Urine Drug Testing and Evolving Genetic Screening:  
Do They Really Impact Outcomes?

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Objectives

• Understand the general relationship between pain management with chronic opioid therapy, concerns about misuse, and implications for UDT  
• Describe the principles supporting the necessity for UDT  
• Describe various clinical basis regarding who should be tested and the frequency of testing  
• Interpret results within limitations of types of UDTs and current technologies  
• Develop a strategy to maximize the utility of UDT in claims management  
• Examine the evolving role of genetic testing  
• Discuss the actual impact that these tests have on patient outcomes
Financial Concerns

“Urine drug testing is how I pay the bills,”
Dr. Robert Wadley, pain specialist in Raleigh, NC

Wall Street Journal, November 10, 2014

Safeguards

- Negotiate a contract with one or more of the UDT companies
- $300 to $400 should be an acceptable rate and should include:
  - A workers’ compensation panel
  - “Add-ons” to the panel should be at no charge
  - Screening and confirmation test should be included at one charge
  - Service should include interpretation of results
  - Confirm that your PBM does not receive financial incentives for recommending a patient for UDT

Background

- Opioid use for management of chronic pain rose dramatically in the US during past 20 years
- Opioids = primary option for severe pain
- Opioids cause euphoria (anxiolysis, relaxation, motivation)
- Opioids can cause dependence (psychological) and addiction
- Predicting who will and will not become “addicted” to opioids is difficult
- Dependence and addiction not easily diagnosed
- The home medicine cabinet is a primary source of drug diversion
Risk Reduction Strategy

UDT is only one part of an overall strategy designed to ensure safe usage of opioids.

The goals of a Risk Reduction Strategy are to:

1) Ensure legitimate patients continue to have access to opioids
2) Keep non-medical patients from accessing opioids (off the streets)
3) Identify and provide medical care to those who become addicted

A Comprehensive Risk Reduction Strategy should include:

1) Baseline risk screening (ORT, SOAPP®)
2) Prescription Drug Monitoring Programs (PDMPs)
3) Pill counts
4) Psychiatric assessments (higher risk of abuse)
5) Objectively monitoring therapeutic benefit
6) Urine Drug Testing
## Why UDT is necessary?

- Illicit drug use is prevalent and on the rise
- The major source of abused opioids comes from prescribers
- Incident of opioid abuse may be higher in people receiving chronic opioid therapy

## Who should be tested?

- Only those at high risk of abuse?
- Everyone regardless of risk level?
- Everyone; high risk more often than low risk?
- Only those that exhibit aberrant behavior?

Insufficient evidence to support any approach as the “best practice”

## What do the guidelines say?


- High risk or [those] who have engaged in aberrant drug-related behaviors clinicians should periodically obtain urine drug screens
- Not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens

*Very physician friendly

http://download.journals.elsevierhealth.com/pdfs/journals/1526-5900/PIIS1526590008008316.pdf

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What do the guidelines say?

**American Society of Interventional Pain Physicians (ASIPP)**

Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain

- UDT must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use.

- Creating a UDT policy that is applicable universally and consistently with all patients assists to "de-stigmatize" UDT and can potentially convince patients that it has nothing to do with an individual patient or their trustworthiness.

*Very practical and appropriate considering the current climate of surrounding the opioid abuse epidemic*


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What do the guidelines say?

**Official Disability Guidelines (ODG)**

- Onset of treatment
  - When patients ask for a specific drug
  - Patient has a positive or "at risk" addiction screen (including history of psychiatric disorder)
  - If aberrant behavior
  - If dose increases are not decreasing pain and increasing function
  - The frequency of urine drug testing may be dictated by state and local laws.

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What do the guidelines say?

**American College of Occupational and Environmental Medicine (ACOEM)**

- All patients on chronic opioids for chronic pain
  - At baseline
  - Randomly at least twice and up to 4 times a year
  - “for cause” (i.e. observed or suspicion of aberrant behavior)
Prescriber's Perspectives

2 main types

Prescriber A
• Demographic information
• Assumed risk factors
• "gut instinct"
• Random for everyone

Prescriber B
• Strict policy
• Everyone gets treated the same

Evidence supporting a strict policy where everyone is treated the same may be more convincing:

• Deception is notoriously difficult to detect: A Cornell University study found that doctors correctly identified a lying patient only 10% of the time and “some real patients were erroneously identified as actors”1

• "Gut instinct" does work because prescribers often can’t predict who will abuse opioids: A 2011 study involving 549 patients from 50 practices revealed that doctors “missed 60% of patients who went on to have abnormal urine drug test”2

• Numerous retrospective studies reveal significantly high numbers of abnormal UDTs


OBJECTIVE:
To examine the incidence of abnormal urine toxicology screening among chronic pain patients prescribed opioids for their pain and to relate these results to patient descriptors and type, number, and dose of prescribed opioids.

METHODS:
UDT data from 470 patients at a pain management program in an urban teaching hospital.

RESULTS:
-45% had abnormal UDT
  -Presence of illicit drugs: 25%
  -Presence of non-prescribed Rx drugs: 14%
  -Absence of prescribed drugs: 10%
Prescriber's Perspectives

Urine Drug Testing in the Treatment of Chronic Noncancer Pain in a Kentucky Private Neuroscience Practice: The Potential Effect of Medicare Benefit Changes in Kentucky

BACKGROUND:
July 1, 2009, Medicare changed its policy to stop reimbursing doctors for performing qualitative drug screening for patients with chronic noncancer pain unless the patient presents with suspected drug overdose.

METHODS:
An audit of urine drug testing services provided during 2007

CONCLUSIONS:
- UDTs were used as an effective tool in adherence monitoring
- UDTs were instrumental in referring 40% of patients for evaluation and treatment by behavioral health and addiction medicine specialists
- UDTs were also instrumental in discovering signs of drug abuse or addiction in 19.6% of patients

Pain Physician 2010;13:187-194 • ISSN 1533-3159
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Types of Test

**Immunassay**
- Inexpensive and relatively quick
- Point-of-collection or laboratory qualitative results
- More useful to detect illicit drugs
- There may be cross-reactivity with chemically related substances
- Sensitivity and specificity vary between brands
- Cut-off concentrations for detection
- Designed to identify patients that need closer scrutiny

**Chromatography**
- Used for confirmation testing
- Laboratory based
- Relatively expensive
- GC/MS is "gold standard"
- Turnaround time varies
- Quantifies amount of drug/metabolite

Indications of testing

**What can be determined:**
- Presence of illicit drugs
- Presence of non-prescribed Rx drugs
- Absence of prescribed Rx drugs

**What cannot be determined:**
- Amount or time drug was taken
- Whether concentration is toxic
- Concentrations correlate with prescribed dosages

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Interpreting results

- Results can have very serious repercussions
- False positives and false negatives are major concern
- False positives of greater consequence in workplace settings
- Both circumstances can cause harm in a clinical setting

Urine drug test interpretation: what do physicians know?
Journal of Opioid Management. 2007 Mar-Apr;3(2):80-6

OBJECTIVE:
To determine the level of urine drug test (UDT) interpretive knowledge of physicians who use these instruments to monitor adherence in their patients on chronic opioid therapy

METHODS:
A seven-question test was given to 114 physicians (77 who employ UDT and 37 who do not)

RESULTS:
- None of the physicians who employ UDT answered all seven questions correctly
- Only 30 percent answered more than half correctly.
- No difference between those that use UDT and those that don’t

Immunooassays (in-office point-of-care testing; “screening”)

Intensity of the color line is not a factor. Even a faint line indicates a negative result.
Interpreting results

Immunoassays (in-office point-of-care testing; "screening")

- Amphetamine
- Barbiturates
- Benzodiazepines
- Buprenorphine
- Cocaine
- MDMA
- Methadone
- Methamphetamine
- Opiates (morphine; codeine; hydrocodone; hydromorphone)
- Oxycodone
- PCP
- Marijuana
- Tricyclic antidepressants

*Immunoassays will only show positive or negative (no quantities)

False Positives (applies only to immunoassays)

*when patients deny taking substance found to be positive

<table>
<thead>
<tr>
<th>Substance</th>
<th>Likelihood that patient is telling the truth is stronger if patient has taken:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine or Methamphetamine</td>
<td>OTC allergy medications containing antihistamines (brompheniramine or decongestants) (phenylephrine)</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Dextromethorphan (OTC cough and cold)</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Effervescent (HIV)</td>
</tr>
<tr>
<td>Opiates</td>
<td>Dextromethorphan</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Chlordiazepoxide (NSAID)</td>
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<td></td>
<td>Imipramine</td>
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Maximizing Utility of UDT

Main Goals: Ensure that testing occurs, inconsistent results are addressed, and appropriate action takes place

1) Understand the prescriber's perspective/policies concerning UDT

Suggested survey questions:
- a) Have you designated yourself as the only prescriber of controlled substance to this patient?
- b) Will you be performing UDT to monitor compliance and aberrant behavior on this patient?
- c) How often will the patient be tested?
- d) Will the tests be random?
- e) Do you typically give allowance for first infraction?
- f) What is your policy regarding second infractions? Deposits □ Refer to substance treatment □ Wean patient
- g) Do you consider cannabis to be an illicit drug?
- h) Will you agree to discuss results with a toxicologist before making final conclusions associated with aberrant results?
- i) What is your policy regarding patients that refuse testing or who cannot produce a sample?

2) Initiate referrals at appropriate times

Coordinate with pharmacy benefits manager

a) To ensure that patient has medications on hand (quantities/day supplies)

<table>
<thead>
<tr>
<th>Date of Service</th>
<th>Medication</th>
<th>Strength</th>
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<tbody>
<tr>
<td>1/2/14</td>
<td>Oxycodone</td>
<td>30 mg</td>
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3) Solicit (demand) a response

Suggested verbiage: Absence of prescribed drug

Dear Dr. Doe,

On 1/10/14, the above patient submitted a urine sample for toxicology testing. The patient is currently being prescribed: Oxycodone 30 mg twice daily.

This medication was last dispensed to the patient on 1/1/14 indicating that the patient should have had sufficient medications on-hand if he/she were taking the medication as prescribed.

The test results confirm that oxycodone was not detected in the patient’s urine. Our concern is that this may indicate a possibility of drug diversion which can be viewed as a public health risk. We therefore greatly appreciate your clinical conclusion regarding this urgent matter.
Maximizing Utility of UDT

Main Goals: Ensure that testing occurs, inconsistent results are addressed, and appropriate action takes place.

3) Solicit (demand) a response

Suggested verbiage: Absence of prescribed drug

Prescriber response:
- I conclude that the results of the test are inconsistent and plan to:
  - Discharge the patient
  - Refer patient to substance treatment
  - Wean patient
- I conclude that the results of the test are NOT inconsistent for the following reasons:

Adverse Drug Reactions

2.2 million severe adverse drug reactions per year
Fouth leading cause of death in the U.S.
100,000 deaths per year from preventable drug errors
80,000 deaths per year from prescription drug misadventure

Cost Leader for malpractice payouts

Personalized Medicine

More than 75% of the population has genetic variations that affect the CYP450 drug metabolizing enzymes.
Personalized Medicine may be Expensive

• A full panel screen of all genes may cost $4000
• A screen for only those genes involved with pain may be only $1000
• However, rarely is pain the only concern – need to examine impact on psych drugs as well
• Furthermore, group healthcare considers this a once in a lifetime test, and will only pay once, but that requires a full panel

What is pharmacogenomics?

• Pharmacogenomics is the science that examines the inherited variations in genes that dictate drug response
• Pharmacogenomics can predict whether a patient will have a good or bad response to a drug or no response at all

How does Pharmacogenomics affect treatment?

• Experts estimate that approximately $300 billion is wasted each year on drugs that do not work in the individuals receiving them because they carry certain genes.
• Drugs, including common pain medications, may not be metabolized resulting in decreased or no efficacy or they may be metabolized more extensively or more rapidly resulting in adverse effects that are potentially life threatening.
• Without knowing a patient’s specific genetic code, a physician may go through months of trial and error – finding the right drug at the right dose to provide effective treatment without side effects.
• Finding the right drug at the right dose is the basis of a growing industry called pharmacogenetics or pharmacogenomics. The terms “personalized” or “individualized” medicine are also common catch phrases for this field.
Pharmacogenetic Testing

- Cytochrome DNA testing for drug sensitivities and metabolism
  - DNA test panel covering all clinically significant genetic variants in CYP3A4, CYP3A5, CYP2D6, CYP2C9, CYP2C19, and VKORC1
- Other available tests include
  - CYP1A2
  - DPD (5-FU toxicity)
  - SHTT (serotonin transporter for S(+)s)
  - HLA-B*5701 (abacavir sensitivity)
  - NAT2
  - UGT1A1 (rinotocan)
- Important for patients taking multiple medications or those who have a history of ADR's or treatment failures
- Pharmacogenetic testing reduces the cost and hassle of trial and error prescribing

Pharmacogenomics and Pain Management

- Response to opioids varies widely among patients
  - Opioid dose requirements vary in the clinical setting by as much as 40-fold
- Genetics may explain the variability of responses and predict more effective or less dangerous medication choices

Opioids and Pharmacogenomics

- The prescriber must balance pain control with the known side effects of opioids including sedation, respiratory depression, cardiac arrhythmias and risk of addiction.
- Approximately half of the population has genetic variants that alter the function of Cytochrome P450 enzymes, specifically CYP2D6, which is required to activate many common pain medications.
  - Codeine
    - CYP2D6, a cytochrome P450 liver enzyme, metabolizes codeine, an inactive parent drug, to active morphine.
    - Morphine binds with a 200-fold greater affinity than codeine to the mu-opioid (pain) receptor.
    - Variants or mutations in the CYP2D6 gene that affect codeine metabolism may cause decreased metabolism, thus rendering the drug less effective in controlling pain or may increase codeine metabolism, resulting in higher morphine levels than expected and the associated adverse events.
  - Hydrocodone
    - CYP2D6 is responsible for 95% of conversion to hydromorphone.
    - Hydromorphone has a much greater affinity for pain receptors.
- If a patient taking an opioid is experiencing no pain relief and also no side effects, he may have a genetic variation that is affecting how the drug is handled by his body—otherwise known as pharmacocokinetics. Pharmacodynamics—how the body responds to the drug—is also affected by genetics in that receptors for specific medications may be more responsive or less responsive to specific drugs or their active metabolites.
**CYP2D6 Influence on Codeine**

- **Codeine** is an inactive compound, metabolized by CYP2D6 into its active form, **morphine**
  - Polymorphisms of CYP2D6 can result in either low or dangerously high levels of morphine at standard doses
- Other drugs affected by CYP2D6
  - Tramadol, Hydrocodone, Hydromorphone, oxycodone, oxymorphone

**Variability with Pain Management**

- Pain clinicians have always been challenged by the variability of response to pain treatment
- Variability in analgesia seen with opioids due to
  - Differences in the degree of pain stimulation and pain sensitivity
  - Weight and age differences
  - Prior opioid use and tolerance
  - Differences in bioavailability of various opioid formulations

**Clinical Application**

- Genetic testing can be used to explain and confirm ineffective or high opioid use
  - Ex. patients with CYP2D6 deficiencies would be expected to have poor relief from tramadol, codeine, hydrocodone, and oxycodone
- Genetics may also help to predict the response to specific opioids and antidepressants
- By identifying the genetic risks, the clinician could improve the efficacy of the pain medication and decrease the risk for overdose, addiction, and death
How do we use this in practice?

- **Finding the correct drug at the correct dose** is the goal of pharmacogenomics and because analgesics commonly have narrow therapeutic windows, the development of these tests as predictive tools should positively affect patient care for patients needing chronic pain management.
- Pharmacogenomics allows the ability to differentiate potential responders from non-responders (for specific medications), helps the avoidance of adverse events, and helps in optimizing drug dose – all of which has been recognized and acknowledged by the FDA.
- The FDA, who historically has not evaluated laboratory tests, has approved pharmacogenetic information for over 100 medications including tramadol, codeine and carisoprodol.

Who needs pharmacogenomics testing?

Sometimes there are clues that may help avoid testing:

- If a patient has NO pain relief and **also** has NO side effects, despite escalating doses of opioids, the patient may be an ultra-rapid metabolizer. They frequently need double the dose of a "normal" metabolizer – but, we do not always give them the "benefit of the doubt"!
- A poor metabolizer, on the other hand, will have severe side effects at low doses. This patient needs lower doses. Avoid long acting opioids in these patients until the dose is stable. They may never need them. Unfortunately, lowering of the dose is not what usually happens. The prescriber usually changes the drug and the first drug is noted as "not tolerated" in the patient’s chart and never tried again, when a lower dose may have been "the correct drug and the correct dose".

If all else fails:

- Genetic testing is a once-in-a-lifetime test because a person’s DNA never changes!
- Most tests require saliva or a buccal swap to obtain cells from the patient’s inner cheek.
- If looking specifically at pain medications, CYP2D6 may be the only test needed, but it costs no more to run the full gene panel, which may useful in treating this patient should other disease conditions develop.

Additional References


Questions?
Thank You

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