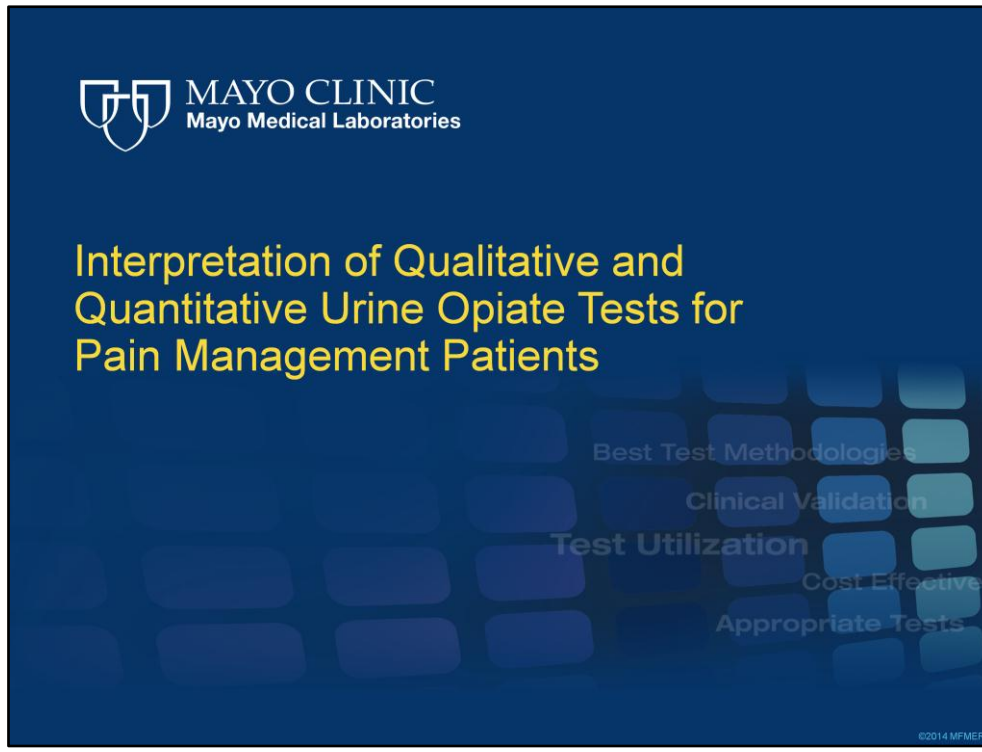
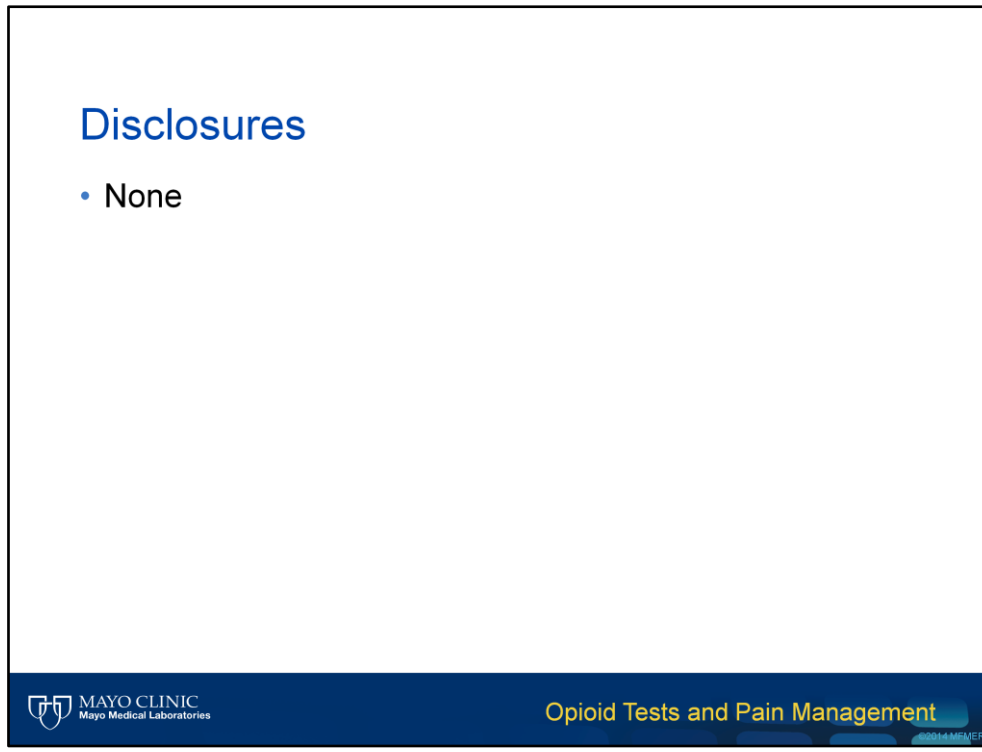


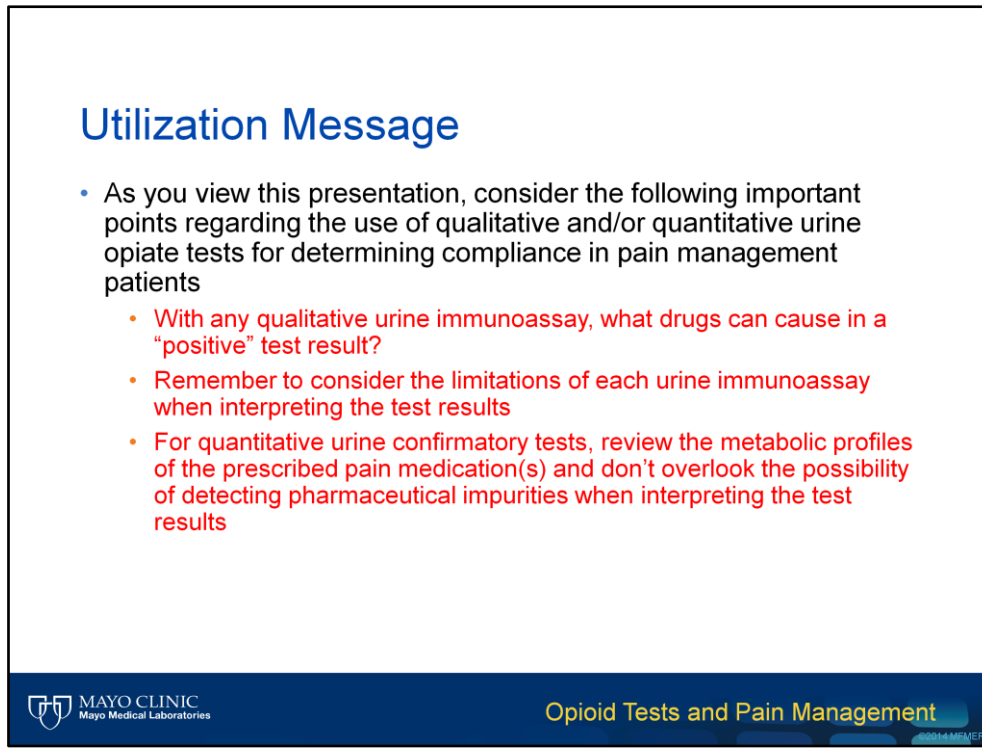
This is the written version of our Hot Topic video presentation available at: MayoMedicalLaboratories.com/hot-topics

Welcome to Mayo Medical Laboratories Hot Topics. These presentations provide short discussion of current topics and may be helpful to you in your practice.

Our speaker for this program is Dr. Paul J Jannetto, Co-Director of the Toxicology and Drug Monitoring Laboratory at Mayo Clinic, Rochester, Minnesota. Dr. Jannetto discusses the interpretation of qualitative and quantitative urine opiate tests for pain management patients.



I have nothing to disclose.



As you view this presentation, consider the following important points regarding the use of qualitative and/or quantitative urine opiate tests for determining compliance in pain management patients

First of all, with any qualitative urine immunoassay you have to ask yourself what drugs will actually test "positive" in that assay. You want to make sure that the right test was ordered to detect the medication that the patient is currently taking.

Secondly, you also need to remember to consider the limitations of each urine immunoassay when interpreting the test results. These tests are not 100% sensitive and specific, so you can get false-positive and false-negative results.

Lastly, for quantitative or confirmatory urine opioid tests, review the metabolic profiles of the prescribed pain medication(s) and don't overlook the possibility of detecting pharmaceutical impurities when interpreting the test results

Pain is a Major Public Health Issue

- Pain is cited as the most common reason Americans access the health care system
- Pain affects more Americans than diabetes, heart disease and cancer combined
- 1 in every 4 Americans have suffered from pain that lasts >24 hours and millions more suffer from acute pain
- Pain is a major contributor to health care costs (~$635 billion/year in medical treatment and lost productivity)
- Sale of opioid pain relievers (OPR) quadrupled between 1999 and 2010
- Enough OPR were prescribed in 2010 to medicate every American adult around the clock (q4h) for a month
- Large number of patients (>40%) still report being inadequately treated for pain

National Institute of Health website: http://www.report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=57 Accessed December 2013. Institute of Medicine of the National Academies. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Report brief June 2011. Available at http://www.iom.edu/relievingpain. Accessed December 2013; Centers for Disease Control and Prevention. Vital Signs: Overdoses of Prescription Opioid Pain Relievers—United States, 1999-2008. *MMWR* 2011; 60(43):1487-1492. National Center for Health Statistics. United States, 2006 With Chartbook on Trends in the Health of Americans. Hyattsville, MD: 2006

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Opioid Tests and Pain Management

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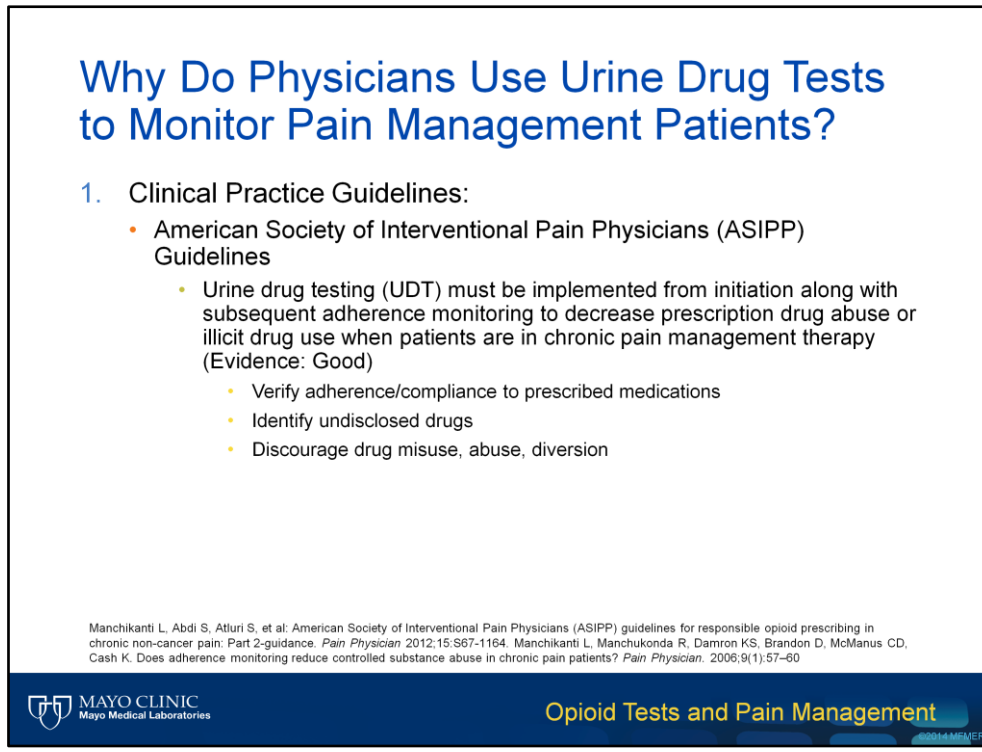
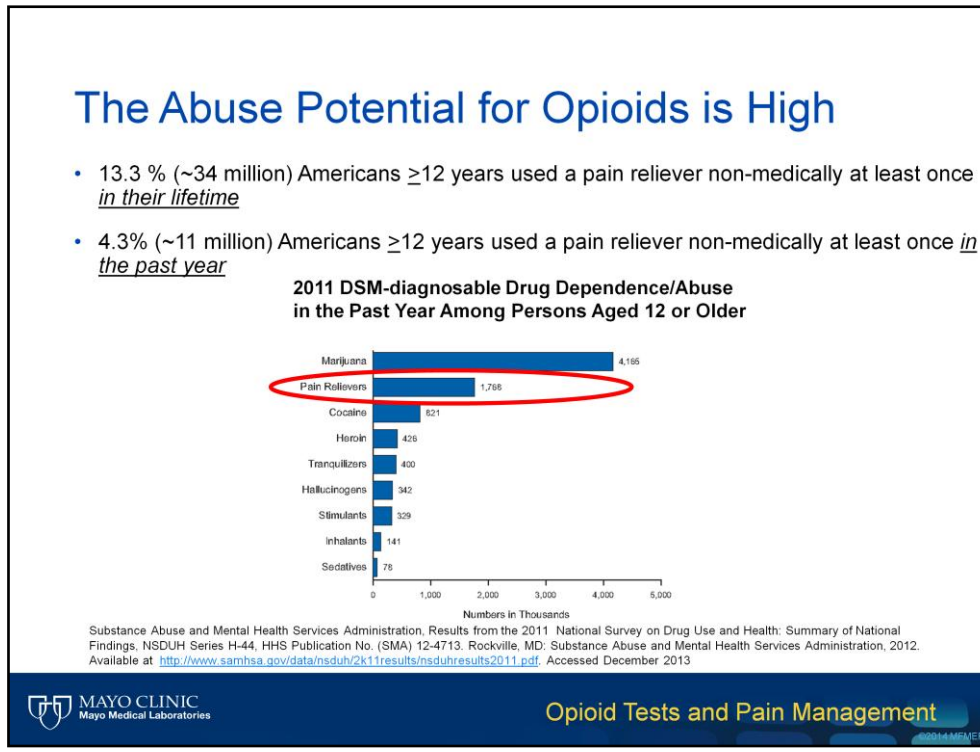
Pain is a major public health issue.
In fact, pain is cited as the most common reason Americans access the healthcare system.
Pain affects more Americans than diabetes, heart disease, and cancer combined.
According to the National Center for Health Statistics, 1 out of every 4 Americans have reported that they suffered from pain that lasted >24 hours and millions more suffer from acute pain.
As a result, pain is a major contributor to healthcare costs which is estimated at over $635 billion dollars per year in medical treatment and lost productivity.
Between 1999 and 2010, the sale of opioid pain relievers used to manage pain has actually risen over 4-fold.
In 2010, enough opioid pain relievers were prescribed to medicate every adult in America around the clock taking 1 pill every 4 hours for a month.
Yet despite the use of potent narcotics to manage pain, 40% of patients still report being inadequately treated for pain.

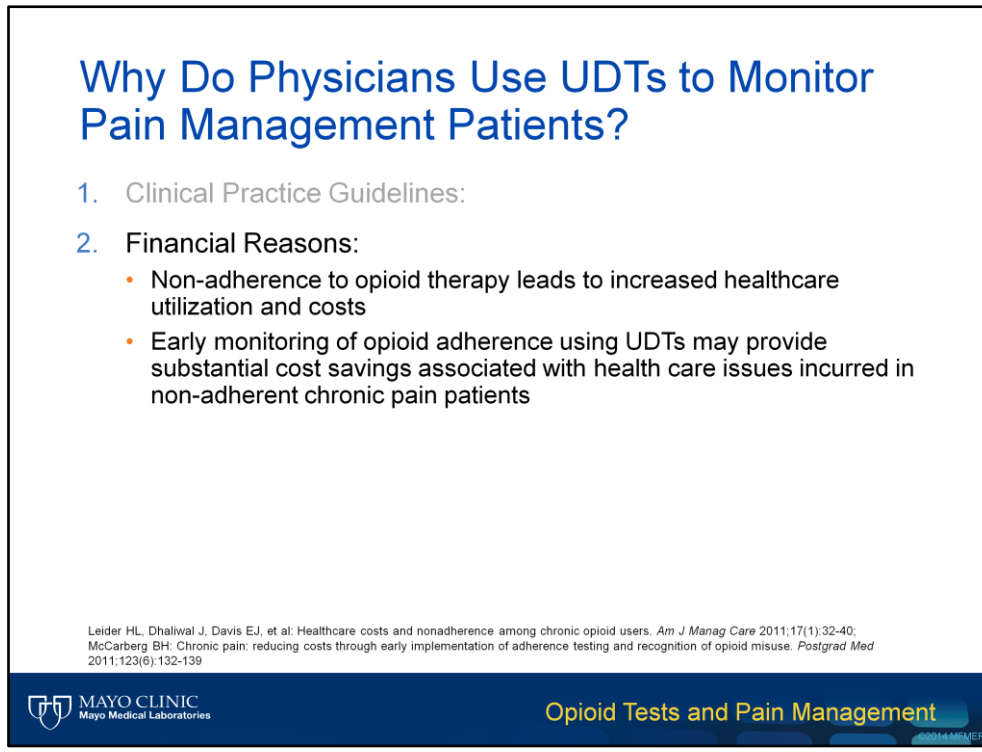


Why do physicians use urine drug tests to monitor pain management patients? Currently, there are numerous clinical practice guidelines published which support the use of laboratory tests to monitor compliance in pain patients.

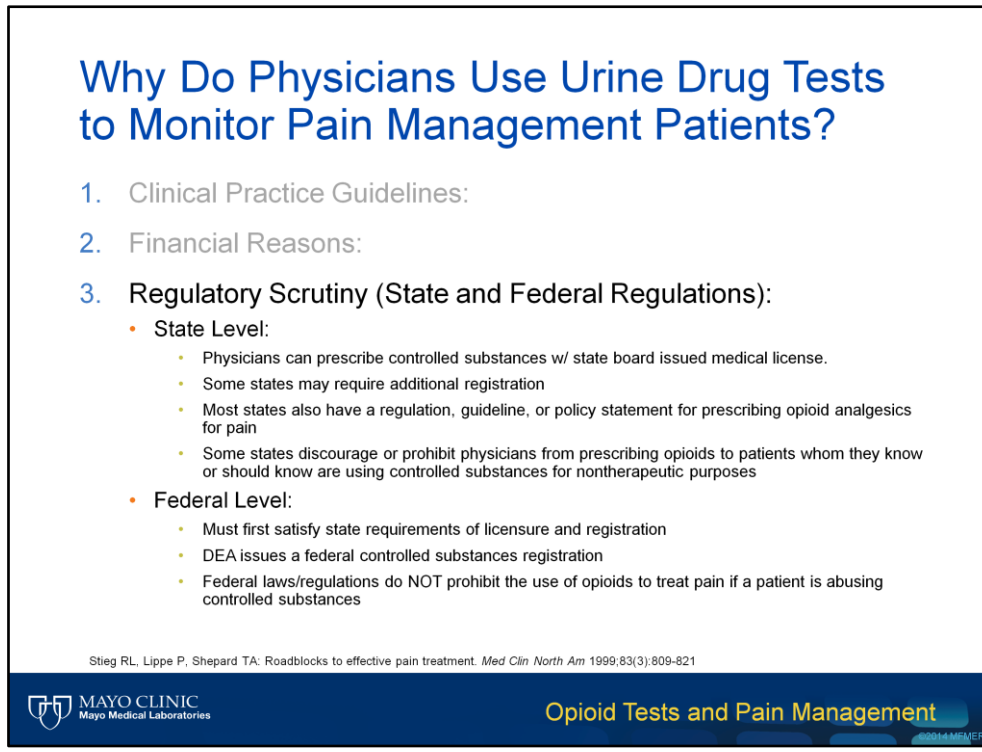
For example, the American Society of Interventional Pain Physicians have a guideline which states that urine drug testing must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. The purpose of urine drug testing is to verify adherence to prescribed medications, identify undisclosed drugs, and discourage drug misuse, abuse, and diversion. The actual use of urine drug tests as part of adherence monitoring has been associated with a 49% reduction in opioid abuse according to a publication by Manchikanti.



The abuse potential for opioids is very high. According to the results from the 2011 National Survey on Drug Use and Health, approximately 13% of Americans age 12 or older have admitted to using a pain reliever for non-medical reasons at least once in their lifetime. Approximately 11 million Americans age 12 or older have admitted to using a pain reliever non-medically at least once in the past year.
In 2011, pain relievers had the second highest level of past year dependence or abuse after marijuana.

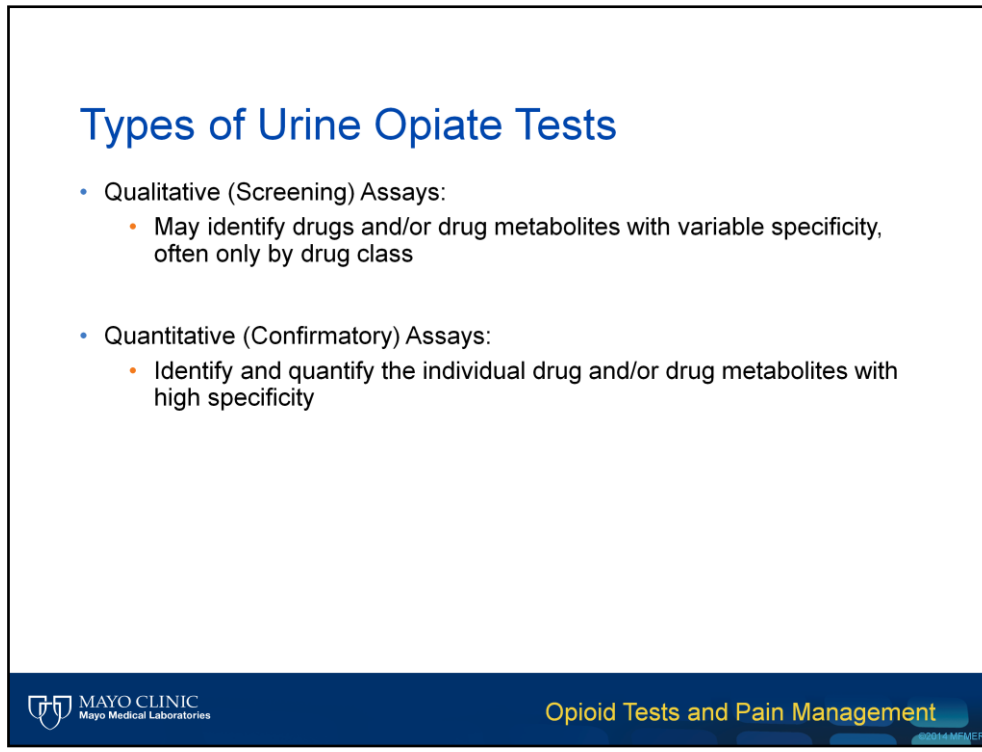


There are also financial reasons to use urine drug tests to monitor pain management patients.
For example, it has been shown that non-adherence to opioid therapy leads to increased healthcare utilization and cost. Furthermore, the early monitoring of opioid adherence using urine drug tests may provide substantial cost savings associated with healthcare issues incurred in non-adherent chronic pain patients.

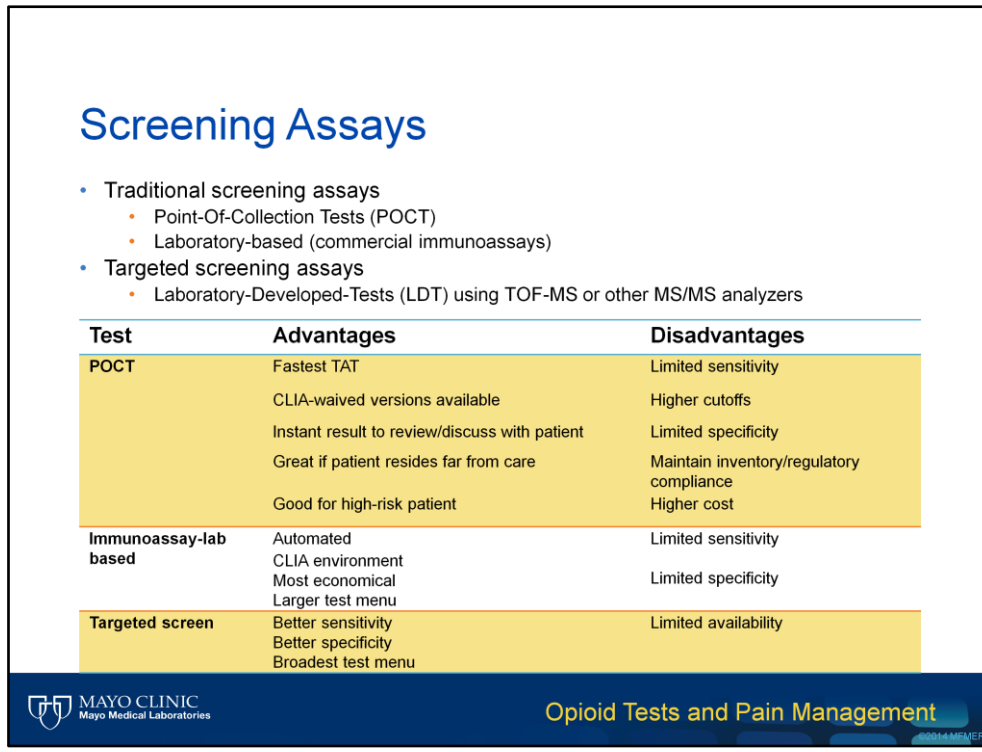


. Finally, there is also the fear of regulatory scrutiny and both state and federal regulations that cause physicians to use urine drug tests to monitor pain management patients.

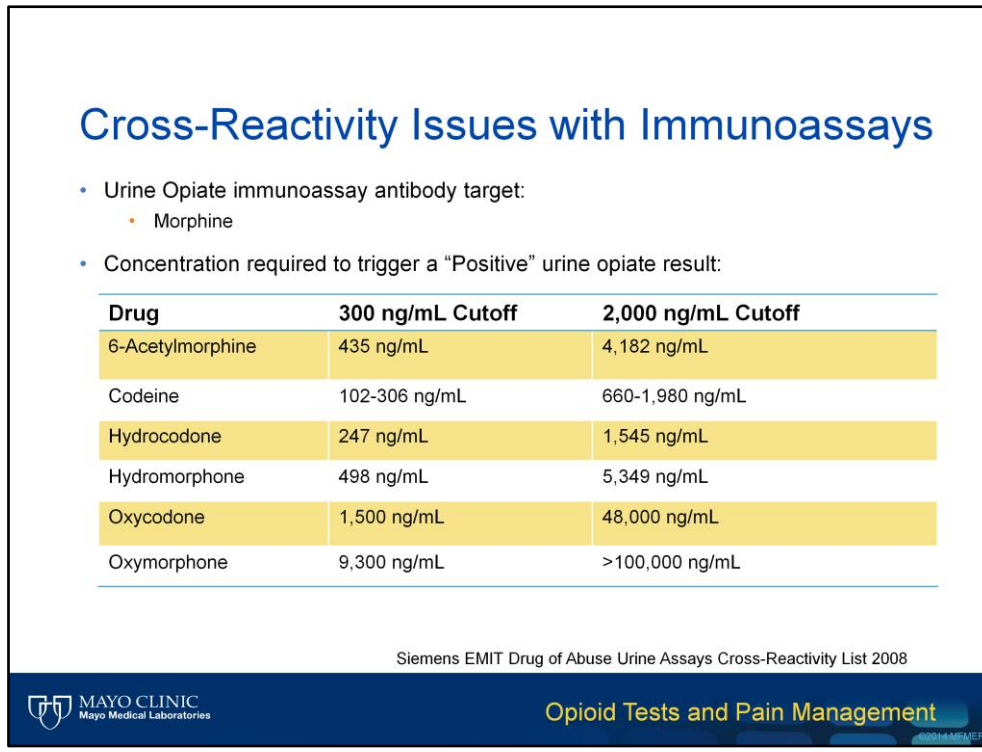
Currently, most states have specific regulations, guidelines, or policy statements for prescribing opioid analgesics for pain management. Some states actually discourage or prohibit physicians from prescribing opioids to patients whom they know or should know are using controlled substances for non-therapeutic purposes. On the other hand, the federal regulations do not prohibit the use of opioids to treat pain if a patient is abusing controlled substances.



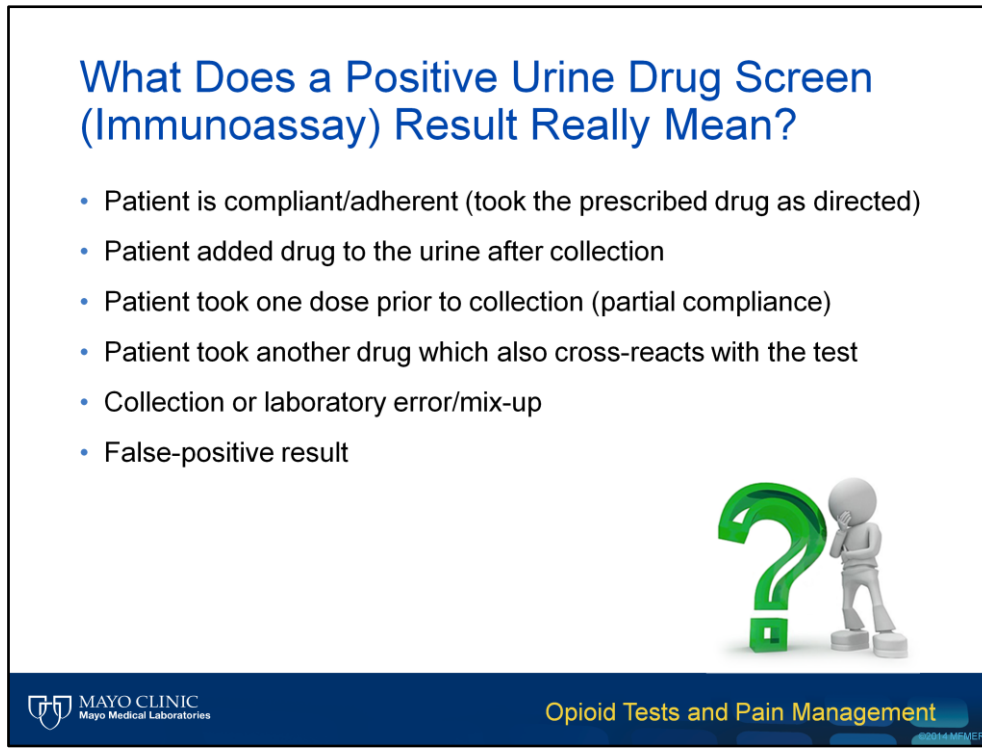
So what types of urine opiate tests are being used by physicians to determine compliance to opioid pain management therapy? Routinely, physicians may use qualitative or screening assays. These tests typically identify the drug and/or drug metabolite with variable specificity and often only by drug class. Alternatively, physicians may use quantitative or more confirmatory assays where they can identify and quantify the individual drug and/or drug metabolite with high specificity and better sensitivity.



However, physicians are primarily using screening assays with or without confirmatory assays to verify adherence in pain management patients. There are 2 types of screening assays. Traditional screening assays that use antibodies directed against a drug or drug metabolite. These immunoassays may be in a point-of-care format so the test can be done right in the physician's office or clinic or they can be commercially based immunoassays run in CLIA-certified laboratories. Alternatively, new targeted laboratory-developed screening assays using mass spectrometry have also started to emerge as a screening tool. Each of these types of assays has advantages and disadvantages. Point-of-care tests have the advantage of having the fastest turnaround time , so the physician can get an immediate result which is good for patients that have a high-risk for abuse or reside far from care. Laboratory-based immunoassays typically have a larger test menu and are more economical. However, all immunoassays suffer from higher cutoffs, limited sensitivity and specificity. On the other hand, targeted screens have better sensitivity and specificity, but aren't widely available at all laboratories.

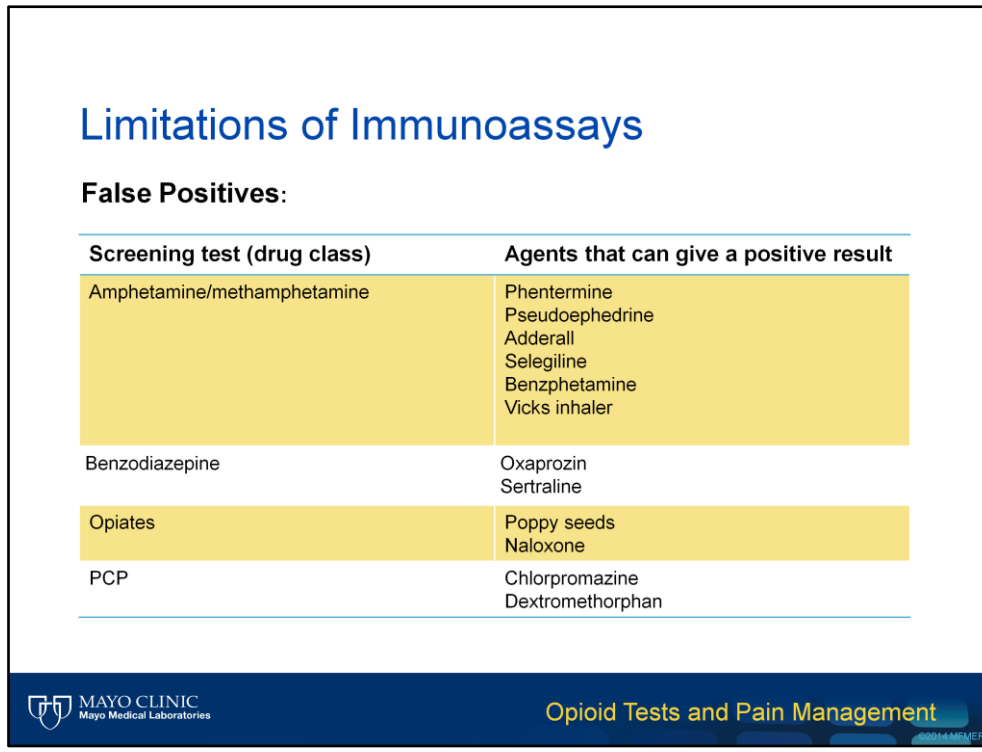


Cross-reactivity with immunoassays is a big issue that needs to be considered when interpreting test results. For example, in the urine opiate immunoassay the antibody used in most manufacturer kits is directed against morphine. It has limited to no cross-reactivity with all of the opioids used in pain management. As you can see from this package insert from the Siemens EMIT urine opiate assay, it has a pretty good cross-reactivity with codeine, hydrocodone, and the metabolite of heroin (6-acetyl morphine). However, a patient's urine sample would need to have a much higher concentration (higher than the cutoff) of oxycodone and/or oxymorphone to get a "positive" result using this assay. In addition, you will notice that other opioids like methadone, tramadol, fentanyl, or tapentadol are absent from this list since they do not cross-react at all with this assay and you will get a "negative" result even if these drugs are present in the patient's urine.

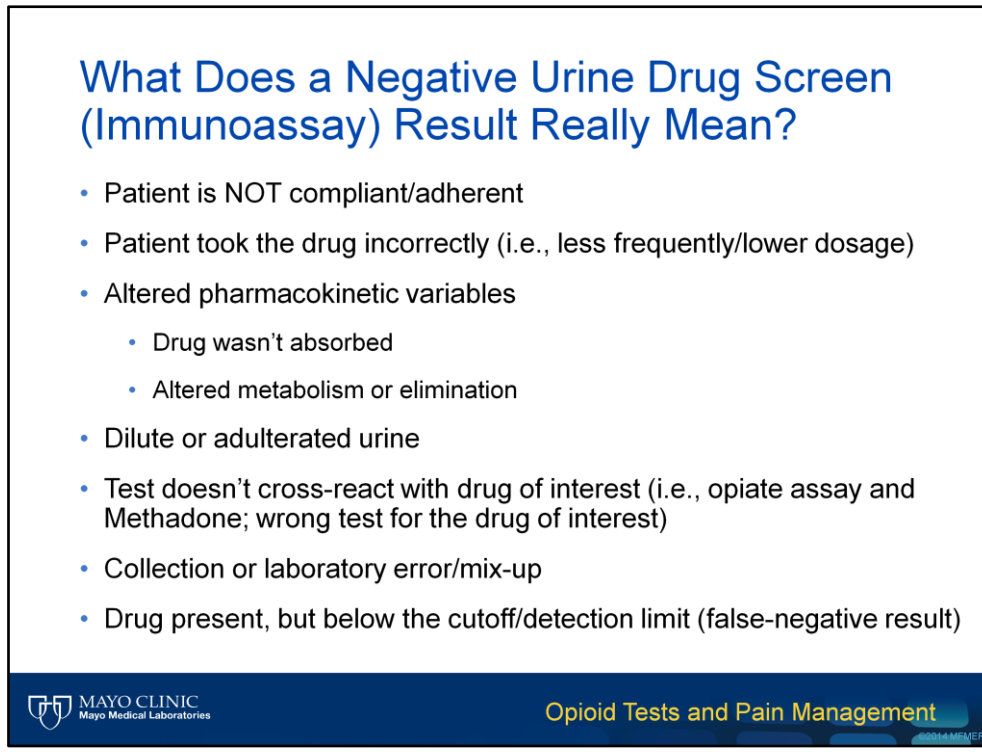


As a result, what does a “positive” urine drug test result on an immunoassay actually mean?

It could mean that the patient was compliant and took the prescribed drug as directed. However, it could also mean the patient was only partially compliant and just took 1 dose prior to collection. Alternatively, the patient could have directly spiked/added the drug into the urine sample after collection. Other possible explanations include that the patient took another medication that cross-reacted with the immunoassay causing a false-positive result.

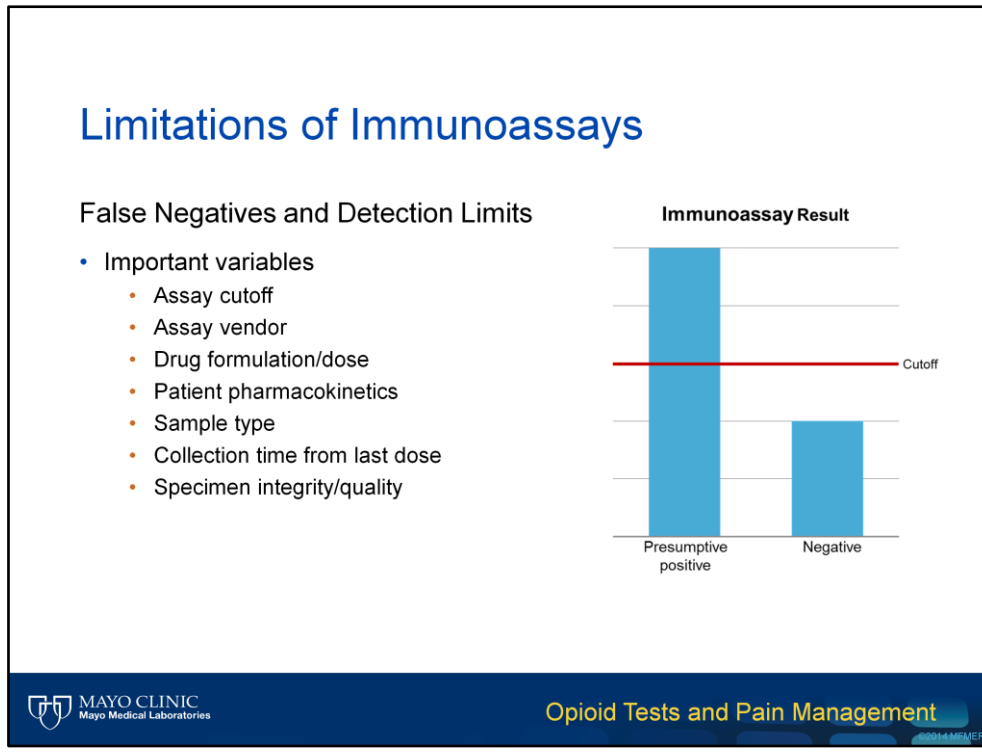


False-positive results are one of the limitations of using an immunoassay. Shown here is a partial list of other medications that can give a “positive” result in various screening immunoassays. In the case of amphetamine, you will see that other over-the-counter medications like pseudoephedrine can result in a “positive” result.



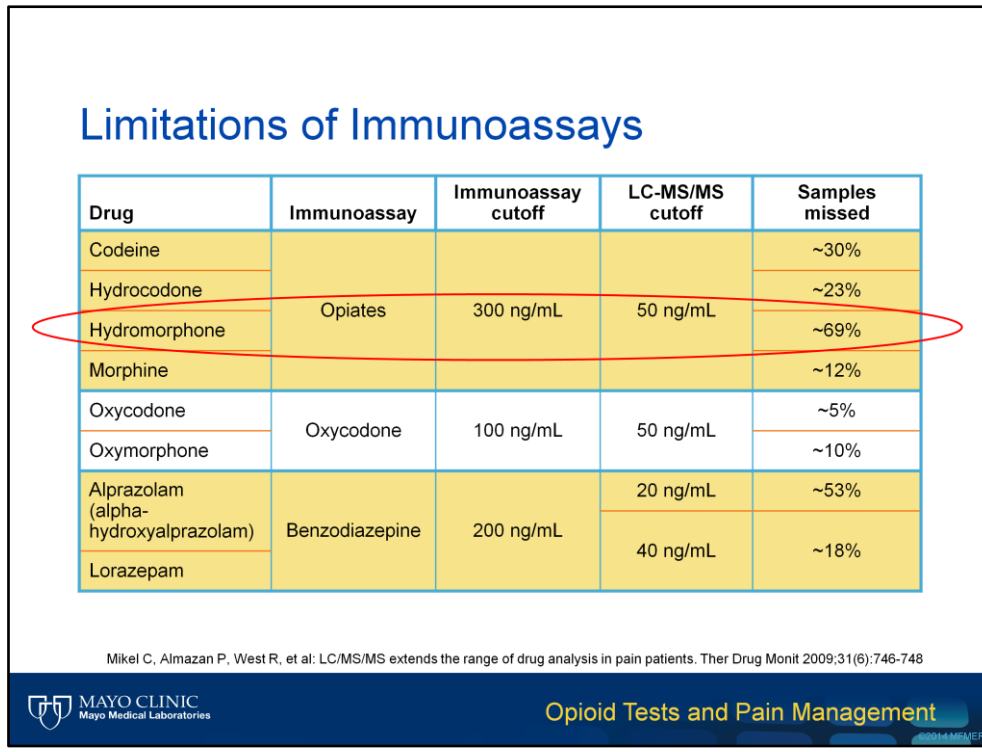
Alternatively, what does a "negative" urine drug test result on an immunoassay really mean?

It could mean the patient is not compliant with their prescribed medication. It could also mean they were partially compliant and maybe missed a few doses, or took less medication. Maybe the patient is well hydrated and the urine is dilute or possibly adulterated. Alternatively, the wrong test might have been ordered and the test may not cross-react with the patient's medications. However, another explanation is that the drug may actually be present, but it is below the cutoff or detection limit of the assay leading to a false-negative result.



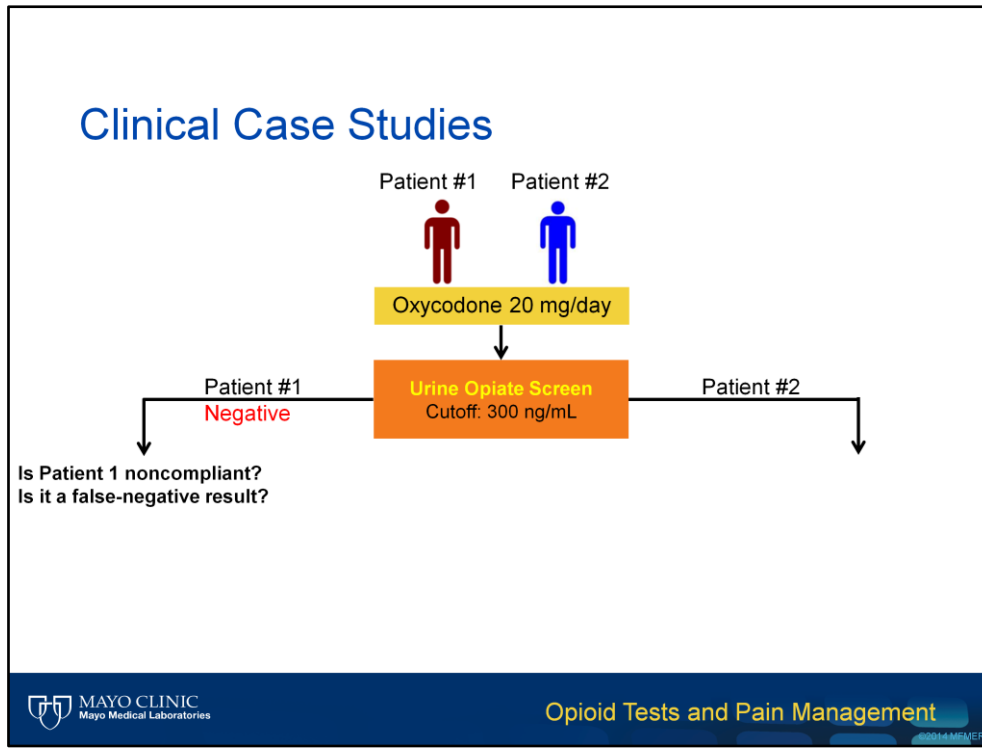
False-negative results can happen as easily as a false-positive result with immunoassays. Therefore, it is important to look at the assay cutoff or detection limit when interpreting test results. A call to the laboratory can determine the cross-reactivity of the patients medication with the assay ordered. Other information that is important and should be considered is the timing between when the patient last took their medication and when the urine sample was collected. For most opiates, you typically have a 1 to 3 day window of detection, but if the patient stopped taking their medication several days ago, you might get a “negative” result.

Specimen validity testing can also be used to help determine the integrity and quality of the patient’s sample. For example, if the creatinine is <20 mg/dL and the specific gravity is between 1.001 and 1.002, the patient’s urine sample is unusually dilute. Therefore, the drug may actually be present, but below the detection limit of the assay which will give a negative result.

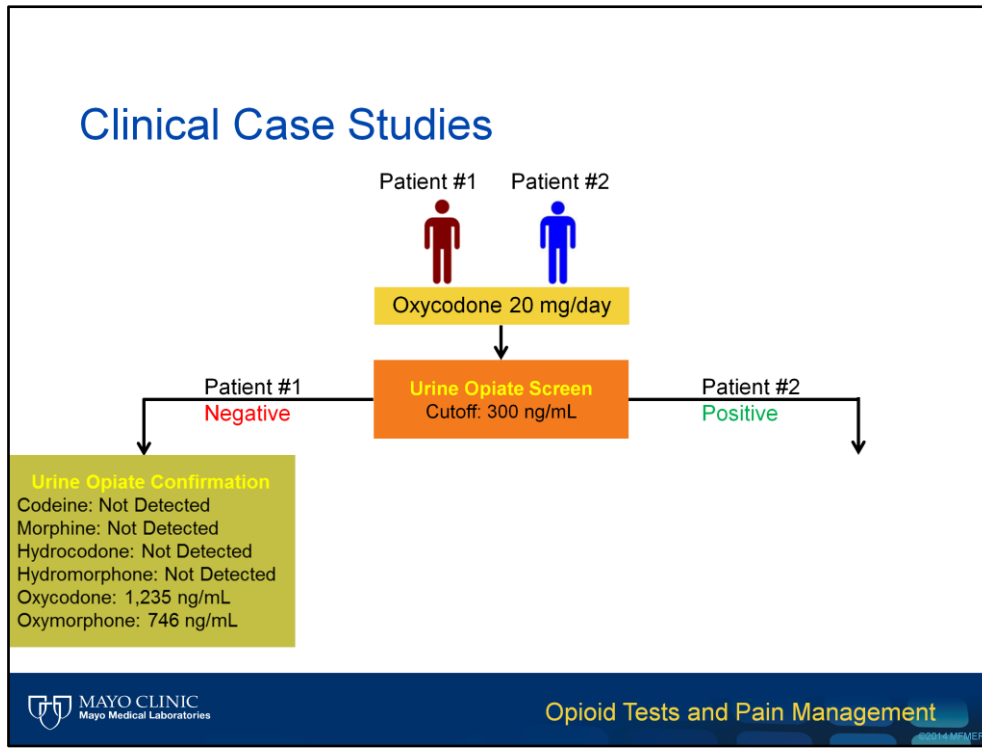


The following slide demonstrates how a patient may test “negative” on a urine immunoassay which has a higher cutoff or detection limit compared to a liquid chromatography tandem mass spectrometry-based assay (LC-MS/MS). In this study, Mikel and colleagues took the urine of pain management patients and tested it using both an immunoassay and a LC- tandem mass spec assay. The urine opiate immunoassay had a cutoff of 300 ng/mL while the LC- tandem mass spec assay had a cutoff or detection limit of 50 ng/mL.

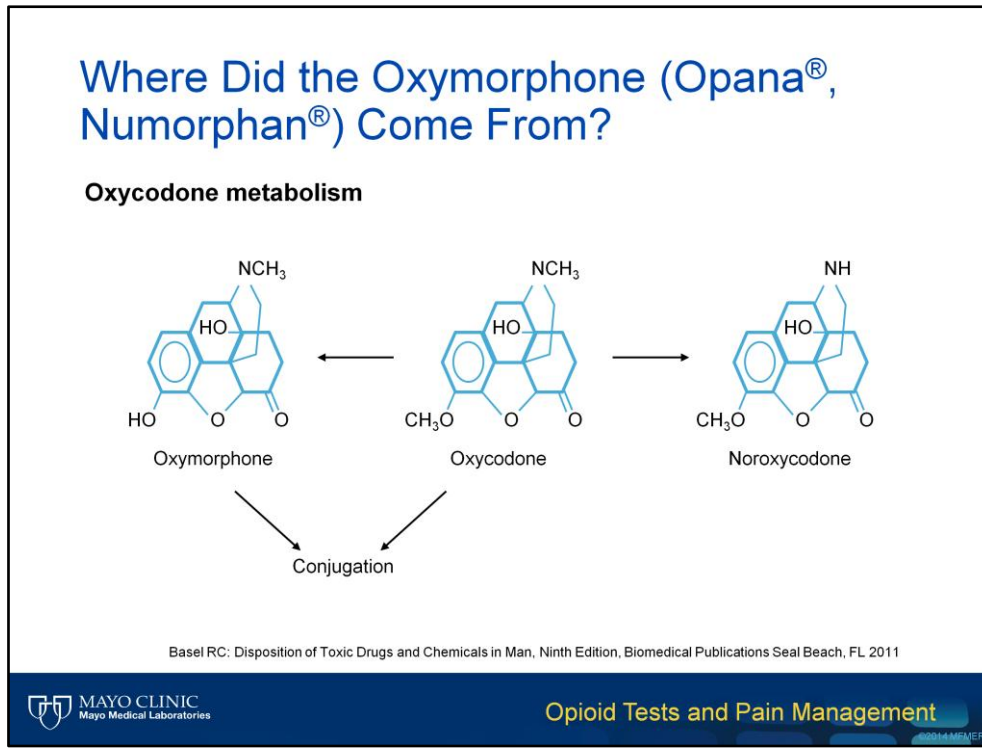
If you look at the hydromorphone results, you can see that approximately 69% of patients who were prescribed and taking hydromorphone tested “positive” or had detectable concentrations on the LC- tandem mass spec assay, but tested “negative” on the immunoassay due to the higher cutoff and poor cross-reactivity with the antibody used in the immunoassay.



Now let's look at 2 clinical case studies. In these examples, patient #1 and #2 are both prescribed and taking 20 mg/day of oxycodone. The ordering physician orders a urine opiate immunoassay screen with a 300 ng/mL cutoff to determine if both patients are compliant. Patient #1 test results come back "negative".
The ordering physician now wonders if patient #1 is noncompliant. Or is this just a false-negative result?

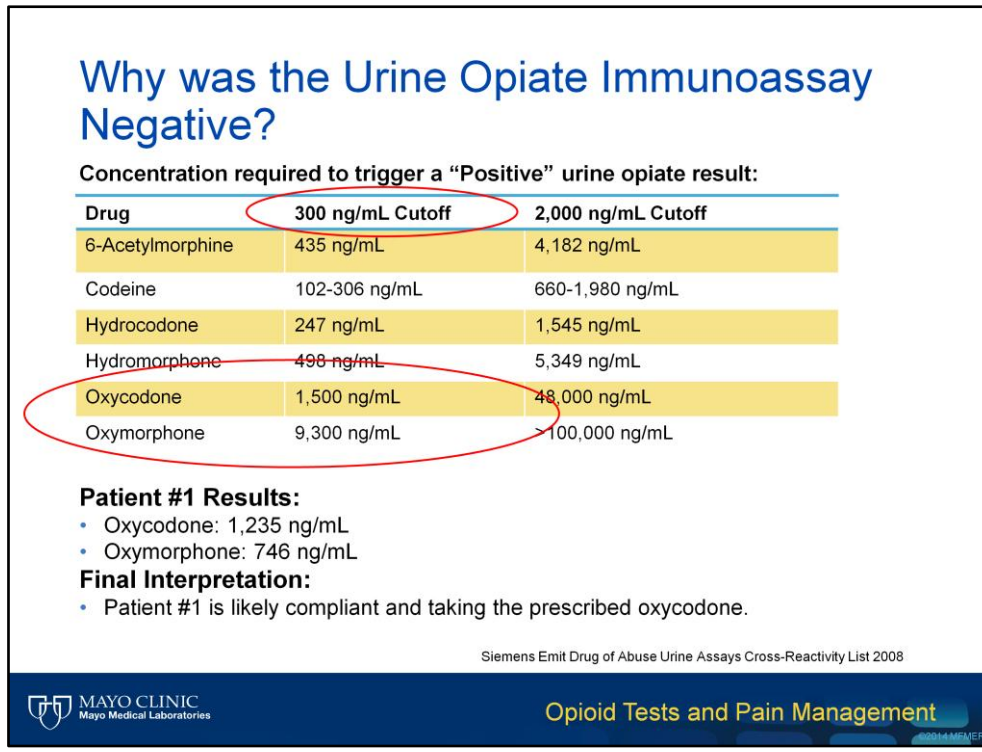


Since the ordering physician knows the urine opiate screening assay is not 100% sensitive or specific for oxycodone, they order a urine opiate confirmatory test. The results of the confirmatory test come back positive for oxycodone at a concentration of 1,235 ng/mL and oxymorphone at a concentration of 746 ng/mL.



As a result, the physician know wants to know why is oxymorphone present since it is another opioid medication under the brand names of Opana or Numorphan which can be prescribed for pain.

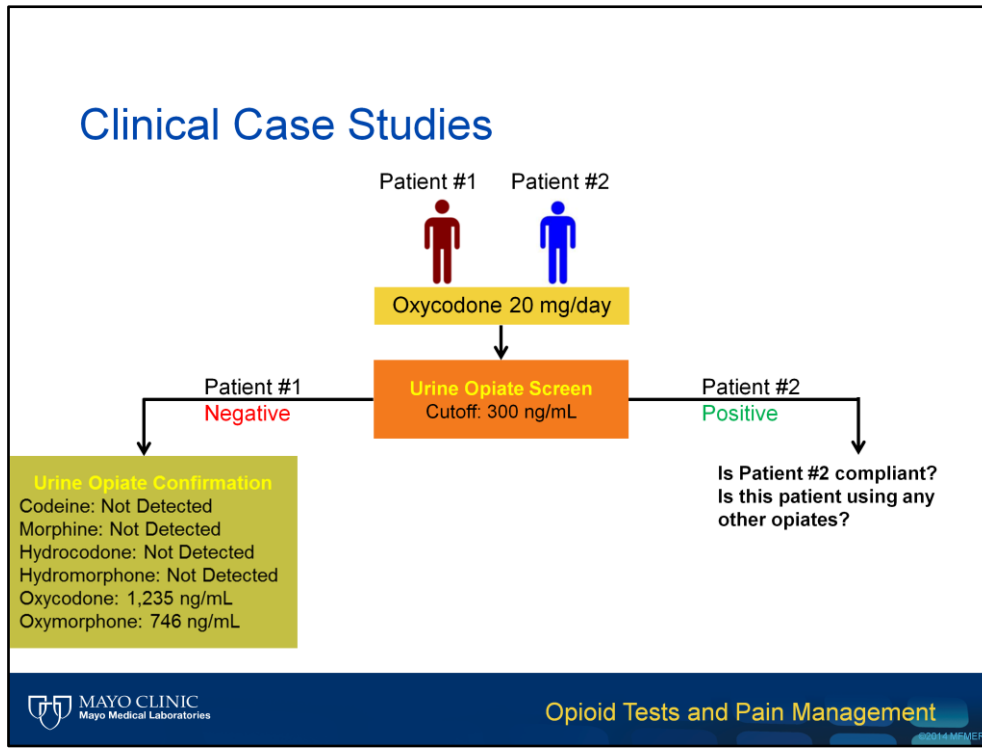
However, oxymorphone is also a metabolite of oxycodone as you can see from this slide. Oxycodone is metabolized endogenously to noroxycodone and oxymorphone by the cytochrome P450 system. Based on the concentrations and the metabolic ratio of oxycodone to oxymorphone, patient #1 results are most consistent with the oxymorphone being a metabolite of oxycodone.



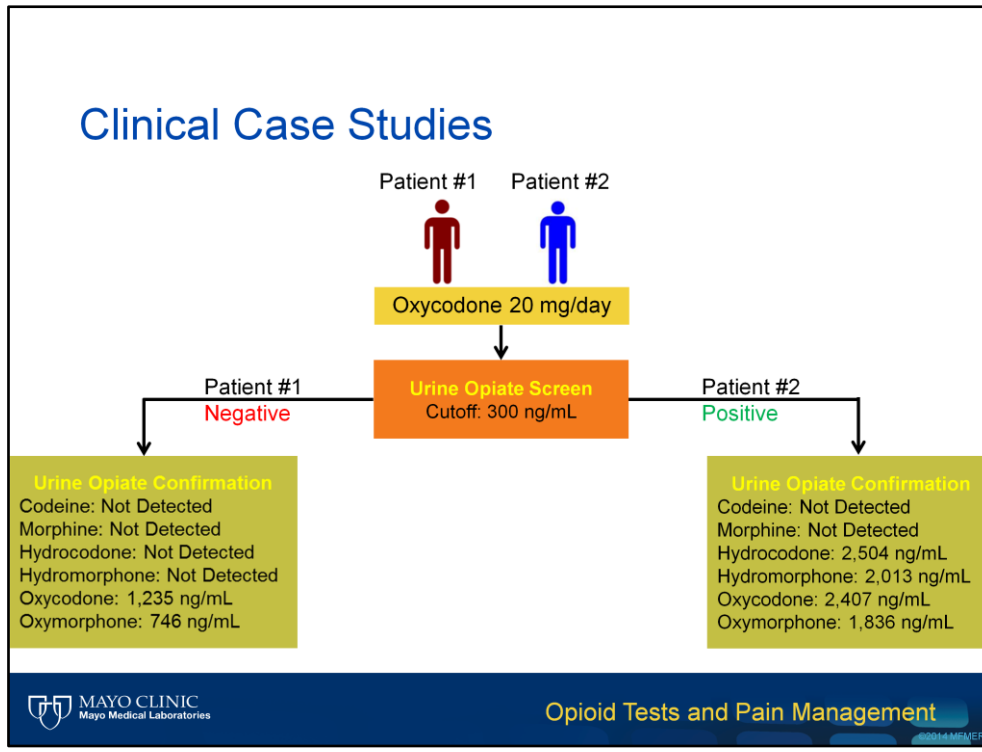
.However, the physician wants to know why was the urine opiate immunoassay originally "negative" while the confirmatory LC-tandem mass spec assay result came back as "positive". To explain these results, we must first go back to the cross-reactivity of the urine opiate immunoassay.

As you can see, if you use a 300 ng/mL cutoff on the urine immunoassay, the concentration of oxycodone must be greater than or at least equal to 1,500 ng/mL to cause a "positive" result.

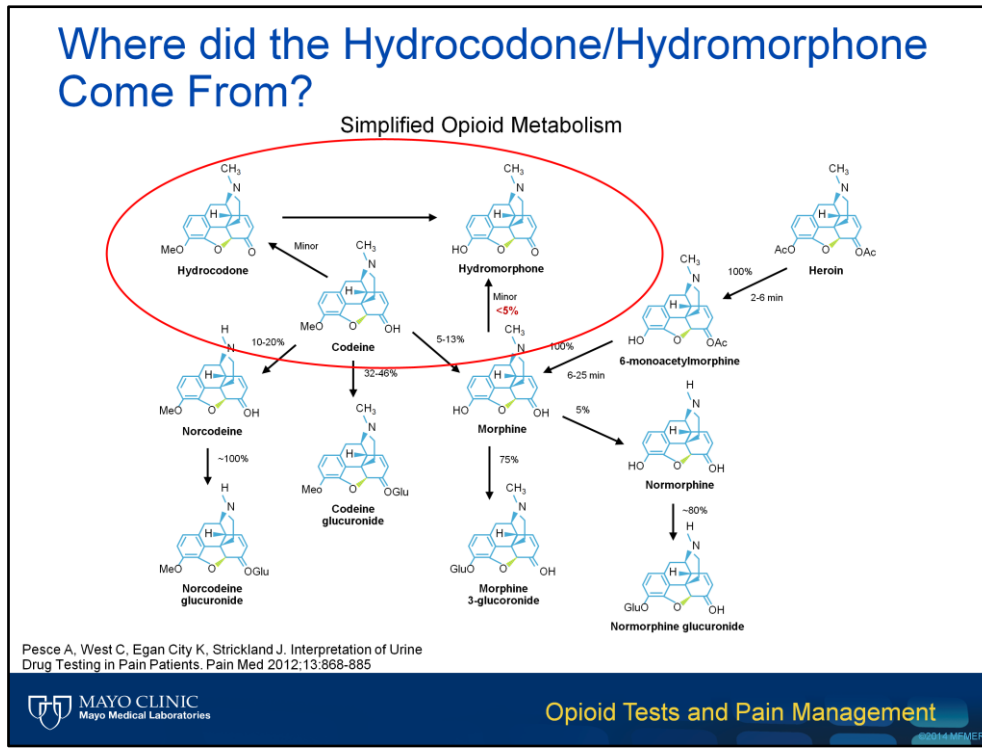
In this case, the oxycodone concentration in the patient's urine was only 1,235 ng/mL which resulted in a "negative" result. The confirmatory test had a lower detection limit of 100 ng/mL and specifically can identify oxycodone.
Therefore, the final interpretation in this case is that patient #1 is likely compliant and taking their prescribed oxycodone.



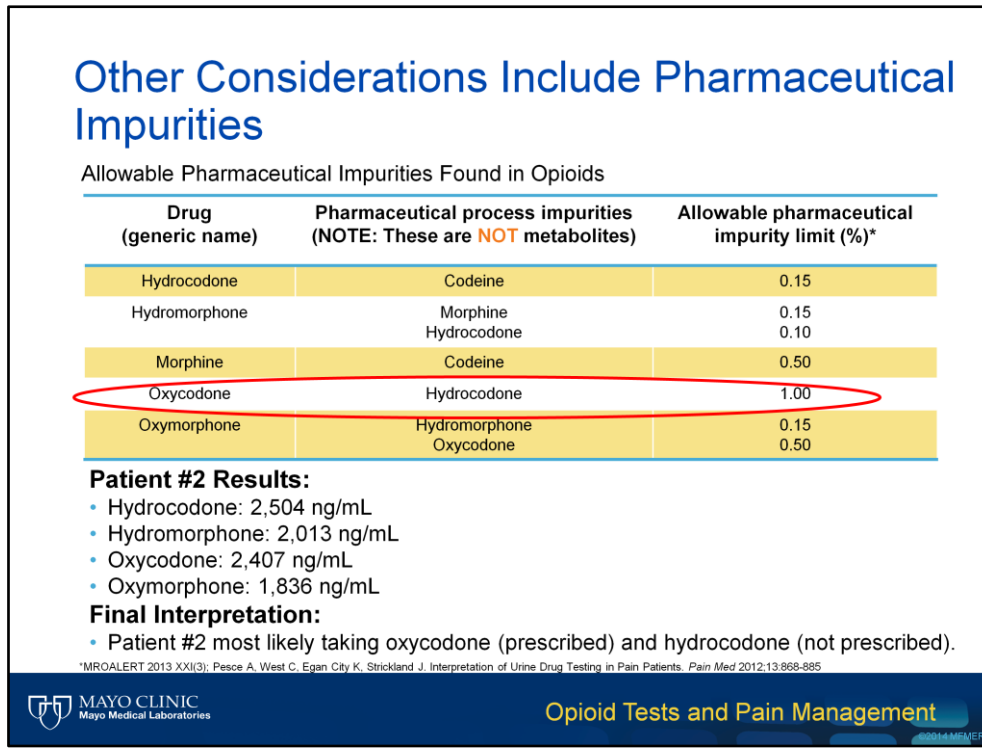
For patient #2, the original urine opiate immunoassay was “positive.”
However, the physician wanted to know if this meant the patient was compliant or could they be taking another opiate which is causing the “positive” test result?



As a result, the physician decides to order the urine opiate confirmatory test. In this case, the LC-tandem mass spec test comes back positive for hydrocodone at a concentration of 2,504 ng/mL, hydromorphone at a concentration of 2,013 ng/mL, oxycodone at a concentration of 2,407 ng/mL, and oxymorphone at a concentration of 1,836 ng/mL. Similar to patient #1, the physician was expecting oxycodone and its metabolite oxymorphone. However, the physican was surprised by the hydrocodone and hydromorphone results.



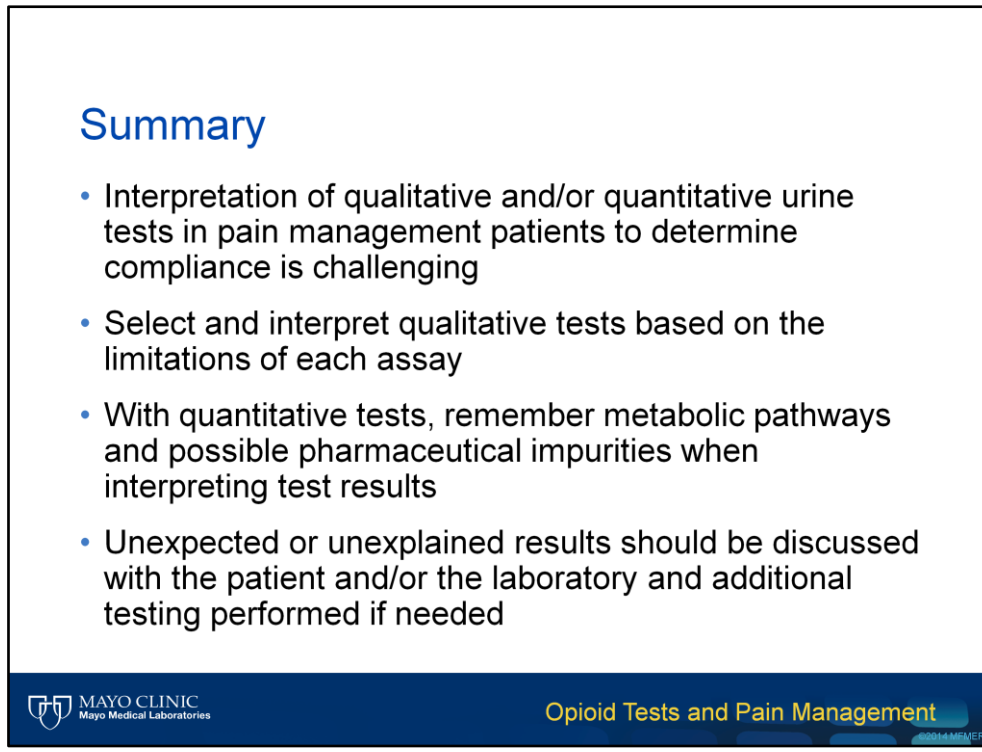
Now, the physician wanted to know where did the hydrocodone and hydromorphone come from? Are those compounds also metabolites of oxycodone? Are they false-positive results? The answer to both of these questions is “no”. Hydrocodone and hydromorphone are not metabolites of oxycodone and the LC-tandem mass spec confirmatory assay can specifically identify both of these compounds. As a result, you can see from the following slide the metabolic pathway of opioids is rather complex. Both hydrocodone and hydromorphone are available as individually prescribable medications, but they can also be minor metabolites of codeine and morphine, respectively. Since the morphine and codeine were not detected in the confirmatory LC-tandem mass spec assay, it is unlikely that the hydrocodone and hydromorphone represent minor metabolites of these drugs. From the metabolic pathway, you can also see that hydromorphone is a metabolite of hydrocodone similar to how oxymorphone is a metabolite of oxycodone. As a result, the hydrocodone and hydromorphone results are most consistent with the use of hydrocodone.



Nevertheless, the ordering physician also knows that prescription medications aren't 100% pure and maybe these unexpected results are due to pharmaceutical impurities. Prescription medications can contain a small amount of an allowable process impurity. In the case of oxycodone, you can find up to 1% present as hydrocodone. Therefore, if you have a case with really high concentrations of oxycodone, you could see detectable levels of hydrocodone. For example, if the oxycodone concentration was approximately 10,000 ng/mL, you could see hydrocodone concentrations up to 100 ng/mL.

However, the concentration of oxycodone in this case was only 2,407 ng/mL and the hydrocodone concentration was actually slightly higher at 2,504 ng/mL which is not consistent with being a minor impurity.

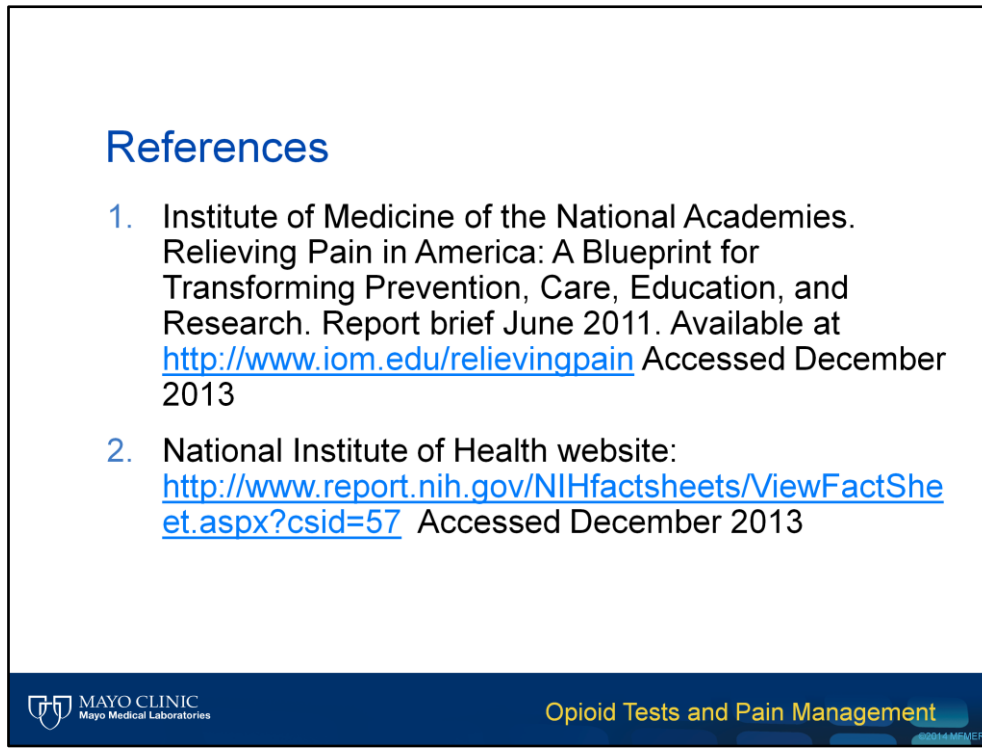
As a result, the final interpretation in this case is that the patient is most likely taking both the oxycodone which was prescribed and hydrocodone which was not prescribed.



In summary, the interpretation of qualitative and/or quantitative urine opiate tests in pain management patients to determine compliance is challenging.

You need to select and interpret the qualitative tests based on the limitations of each assay.

In addition, you need to remember metabolic pathways and possible pharmaceutical impurities when interpreting quantitative test results.
Lastly, if you have any questions or get unexpected or unexplained results, you should discuss these with the patient and/or laboratory to determine if any additional testing is needed.



Thank you for your attention. I hope you found this presentation useful. If you have any questions, please contact Mayo Medical Laboratories.

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