OVERVIEW OF URINE DRUG TESTING

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Modified from: Addictions and Their Treatment Urine Drug Testing by Kevin A. Sevarino, MD, PhD and AAAP

OUTLINE

- Purpose and use of UDT
- Types of UDT
- Interpretation of UDT
- Forensic issues

PURPOSE AND GOALS

- Clinical: Improve Patient Care and Safety –

NOT GOTCHA!!!

  - Facilitate doctor-patient communication
  - Provide objective information
  - Confirm use of prescribed medication: Adherence testing
  - Confirm lack of use of non-prescribed medications or illicit drugs

- Legal:
  - As a condition of parole/probation
  - Custody/parental issues
  - Workplace testing, including federal testing

RECENT TRENDS IN UDT

- Don't refer to a urine as "dirty" instead report as unexpected/expected, positive/negative etc.
- Testing will become increasingly individualized and broader based profiles will be less common (due to legal challenge and cost-containment)
- Testing should reflect regional drug use trends.
- Justification based on medical necessity, especially for definitive testing:
  - A baseline test to support diagnostic assessment
  - Assess adherence to prescribed medication
  - Assess abstinence from non-prescribed substances
  - Behavior not matching patient self-report
  - To confirm safety of prescribing
  - Confirm adherence to new medication
  - New life stressors, dangerous situations etc.

Modified from: Peter LoIacono, MA, LADC, the New England Addiction Technology Transfer Center and NHADACA

CHOICE OF MATRIX

- Urine by far most widely used
- Hair - 7 - 90d; directly observed but poor for marijuana; dark hair bias.
- Saliva - <24 hrs, directly observed but poor sensitivity,
- especially marijuana
- Sweat Patch - resistant to cheating, prospective
- Breath - not as developed, except alcohol.
- Blood – invasive, shorter detection windows

WHY URINE?

Positives:

- Supported by extensive research and practical experience
- Urine contains higher concentration of drug metabolites, allowing for a greater window of detection.
- Extensive testing options, non-invasive, easily stored
- Reasonable cost

Negatives:

- Short to intermediate window of detection
- Collection of sample can be challenging, e.g. do you observe?
- High potential for adulteration or substitution, esp. w/o observation
- Shy bladder syndrome may occasionally prevent sample acquisition.

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HOW TO DISCUSS UDT

- New patient initiating on opioids: (as part of treatment agreement discussion)

— "This is our routine practice for patient safety and treatment."

- Patient who has been on opioids for a while:

— "Why now?" ⟶ "New clinic policy started recently"

- Patient says: "But I'm not a drug addict":

— "Routine (universal) testing…not singling anyone out."

- Patient says: "I refuse":

—"We can't prescribe if we're unable to do the routine safety monitoring discussed in the treatment agreement."

Heit, H.A.; Gourlay, D.L. J Pain Sympt Mgt. 2004

HOW TO CONDUCT COLLECTION

- Specimen can be collected:
  - unsupervised (least intrusive and least staffing)
  - supervised (staff in room)
  - observed (intrusive, issues with shy bladder, those trauma-exposed
- Clinical guidance recommend the least intrusive approach, without clear support for validity of recommendation
- Scheduled vs. non-scheduled: the latter is strongly recommended by ASAM (2017), but often impractical

VALIDITY OF SPECIMEN COLLECTED

- Temperature between 90- and 100-degrees Fahrenheit
- pH between 4.5 and 8.5
- Creatinine greater than 20 mg/dL; <5 red flag
- Color/Shake Test (protein/soap)
- Specific Gravity (1.002); 1.000-1.001 red flag
- Adulterants: salt, bleach, sodium/potassium nitrites, chromates, iodine, peroxide/peroxidase, vinegar, lemon juice, ammonia, pyridinium chlorochromate, glutaraldehyde
- There are dipstick tests to assess sample validity in the field.

Moeller et al., 2017

- An approach to determine if a current positive THC result reflects new marijuana use or prior use is to follow the THC/Cr ratio.
- The rule-of-thumb is that the THC/Cr ratio should decrease by 50% every two to ten days depending on the individual.
- A light or infrequent user will decrease faster than a heavy or frequent user
- In increase of 50% supports use during the preceding interval

http://www.micro-distributing.com/faq_qa.cfm?id=10

https://www.redwoodtoxicology.com/docs/resources/creatinine_interpretation.pdf

Adapted from: Peter LoIacono, MA, LADC, the New England Addiction Technology Transfer Center and NHADACA

URINE POINT OF CARE TESTING

- POCT is rapid, but detrimental if treatment or other important decisions are based on unconfirmed results.
- POCT does not give quantitative drug or metabolite information (e.g. bup/norbup ratios).
- The cutoffs of some POCT devices may not provide adequate sensitivity - A KEY LIMITATION!
- FDA approval is required for approved home use. POCT kits most rigorously tested are CLIA-waived. At the present, there are two FDA-approved kits for home use that test for fentanyl.

- From: Peter LoIacono, MA, LADC, the New England Addiction Technology Transfer Center and NHADACA;
- and Beck et al. (2014) Scand J Clin Lab Invest 74:681-686

METHODOLOGIES

- Presumptive (preliminary, qualitative, immunoassay) testing: Will not definitively identify a specific analyte.
  - Point of Care Testing (POCT) and EIA (Enzyme Immunoassay)
  - Less expensive
  - Quick turnaround time
  - Potential of cross-reactivity
  - Significant false positive and negative rates
- Definitive (quantitative, confirmatory) testing:
  - Usually GC/MS
  - No false positives
  - Superior specificity and sensitivity
  - Will definitively identify a specific analyte

Bartwell et al 2018

IMMUNOASSAYS

- Widely available cost-effective and well understood, but prone to cross reactions and false positives – should consider this a "screening" tool for all but cannabis.
- Most standard panels today include amphetamines, benzodiazepines, opioids, methadone, cocaine, cannabis and PCP – BUT KNOW WHAT'S IN YOUR LAB'S PANEL!
- Often won't include fentanyl, buprenorphine, synthetic cannabinoids, etc.
- Common EIA methods include:
  - CODI (cloned-enzyme donor immunoassay)
  - EMIT (enzyme-multiplied immunoassay technique)
  - FPIA (fluorescence-polarized immunoassay)
  - Immmuno-turbidity assay
  - RIA (radioimmunoassay)

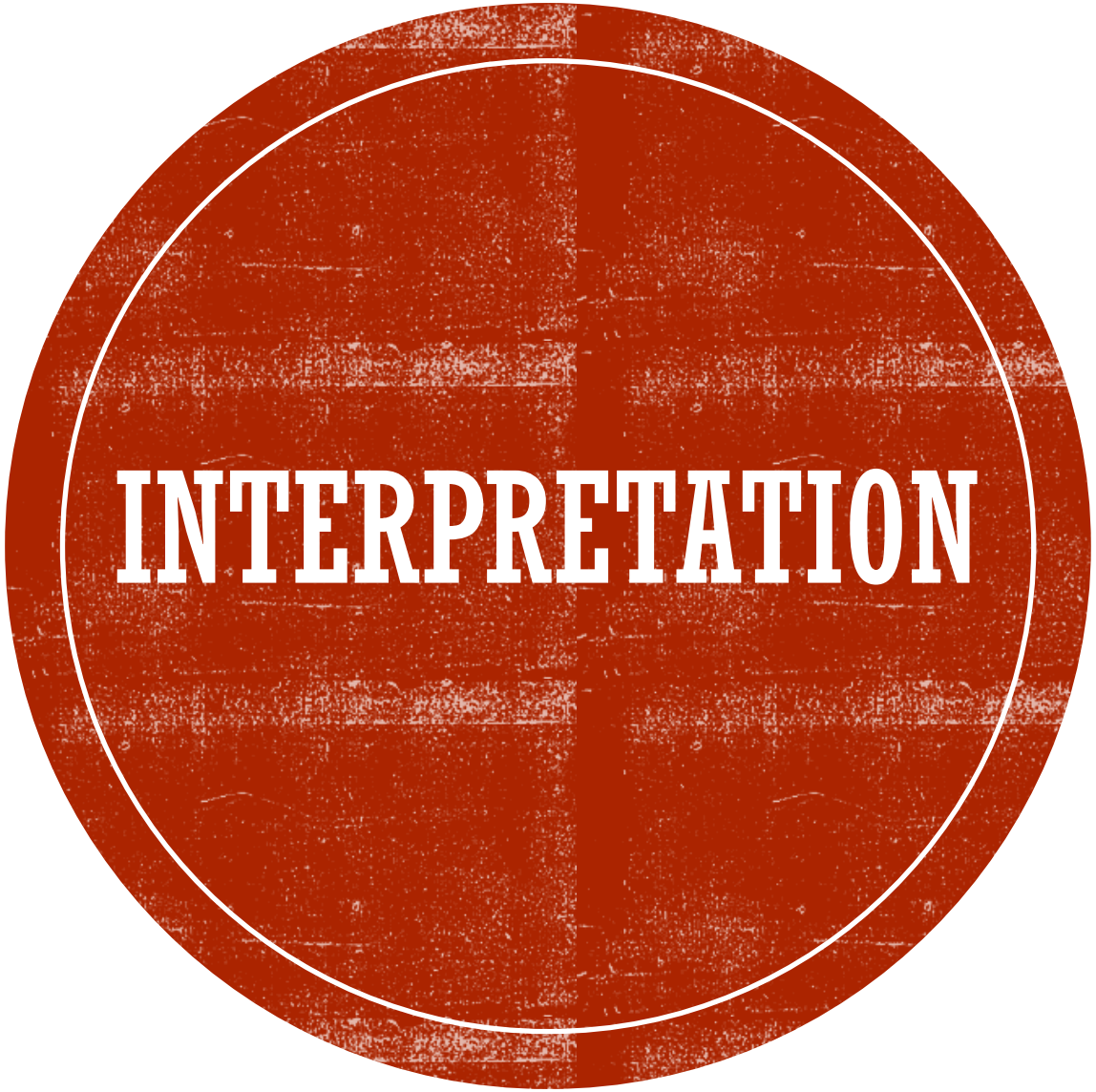
FALSE POSITIVES

- Amphetamines: amantadine, chlorpromazine, bupropion, DMI, fluoxetine, nasal decongestants w/ L-methamphetamine, pseudoephedrine, ranitidine, trazodone, selegiline, amantadine
- Benzodiazepines: efavirenz, oxaprazin (Daypro), sertraline,
- Cannabinoids: efavirenz, NSAIDs, PPIs, baby wash products;
- dronabinol yes, nabilone no
- Synthetic cannabinoids: lamotrigine (LMG)
- Cocaine metabolite: none (NB: coca tea leaves, topical cocaine solutions)
- EtG: IPA, alcohol-cont. mouthwash, lotions, etc., Nyquil
  - See more inclusive list: Moeller et al. (2017)

- PCP: dextromethorphan, diphenhydramine, ibuprofen tramadol, venlafaxine, IMI, MDPV, ketamine, doxylamine, LMG, thioridazine, meperidine
- Opioids: dextromethorphan, diphenhydramine, doxlyamine, rifampin, poppy seeds, quinine, fluoroquinolones, verapamil
- Buprenorphine: sulpride, codeine, morphine, methadone, tramadol
- Methadone: verapamil, tapentadol, diphenhydramine, quetiapine, doxylamine
- See more inclusive list:

CONFIRMATORY TESTS

- When the result of a drug test is:
  - contested,
  - not explained by patient self-report
  - guiding clinical decision-making, or
  - done for forensic purposes,
- the immunoassay must be confirmed
- with GC/MS, GC/MS/MS or LC/MS.



Understanding of the pharmacology of substances

UDT DETECTION TIMES

Δ9 THC acute use <6 d chronic use <30 d	Benzoylecgonine <4 d	Codeine/morphine/ heroin 2 d	PCP acute 8d chronic 30d
Amphetamines ≤ 3d	EtG/EtS 3 – 5d	Synthetic cannabinoids + 3d	

UDT DETECTION TIMES

Oxycodone 1 - 3d	methadone 2 – 11d	buprenorphine 1 – 7d
diazepam* 1 – 21d	lorazepam* 1 – 3d	alprazolam* 1 – 2d

- Natural opioids (the opiates) include codeine and morphine - well detected by standard opioid screens. Opium and thebaine also in this class.
- Hydrocodone and hydromorphone (semisynthetic opiates) are less well detected. Tests for these are now included in the Mandatory Guidelines for Fed. Workplace Drug Testing (UrMG*).
- Oxycodone (semisynthetic opioid) and its metabolite oxymorphone are not well detected. Testing is now included in UrMG.
- At high levels semi-synthetic opioids like oxycodone are detected in standard opiate screens.
- Buprenorphine is a semi-synthetic but is NOT detected in standard screens.
- Methadone, fentanyl, meperidine, tramadol are synthetic opioids and ARE NOT detected and require separate tests

*Federal Mandatory-Guideline for UDT

Sample Two-Stage EIA then GC/MS (Rx is oxycodone CR 20 mg TID)

- EIA:
  - Amph (-)
  - BZD (-)
  - Barb (-)
  - Cannab (-)
  - Cocaine (-)
  - Methadone (-)
  - Opiate (+)
  - Oxycodone (+)
  - PCP (-)

Opiate GC/MS:

Codeine (-)

Morphine (-)

Hydrocodone (-)

Hydromorphone (-)

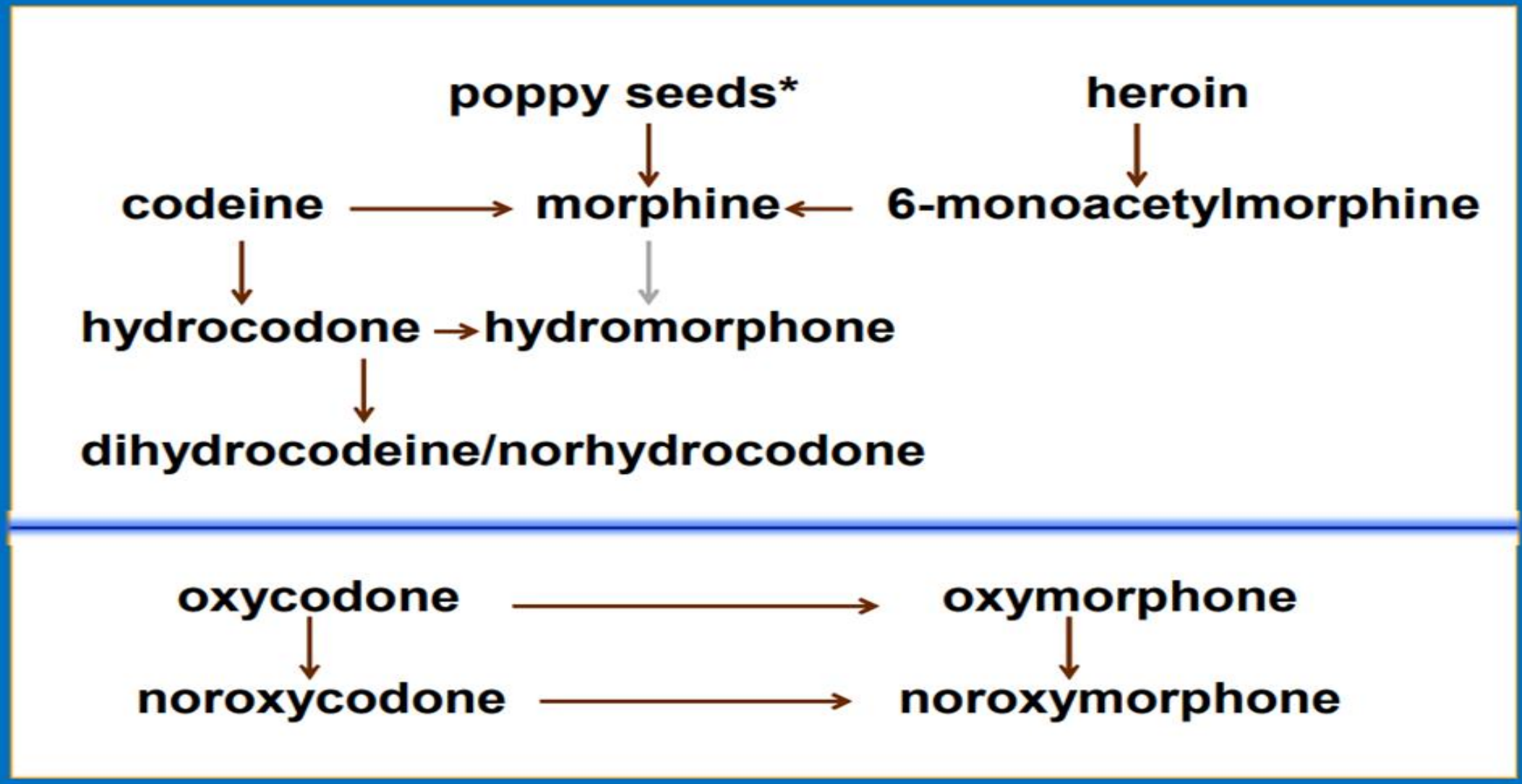
Oxycodone 1000 ng/ml

Oxymorphone 730 ng/ml

6-acetylmorphine (-)

Meperidine (-)

OPIOID METABOLISM



OPIOID METABOLISM

buprenorphine → **norbuprenorphine**

naloxone → **dihydro-14OH-normorphinone** → **N-*allyl*-dihydro-14OH-normorphinone**

The ratio of norbuprenorphine to buprenorphine in definitive testing should be >1 given the half lives of the two agents, but Hull et al. use a cutoff of 0.02 as cutoff for evidence of "spiking." Holt et al. support a buprenorphine concentration of >700 ng/ml. Detection of elevated naloxone/ buprenorphine may support "spiking" or IV use (Heikman et al., 2014)

Heikman et al.(2014) Drug Test Anal 6:220-5.

Hull et al.(2008) J Anal Toxicol 32: 516-521;
Holt et al. (2017) Drug Alcohol Dep. 180: 46-51

BENZODIAZEPINE METABOLISM

clonazepam* → 7-aminoclonazepam

alprazolam* → a-hydroxyalprazolam

lorazepam* → lorazepam-glucuronide

flunitrazepam* → 7-amino flunitrazepam

** Poorly detected by immunoassays*

FORENSIC ISSUES IN UDT

Most Judicial and federal testing relies on presumptive testing almost exclusively, and test for a limited number of agents. The goal of testing is not therapeutic but are meant to ensure safety and compliance.

FEDERAL REGULATIONS

- Federal Employees- see "Mandatory Guidelines for Federal Workplace Drug Testing Programs"
- Public/Private Sector workers in transportation and pipeline industries (any hazardous material)
- DOT vs non-DOT testing for private sector
- All other drug testing regulated by states, ½ have drug testing statues.

REQUIREMENTS FOR SPECIMEN COLLECTION

- Appropriate collection site, with proper space, equipment and security
- Trained collection personnel
- Inspect sample immediately after collection
- Specimen in view of testee and collector at all times until labeled, and the testee confirms the label
- Immediately record temperature/pH (no longer than 4 min)
- Logbook completed, signed by collector; testee signs certification statement

- Collector completes a CCF (chain-of-custody-form)
- Securely store the sample
- Use colored toilet water
- Any handling or transfer of the sample must be noted on the CCF
- Seal the container with tape, sign, and package for approved transportation to certified lab; attach the CCF

Please see https://www.transportation.gov/sites/dot.gov/files/docs/resources/partners/drug-and-alcohol-testing/2567/urine-specimen-collection-guidelines-january-2018.pdf

(49 CFR Part 40 DOT Urine Specimen Collection Guidelines)

MEDICAL REVIEW OFFICER

2001 Regulations:

- Licensed physician
- Clinical experience in substance use disorders
- Training course every 3 years
- Certified by MRO Coordinating Council or American Association of MROs.

FUNCTIONS OF A MRO

If sample is negative MRO confirms:

- The specimen was within expected parameters (e.g., temperature and creatinine).
- Custody and Control Form examination reveals
- all procedures were followed

If sample is positive MRO confirms:

- Sample was confirmed by definitive testing
- "Invalid" samples reported as "test cancelled"(immediate reorder)
- Adulterated or substituted samples reported as "refusal to test"
- If due to a prescribed substance, reported as "negative"

SUMMARY AND TAKE-HOME MESSAGE

- UDT begins with immunoassay-based screening, followed by definitive confirmation if needed. This is not ideal (15% negative rate) but is the most practical.
- False positive EIAs most common for amphetamines & PCP, least common for cannabis and cocaine.
- False negatives common for semi-synthetic and synthetic opioids, and many benzodiazepines.
- Understanding the catabolism of opioids and benzodiazepines is necessary to accurately interpret presumptive and definitive testing results.

You have to understand:

- what your standard panels detect and don't detect
- common false positives and negatives for your lab
- the metabolism of the opioids and benzodiazepines
- the time frame your UDT should detect substances

in order to the understand the results of the tests you are ordering!

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