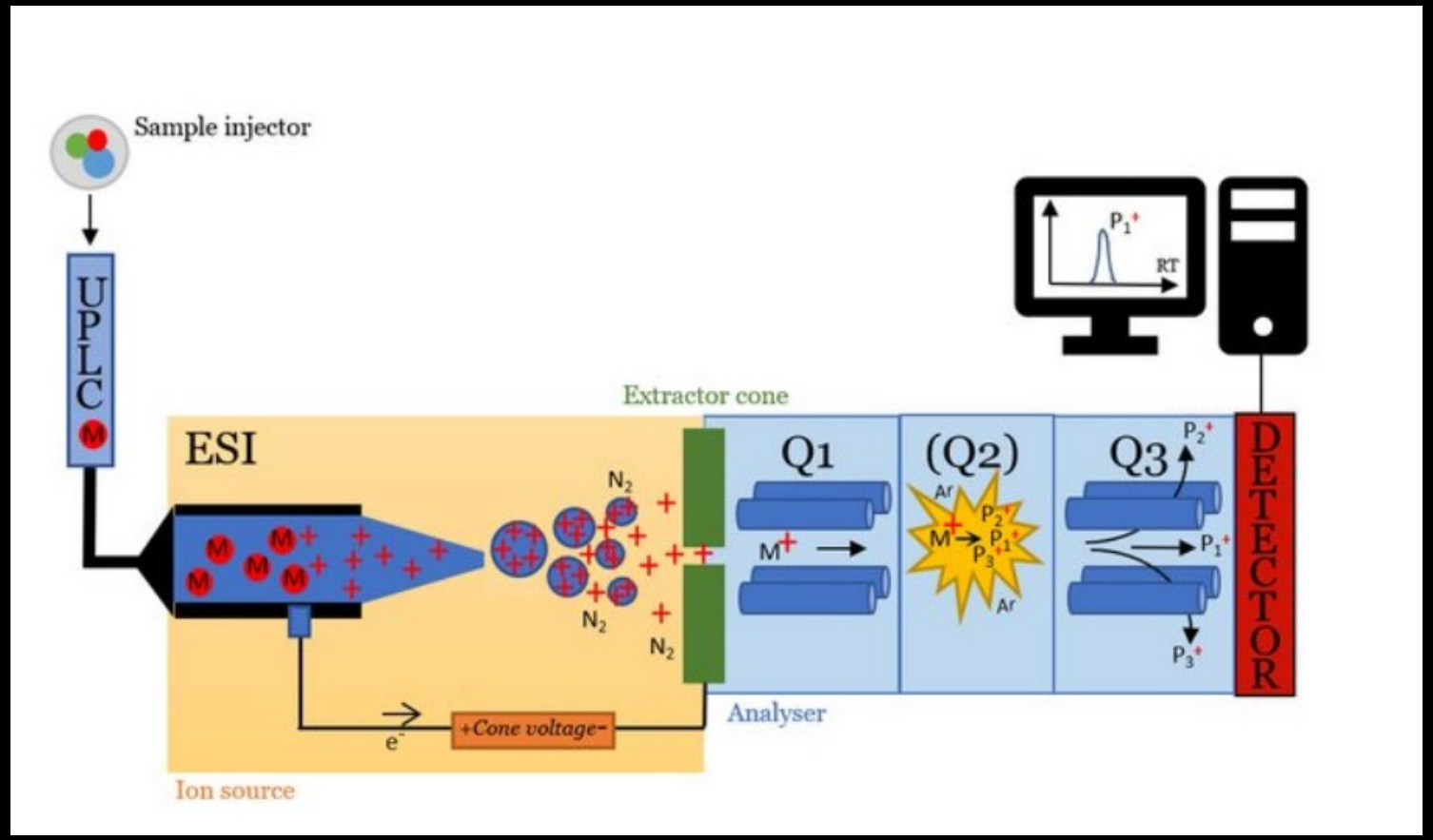
High Performance Liquid Chromatograph (HPLC)



Chromatographic Testing

- In essence, chromatography takes complex mixes of potential analytes and spreads them out “over time” through differential adsorption onto a specialized column
  - Depending on size, polarity, etc, the drugs/metabolites (analytes) spend more or less time loosely attached to the column substrate (ie, silica gel)
  - The “retention time” of each molecular group helps to identify it, when compared to known internal standards
  - When combined with spectroscopic method such as mass spectroscopy, very precise determination of substances can be made

Liquid Chromatography/ Tandem Mass Spectroscopy



UPLC – ultraperformance liquid chromatography column
ESI – electrospray-ionization
Q1,Q3 – quadrupole filters/mass analyzers
Q2 – collision cell
RT – retention time

Mass Spectroscopy

- The preceding graphic shows the combination of chromatography with mass spectroscopy
  - In mass spectroscopy, a sample is “fragmented” into various constituent parts that vary in atomic mass
  - Using a magnetic field, these fragments are separated based on weight and are identified and characterized by sophisticated computer software
- Compared to immunoassay, these definitive tests are more labor intensive, time consuming, and so, more expensive

"You don't need a map if you don't know where you're going!" Dr Walter Ling, UCLA

Testing Strategy or…

Medical Necessity

- For a test to be clinically useful, the following three elements must be present
  - Reason for ordering the test
  - Result(s) obtained and
    - interpretation of these results, relevant discussion with the patient, and appropriate documentation in the medical record
  - Any therapeutic consequences, including “staying the course” if indicated
- Failure to meet this test exposes both patient and practitioner to potential adverse outcomes
  - Patient – over/underestimation of patient stability
  - Clinician – 3rd party payer “claw backs” or worse, criminal allegations of fraud

So, What Test(s) and When?

- First, you need a testing strategy
  - It may be based on clinic policy, by state regulations or both
  - If you want to identify the presence of commonly misused street drugs, immunoassay is often sufficient
    - All presumptive tests DO NOT need to be “confirmed” or “definitively identified”
      - **Only contested results need to go on to further testing**
  - But in the context of clinical testing of pain patients, many/most are being prescribed drugs that would otherwise be considered drugs of abuse except for a “legitimate medical prescription” based on therapeutic need
    - Remember – not all “legitimate” prescriptions are “appropriate”
    - A comprehensive risk management strategy is key to making this distinction

Matrix Selection

- Urine is only one of the bodily fluids that can be used in drug testing. Common alternative choices include:
  - Blood
  - Sweat (even tears!)
  - Breath
  - Hair
- But urine remains “the nearly perfect matrix for clinical testing” if the question you want answered is the right one!
  - If you want to know if the donor is “under the influence” of a drug, urine is a terrible choice
    - Serum levels and urine levels may be an order of magnitude different (concentrating effect of the kidneys contributes to the 2-3 day ‘window of detection’ of many drugs and their metabolites)
  - If you want to know if a donor has used in the preceding 3 months, hair testing is preferred

Quantitative Results

- Despite some lab claims, you can not “count pills” using UDT (or serum, for that matter)
  - There is no reliable relationship between drug concentration in any matrix, and the amount/frequency or temporal order of drug use
  - But you can often comment on trends
    - When corrected for concentration, upward trends in an analyte *typically* reflect ongoing use; similarly, downward trends *typically* reflect discontinuation or dose reduction
  - If you want to know if a prescribed medication is being used, thresholds can give you false “not detected” results
    - Compliance testing should include the phrase “limit of detection” or “limit of reporting” in the request

Patient-Centered Care

- First, lets examine the term Patient-Centered Care
  - Patient-Centered
    - "**Providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions**.*
  - What it doesn't mean is
    - No rules
    - "what the patient wants, I must give – as long as they know the consequences"
    - Patient-Centered Care will not absolve a clinician of their duty of care to their patient – ***primum non nocere***

*https://catalyst.nejm.org/doi/full/10.1056/CAT.17.0559

Patient-Centered Care

- In patient-centered care, if 3 treatment options are equal…
  - It should be (with a clear understanding of the pro/con of each option) the patient that chooses their treatment path
    - But if 2 options are equal, and the 3rd option is “wrong” ie legally/ethically - than the patient must select from the two equal options
    - It is unusual for a patient not be have choices – but some of the choices may be unacceptable to the patient
  - **“In the absence of knowing what to do, knowing what not to do is often a close second!”***

Gourlay, DL. Clinical Pearls*

Who to Test?

- This can be a difficult question
  - It has been long known that using behavioral triggers (ie, how the patient looks or acts) to order drug tests will miss a significant number of abnormal test results
    - 72% of "abnormal" test results showed no behavioral markers that would typically be used to trigger a UDT request*
  - With this in mind, my personal belief is that in the absence of regulations requiring otherwise, I would not recommend testing EVERYONE, but I do recommend discussing possible drug test requests with ALL patients receiving controlled substances
    - UDT is not about patient trust, it's about a commitment to comprehensive risk management
      - How the patient reacts to the possibility of drug testing is often telling in itself

*Katz. *Anesth Analg*. 2003;**97**(4):1097-1102, table of contents.

Presumptive or Definitive Testing– "Choosing Wisely"

- The movement toward rational use of testing in medicine has been well codified in the "Choosing Wisely" initiative by the ABIM in 2012*
  - –The mission of Choosing Wisely is to promote conversations between clinicians and patients by helping patients choose care that is:
    - Supported by evidence
    - Not duplicative of other tests or procedures already received
    - Free from harm
    - Truly necessary
- The routine use of definitive testing in all cases is neither necessary nor cost effective

*www.choosingwisely.org/.
*Faisal. *Postgrad Med J*. 2018;94(1118):716-719.

How Do You Choose?

- First, when you order ANY test, you need to have a reason for that test
  - The practice of doing regular definitive testing as a risk management strategy is not rational
    - The pretest predictive value of such testing is low: a presumptive test panel is much more in keeping with the intent behind periodic UDT: keeping honest people honest!
    - On the other hand, if this is a “for cause” test… ie, in response to evidence of clinical instability, or an unexpected presumptive test result, definitive testing *may* be indicated – if the abnormality is contested
      - A positive presumptive cocaine positive result that the patient acknowledges does not need to be proven by definitive testing. Counselling of the patient AND tightening of boundaries will often be sufficient. If this occurs again, referral on is strongly recommended

Even in High-Risk Patients, You Can Test Too Frequently

- Some have said that “except for cost, in a perfect world, we’d test everyone every day” – This is not true
  - Excessive testing is neither rational nor therapeutic. Unnecessary testing “medicalizes” the patient needlessly. If you feel high frequency testing is necessary, refer the patient for evaluation by a substance use disorder specialist – don’t just keep testing!
- Testing is a key part of a comprehensive risk management program
  - It is NOT a credible strategy alone, or in the absence of rational clinical judgement
  - This is especially true if there is apparent or real financial benefit to the ordering clinician (Stark Law*)
- If you don’t have the skills AND the resources to manage high risk patients, you should
  - 1) Refer on or
  - 2) Limit your treatment options to reflect this risk, ie, tight limits and boundaries, review of the use of all controlled substances and consider lower risk strategies

*https://www.arentfox.com/perspectives/health-care-counsel-blog/changes-stark-law-definitions-impact-innovative-relationships

Therapeutic Options for Unexpected UDT Results

- There are a myriad of potentially “appropriate” responses to the presence of an unexpected analyte or the absence of a prescribed drug in a patients UDT result
  - But there is only one **ABSOLUTELY WRONG** thing to do and that is **TO IGNORE THE RESULT**
  - Hoping that the result will just “go away,” that the patient “will not do ‘it’ again,” or potentially worst of all – “not record the abnormal result in the medical record” will not serve the patient or the practitioner well
  - In the context of a chart review, such actions will be very difficult to defend
- Use the result to open a dialog with the patient and to effect change

So, what do you do with an abnormal UDT result?

- First, you must have a mechanism in place to make certain you review all results for tests YOU order
  - That mechanism should involve a process that prioritizes “critical” results
    - What is a critical result is up to you, but examples might be
      - Absence of a prescribed drug or metabolite from a UDT result
      - Apparent tampering/adulteration of samples
      - Failure to provide required samples ie “Test Ordered – but no results”
      - Presence of prohibited or problematic substances ie ethyl glucuronide +ve
  - The discussion you have with the patient and their response
    - And actions taken and appropriately documented

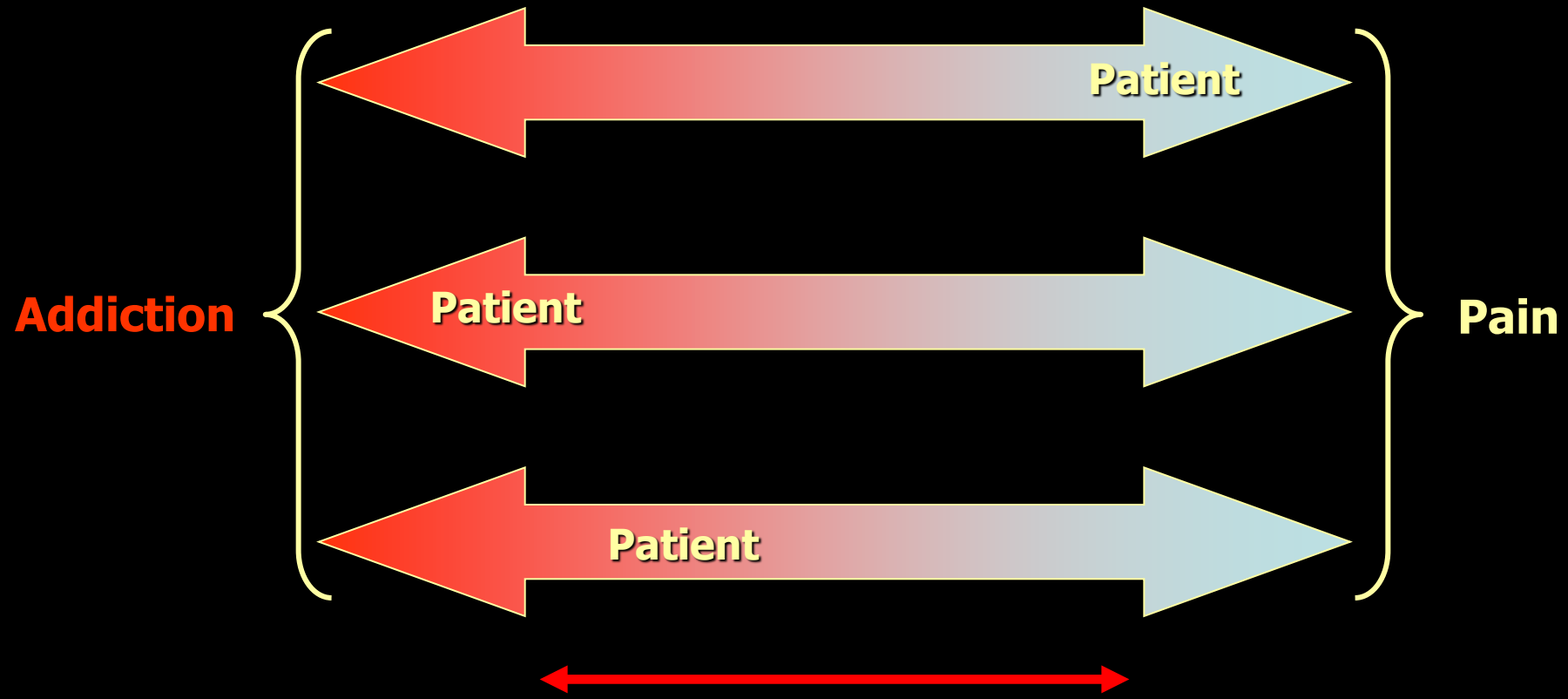
“To fire or not to fire… that is THE question”

- Certainly, discharging a patient from care should be a step of last resort
  - But arbitrarily discontinuing treatment with controlled substances, especially when there may be better options can have devastating results
  - It usually better to be fired by a patient reacting to your concerns and actions taken for safety reasons than it is to defend against wrongful abandonment suits
- But violent or abusive behavior to staff or other patients must never be tolerated

Risk management through healthy boundaries

- Remember, EVERYONE has risk – risk is part of the human condition
  - "If you have a pulse, you have risk…"
    - The risk may be low, medium or high but there is always risk
    - How you manage that risk and dynamically assess it is key

Pain-Addiction Continuum



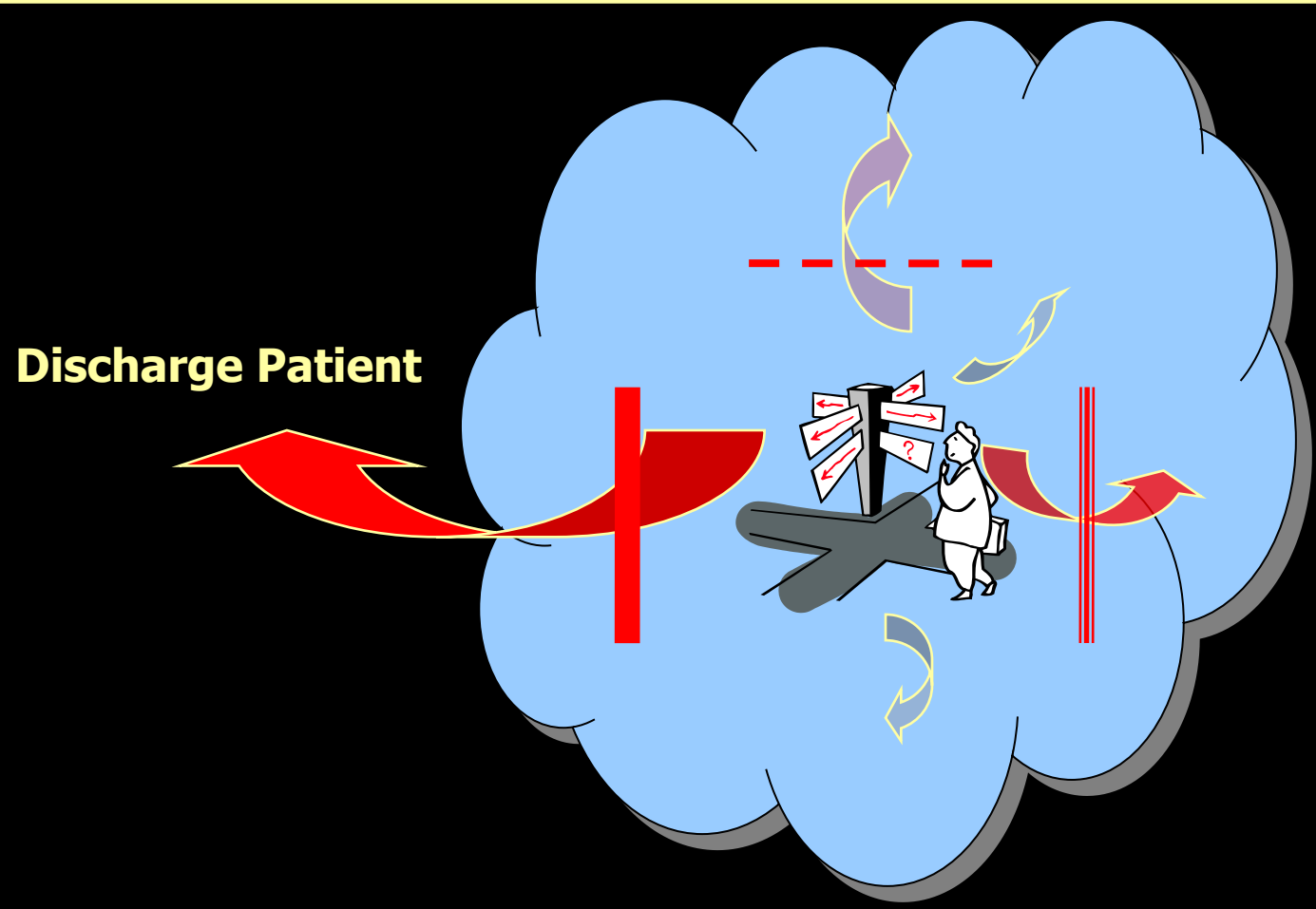
Diagnosis of Addiction in Chronic Pain

- When the drug is both the problem AND the solution in the patient at the same time i.e. problematic opioid use
  - DSM-V is inadequate
  - Addiction is “diagnosis made prospectively, over time”
    - Pseudo addiction is “diagnosed retrospectively”
  - Careful limits and boundary setting will help to make the diagnosis

Boundary Setting

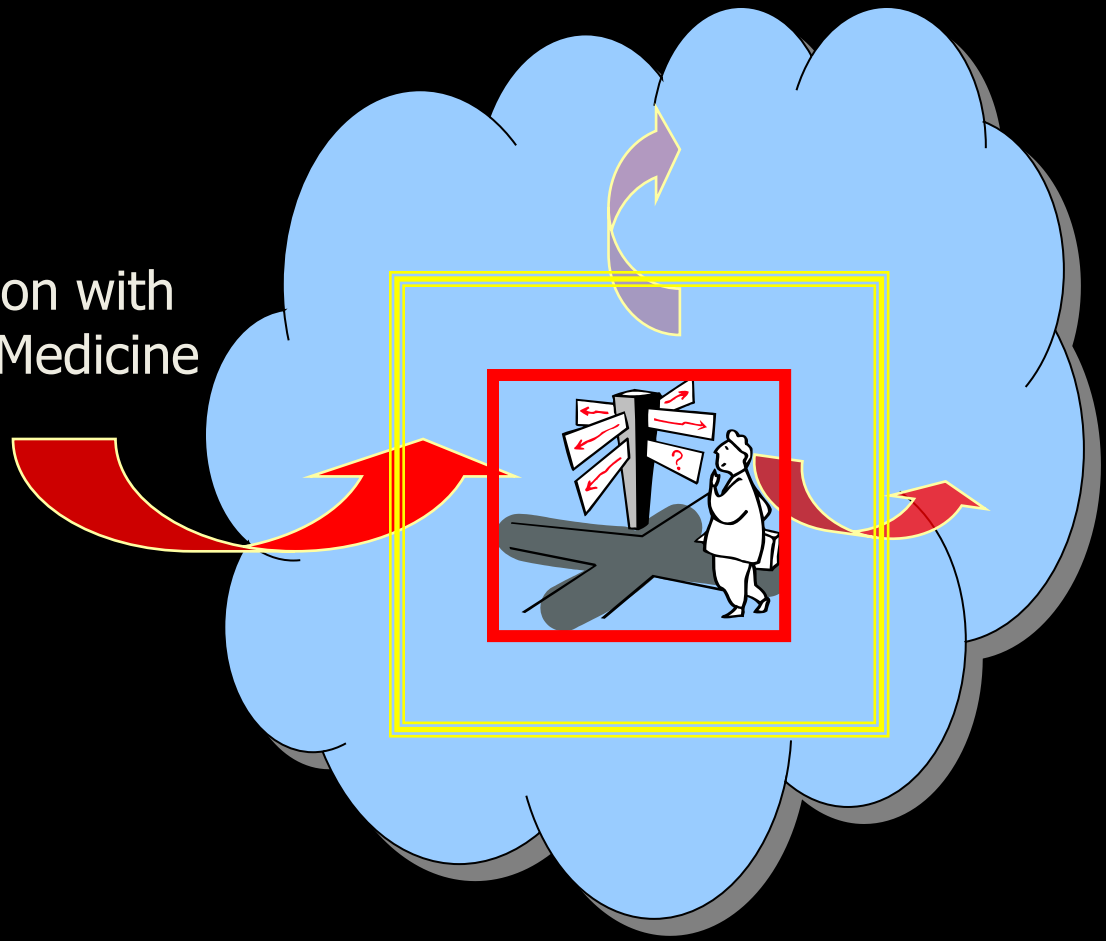
- 90%+ of patients don't need strict boundary setting
  - Most patients have their own internal set
- For remaining ~10%, strict boundary setting is essential
- Treatment Agreements, Drug Testing, interval / contingency dispensing ie "Do not fill until" prescribing

Boundaries – Identification and Enforcement



Boundaries – Identification and Enforcement

Consultation with
Addiction Medicine



Clinical Case 1 Discussion

- 32 yo male with history of recreational cocaine use
  - Although otherwise stable, a random urine drug test result comes back “cocaine metabolite detected”
- What might the prudent practitioner do?
  - 1st bring the patient in to discuss the abnormal result
    - You might consider speaking with the lab director beforehand to ensure that this was not a clerical or other lab error
  - 2nd open a dialog with the patient – “I have just reviewed your recent drug test results and I need some help interpreting it”
    - Give the patient a moment to collect their thoughts after being told of the +ve result; how they respond is often telling. Ask them to take their time

Case Case 1 Discussion

- Sometimes the response is simply “I have no idea why my drug test came back positive for cocaine”
  - Alternatively, the response might include some “qualifiers” that excuse the results as being someone else’s fault
    - “I admit that I smoked a joint on the weekend…. Afterward, my lips felt strange – sort of numb…. Could someone have put some cocaine in the marijuana?”
      - Could this be the case? NO. Nasal cocaine decomposes when combusted…
      - Could it be crack cocaine? YES, but the reality is “he used.” Unintentional intoxication is not a helpful concept to consider here
    - The following approach can be very helpful when the story becomes overly complicated
      - **Remember “truth is inversely proportional to the complexity of the story”**
      - “Listen, take some time before you go further. I can deal with bad choices, but I can’t deal with a story. Our future therapeutic relationship depends on you providing a truthful answer”

Case Case 1 Discussion

- If he did make a bad choice, there must be consequences… but termination of care should be the last option
  - Tighten boundaries
  - More frequent visits to the pharmacy for “interval dispensing of medications” if these are prescribed
  - Referral to someone with more skill and resources to assess the patient to determine what alternative strategies of care might be necessary
  - Taper → termination of controlled substances if appropriate
    - ***There are more people who “think” they are recreational cocaine users than there actually are***
  - IF the patient is unwilling to follow through on these items, they likely will abandon you as a treating clinician
  - BUT this is not the case with this patient

Clinical Case 1 Conclusion

- The patient truly did not know why he had a positive UDT result
  - His response was succinct and to the point
  - He did acknowledge having been to the ER on the weekend for treatment of an epistaxis – following a line drive of a softball, which he stopped successfully with his face!
    - His ENT attending cauterized his nasal bleed: cocaine was used as a topical agent
- The test was correct – the interpretation was faulty
- What if he had both benzoylecgonine (BEG) AND cocaine parent?
  - If the accident occurred more than a few hours before the sample was collected – cocaine parent is unlikely – it is rapidly hydrolyzed to BEG

Clinical Case 2 Discussion

- A 60 yo retired banker suffering from chronic low back pain is prescribed sustained release morphine sulfate (15mg q8hr) on a regular basis. He previously had been prescribed hydromorphone immediate release, which provided excellent relief but left him somnolent much of the day
  - He has participated in your urine drug testing program – without problem but this is the first result since changing to morphine
  - The result is positive for morphine with trace amounts of hydromorphone
- Is he still using hydromorphone?
  - He's been on morphine for nearly 3 months. Could this be residual hydromorphone from before?
  - Could there be another reason?

Clinical Case 2 Discussion

- Yes, there is another reason
  - Some regular users of morphine products can show trace amounts of hydromorphone in urine samples *because* of a morphine → hydromorphone equilibrium that commonly exists*
    - Something similar is seen in codeine users who will frequently test positive for hydrocodone, as well as the expected codeine parent and codeine metabolites**

*Cone. *J Anal Toxicol*. 2006;30(1):1-5.
**Oyler. *J Anal Toxicol*. 2000;24(7):530-535.

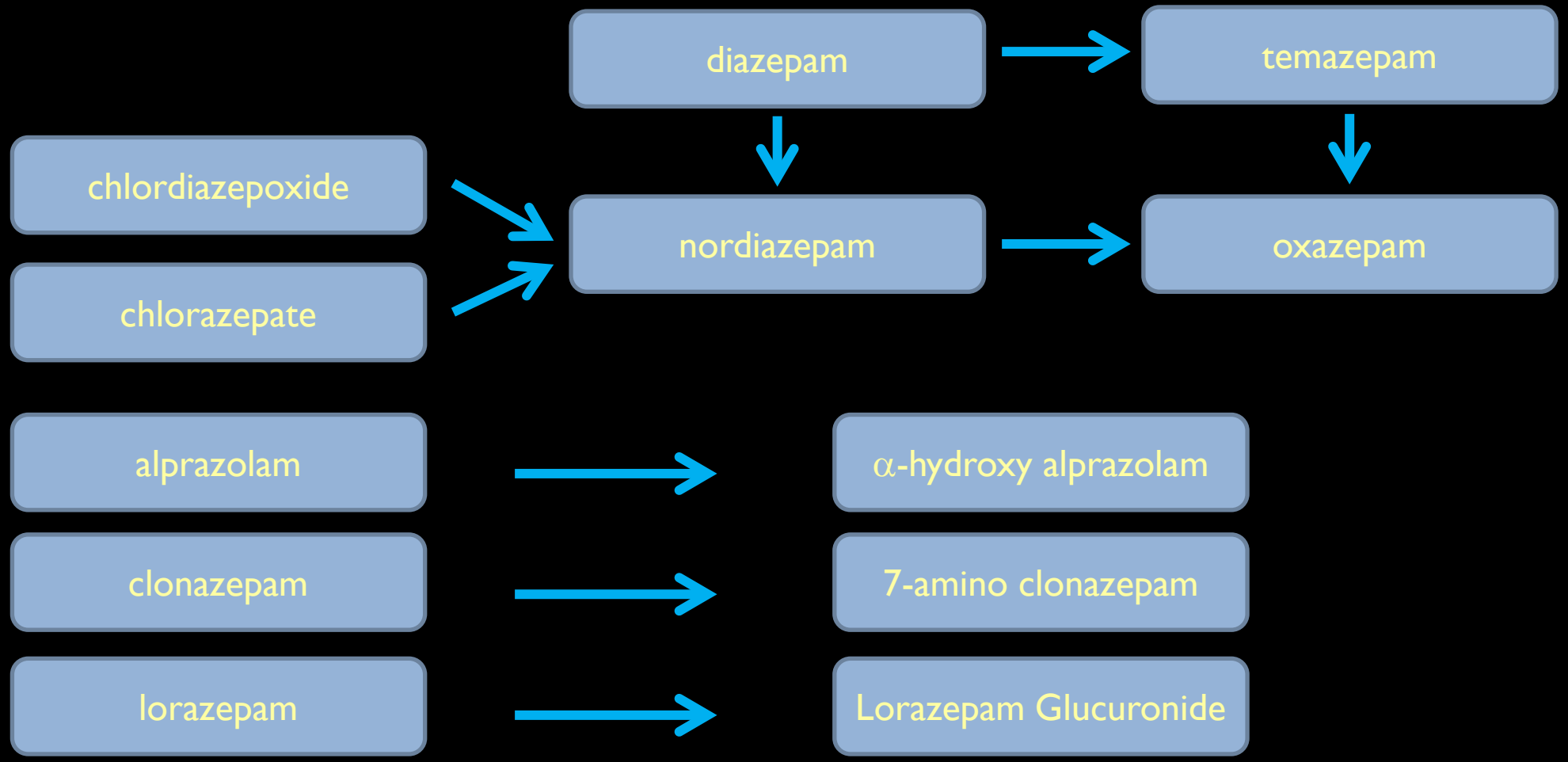
Clinical Case 3 Discussion

- A 42 yo woman has been a long-standing user of prescribed benzodiazepines
  - Her current dose is clonazepam 1mg 3 times per day
    - She indicates that she typically only used twice per day, doubling up the bedtime dose for sleep
  - A routine UDS is reported as “normal” in that no identified analytes are detected
    - Specifically, benzodiazepines is reported as “not detected”
  - Considering the test result, you arrange a telephone appointment with the patient (COVID safety measures)
    - Where do you go from here?

Clinical Case 3 Discussion

- The patient is adamant: “I take them just like I told you. One in the morning and two at bedtime!”
  - At this point, you decide to call the lab
    - The director examines the result and suggests you request more definitive testing, ie, LC/MS-MS
    - The result shows 7-amino clonazepam
  - The lab director confirms this as an expected result for this drug
  - What if other benzodiazepine metabolites were present?

The Complex Path of Benzodiazepine Metabolism



Conclusions

- Urine drug testing in clinical care will be around for a while
  - How you use results will determine if it is adversarial or patient-centered
- "It isn't what we don't know that gets us into trouble, it's what we think we know, but that just isn't so" (loosely by Will Rogers ☺)
  - Don't be afraid to ask for help
    - But these are clinical questions NOT regulated tests: the Medical Review Office may not be your best resource – call a knowledgeable clinician
- Drug testing is a skill easily managed by any practitioner; check out the recommended UDT monograph in the reading list

Reading List

1. Gourlay D, Heit H. *The Treatment of Chronic Pain in Patients with history of substance abuse.* In *Bonica's: Management of Pain*, Ballantyne CM, Fishman SM, Rathmell JP, eds. Wolters Kluwer; 2018:1896.

2. Gourlay DL, Heit H. *The use of drug testing in promoting treatment adherence in pain medicine.* In *Facilitating Treatment Adherence in Pain Medicine* C.M.F. P, Editor. 2017, Oxford University Press: New York, NY.

3. Heit HA, Gourlay DL. Using urine drug testing to support healthy boundaries in clinical care*. J Opioid Manag.* 2015;11(1):7-12.

4. Gourlay DL, Heit H, Caplan Y. *Urine Drug Testing in Clinical Practice - The Art and Science of Patient Care*. Pharmacomm Group: Stamford, CT; 2015.

5. Smith A, Heit H, Gourlay DL. Chapter 39 in Clinical Pain Management: A Practical Guide. Lynch, M.E., Craig, K.D., & Peng, P. (Eds.), Oxford, UK: Wiley-Blackwell Press. *In press*