The Good, Bad and Ugly: Drug Testing in Liver Transplant Evaluations

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*Disclosure Information (Required)

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  - **No disclosures**
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  - **No disclosures**
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Learning Objectives

* 1. Describe the strengths and limitations of the most commonly used drug tests that are currently available for Marijuana (MJ)/Cannabinoid detection in patients requiring liver transplant (LT) evaluation

* 2. Identify clinical circumstances in patients with alcohol-related liver disease (ALD) that may result in variable test results at different times after last alcohol or marijuana use in order to increase accuracy and effectiveness of drug testing in those requiring LT evaluation

* 3. Identify ways of increasing access to equitable care in patients undergoing LT evaluation based on ASAM-appropriate use of urine drug testing

*LT in the U.S.

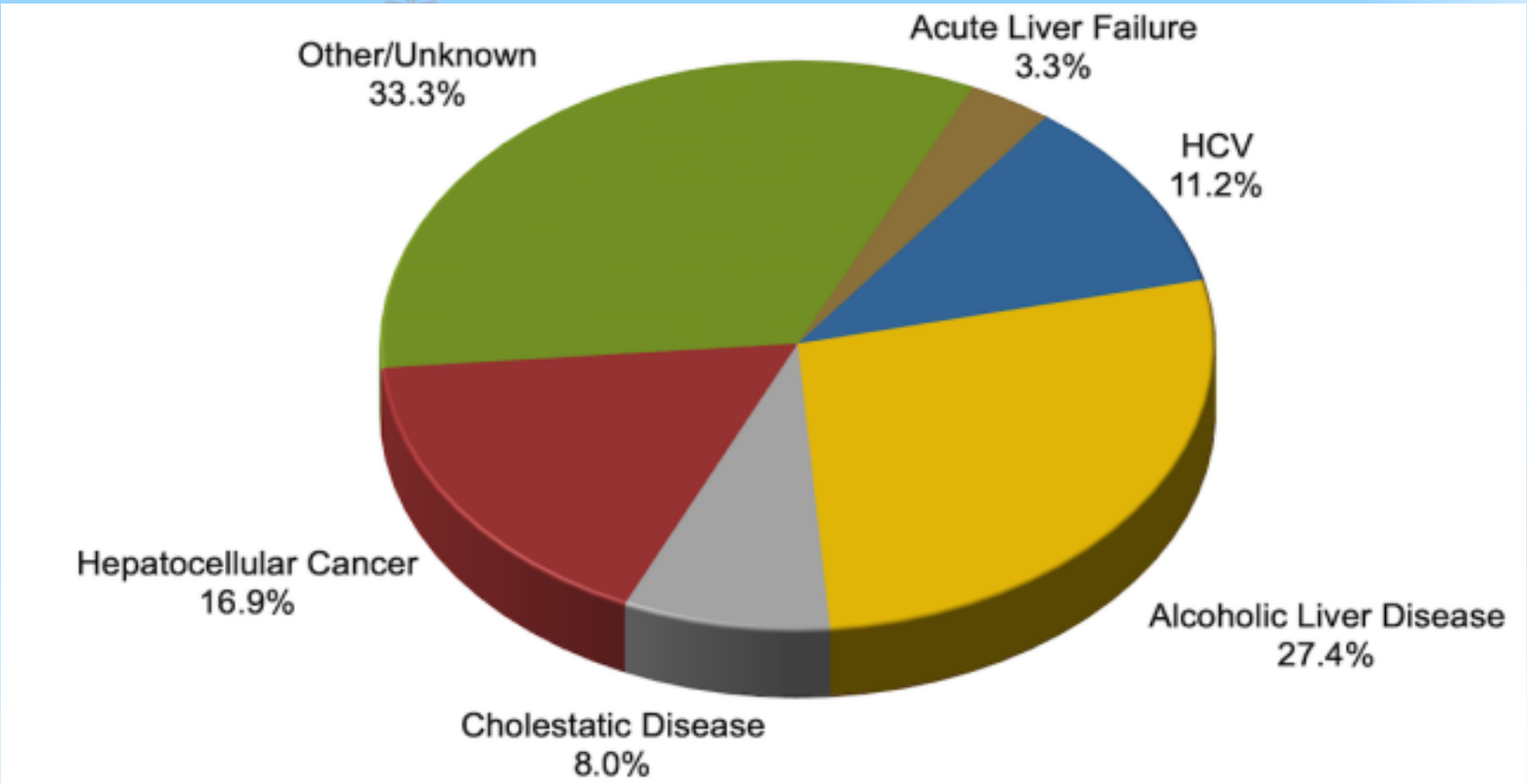


Fig 4 Clinical Characteristics of Adult Liver Transplant Recipients, 2018

Kwong A et. Al; Am J Transplant. 2020; 20 suppl s1: 193-299

LT in the U.S. (cont'd)

- 1st successful LT in 1967
- ALD has become the 2nd leading cause of LT performed in the U.S. and Europe
- 1984- 1st formal LT guidelines after passing National Organ Transplant Act
  - Organ Procurement and Transplantation Network (OPTN)
    - United Network for Organ Sharing (UNOS)
- 140 Transplant Centers in the U.S.
  - 60 Organ Procurement Organizations (OPOs)

Coombes JM, Trotter JF. (2005) Clin Med Res 3:87–92.

Cannabis Use in LT

- Historically most programs require a 6-month abstinence period before LT
  - This often excludes patients with acute alcohol-induced hepatitis
- MJ, recreational or medical, has become legal in more than half the states in the US
- The largest and most active liver transplant programs in North America have variable policies on testing for cannabis

Cannabis Use in LT: Why Worry?

- Once ID as needing LT eval -> referral to a transplant center for further assessment:
  - Medical: cardiac, general health, surgical, anesthetic risk
  - Psychiatric/MH: psychiatric, **substance use**
    - **drug testing (UDS) and MJ is included in most routine UDS (IA)**
  - PsychoSocial: social support and other factors that may reduce likelihood of successful LT

- **Risks vs. Benefits to MJ Use**
  - Respiratory, Cognitive, Stroke, and a few isolated cases of aspergillus (contaminated MJ)
  - Endogenous cannabinoids that bind to CB1 and CB2 receptors are upregulated in liver disease
  - Vs.
  - Role in appetite stimulation, analgesia, nausea/vomiting

Cannabis Use in LT

- What are the policies of current major LT centers regarding cannabis use?
- How common is cannabis use in pre-LT patients/Prevalence?
- What are the associated outcomes of MJ use:
  - Wait Listing/De-listing?
  - Post-LT?

Contemporary Policies Regarding Alcohol and Marijuana Use Among Liver Transplant Programs in the United States

Jiaming Zhu, MD,[1] Ping-Yu Chen, MD,[2] Marla Frankel, LCSW,[3] Robert Rick Selby, MD,[3] and Tse-Ling Fong, MD[1,3]

* Survey of LT programs about policies regarding alcohol, marijuana and methadone use

* 43% required period of abstinence
* 26% enforced 6-month abstinence policy
* 71% waived 6-month abstinence requirement and considered psychosocial factors in acute alcohol-induced hepatitis

* 14% enlisted patients using MJ
* 28% enlisted if stopped by time of LT
* 45% accepted active methadone users

Transplantation 2018;102: 433–439

Cannabinoid Use Among Liver Transplant Recipients

Kathleen Yan and Lisa Forman

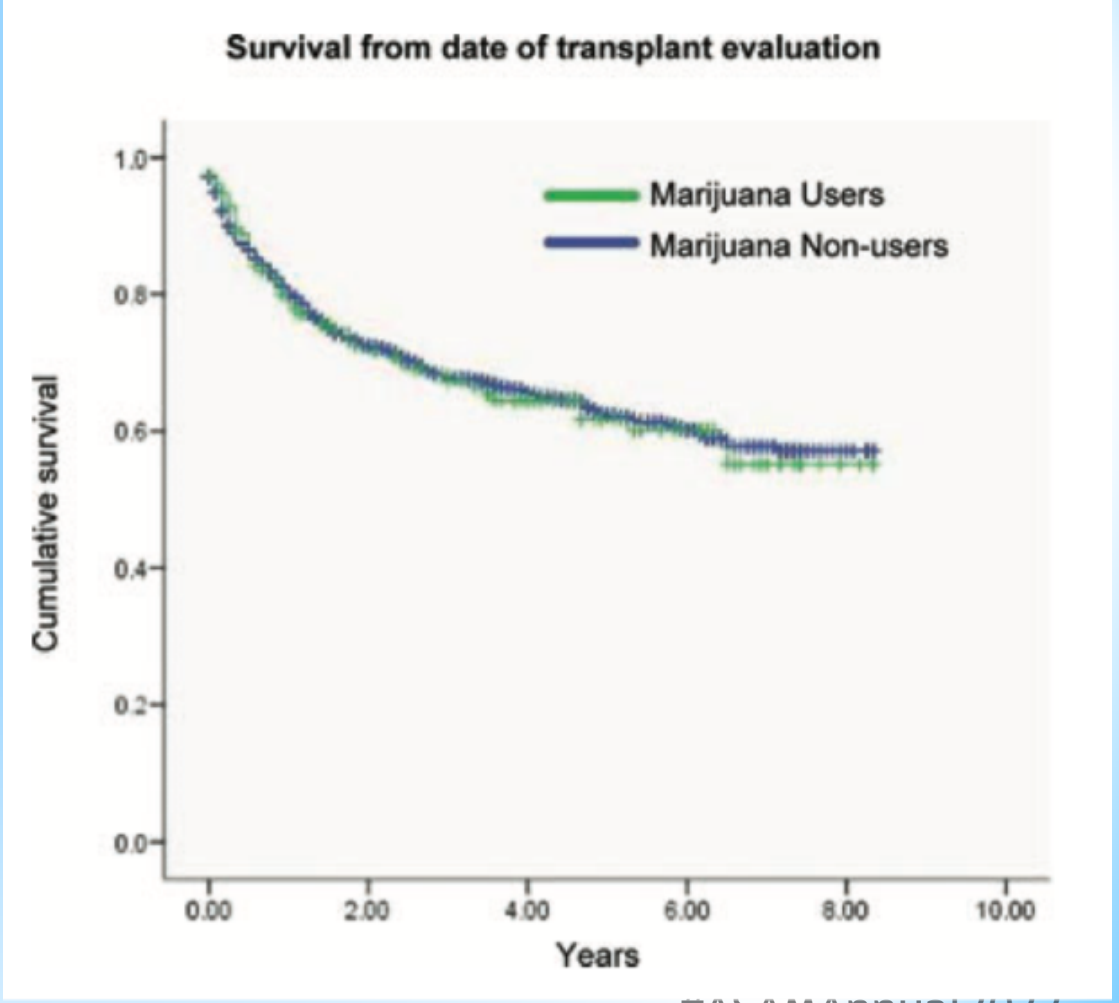
* Exploratory survey to investigate MJ and CBD of LT recipients at a University Hospital

* 23.8% cannabinoid use after LT
* MJ use associated with decreasing age, alcohol-related and HCV cirrhosis, tobacco use
* Anxiety (54%), pain (53%), and recreation (56%) were top reasons

Liver Transplantation 27 1623–1632 2021 AASLD

Cannabis Use in Potential LT Candidates

- Retrospective Cohort Study
  - 1999-2007
  - 55 MJ users, 1334 nonusers
- MJ users
  - younger, male
  - more likely to have HCV
  - less likely to receive a LT
- **Similar survival rates**

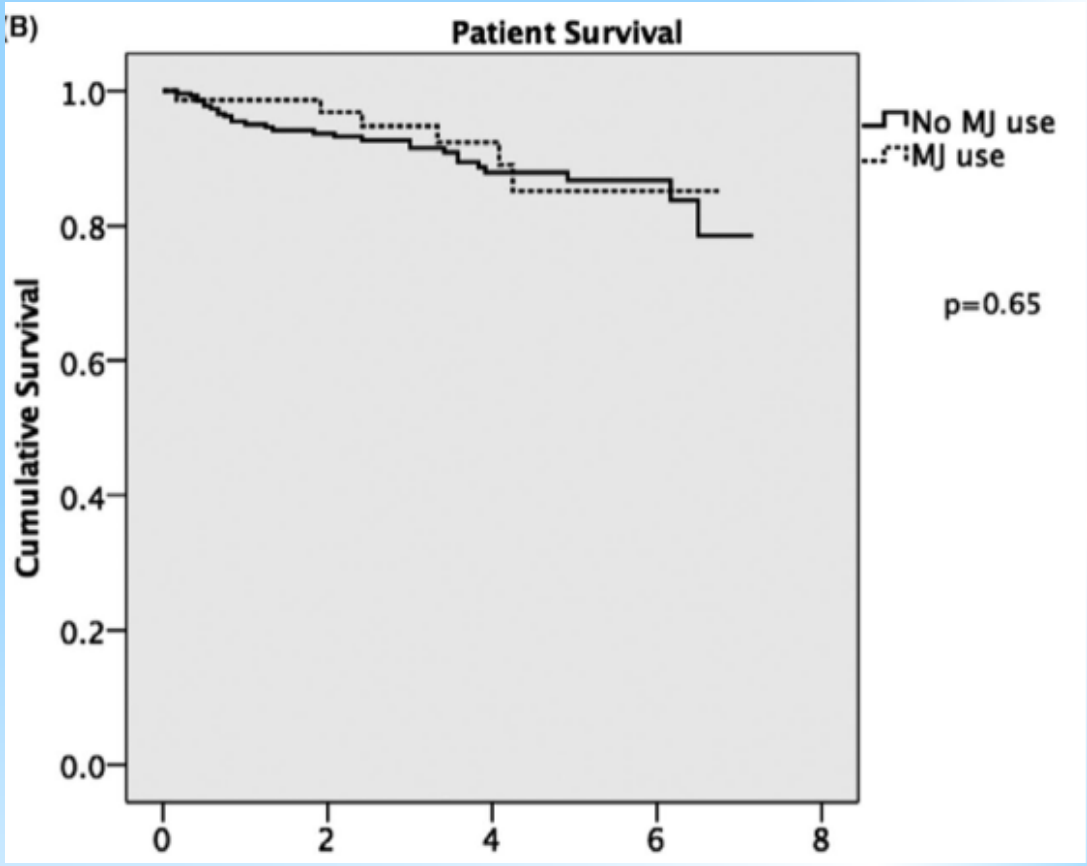


Ranney et al. American Journal of Transplantation 2009; 9: 280–285

Marijuana use among adult liver transplant candidates and recipients

Alisa Likhitsup[1] | Naba Saeed[1] | Gerald Scott Winder[2,3] | Ammar Hassan[1] | Christopher J Sonnenday[3] | Robert J Fontana[1]

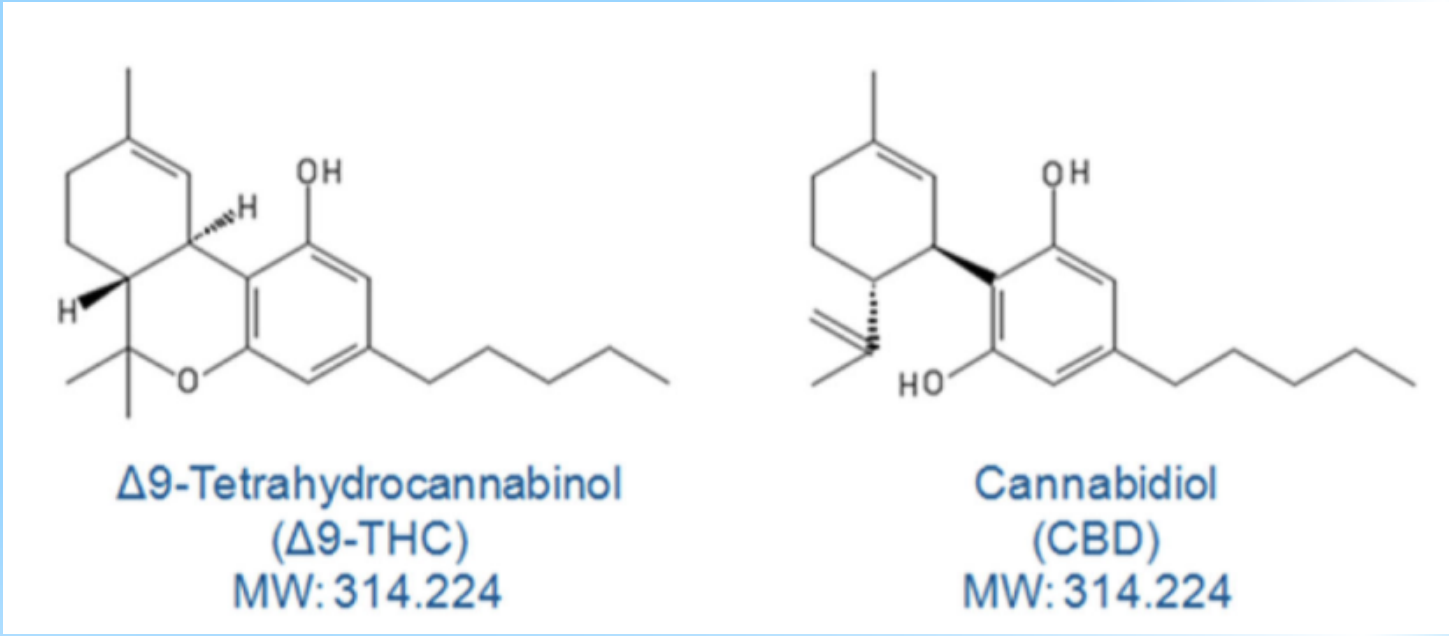
* Incidence and pre/post-LT outcomes
  * self-reported history of MJ use
* 2690 LT candidates
  * 23% history of MJ use
  * 11% use w/in last 12 mos
* MJ use among LT candidates is increasing
* MJ users vs non-users
  * **Similar survival**
  * **Greater burden of psychosocial issues**
  * **Longer median time to listing**



Clinical Transplantation. 2021;35:e14312.

Cannabinoids

* Endocannabinoids
* Phytocannabinoids
* Synthetic Cannabinoids



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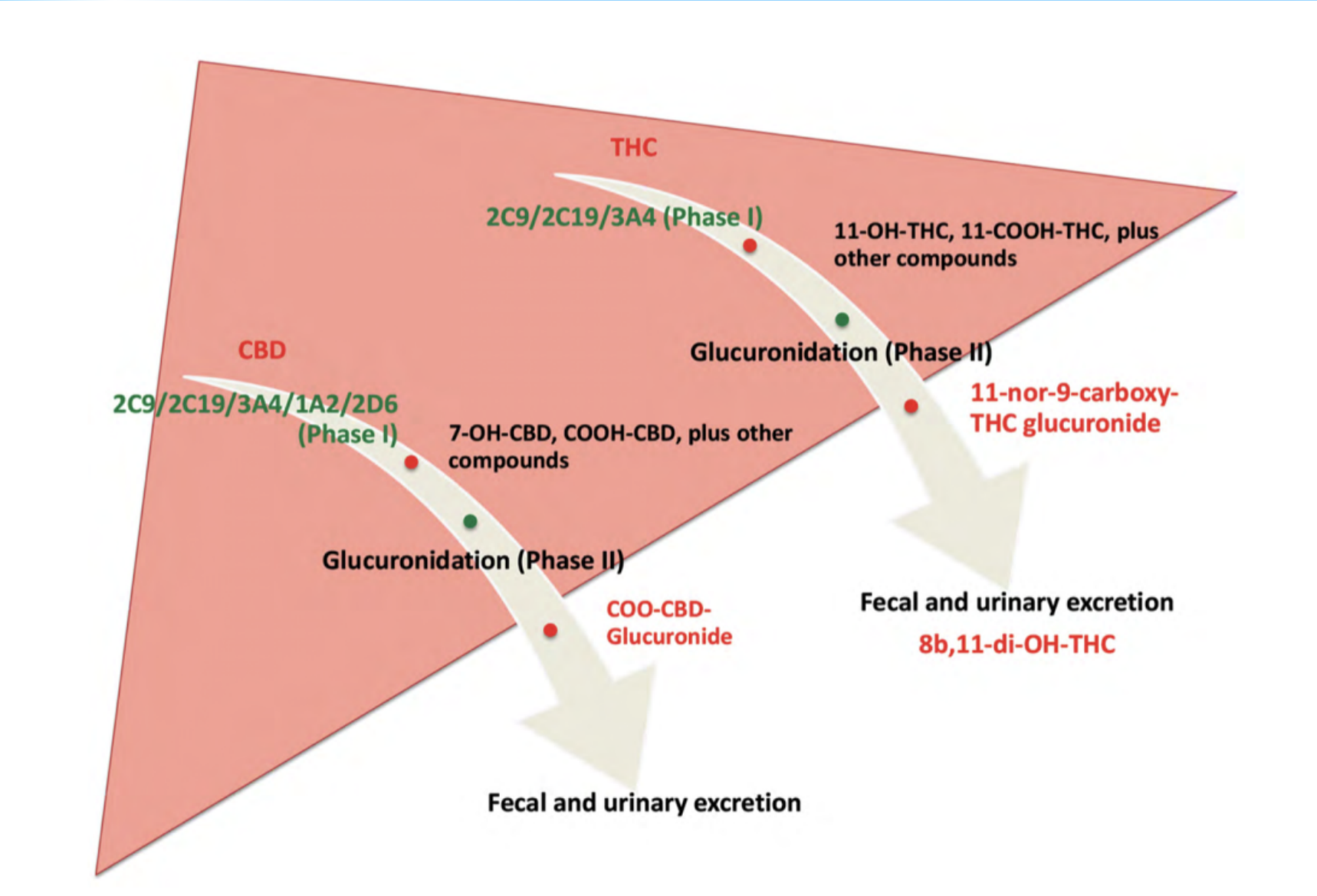
Nie et.al, 2019. "*Journal of the American Society for Mass Spectrometry* 30 (5): 719–30.

Cannabinoids: Pharmacokinetics

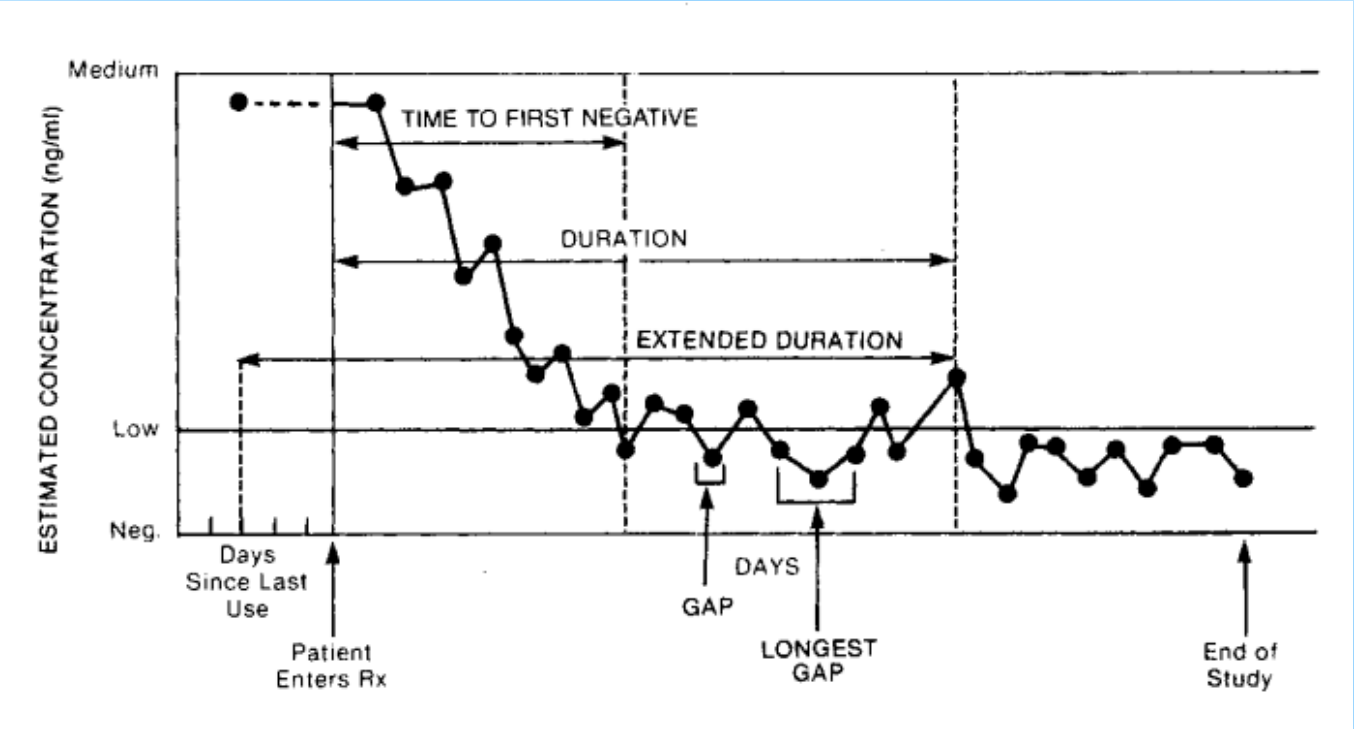
- ABSORPTION
  - **Inhalation**:
    - Bioavailability ~10-35%
    - peak plasma levels ~3-10min
    - Large inter/intrasubject variability
  - **PO**:
    - Bioavailability ~6%
    - peak plasma levels ~120min
  - **Dermal**:
    - very low BA
    - CBD > THC
- DISTRIBUTION
- Blood flow
  - Adipose tissue
  - Vd
    - CBD = 31L/kg
    - THC = 10L/kg
  - High protein binding (>95%)

Lucas et al, 2018. *British Journal of Clinical Pharmacology* 84 (11): 2477–82.



* THC and CBD
  * Fast Initial $T_{1/2}$
    * ~6 min
  * Terminal $T_{1/2}$
    * THC ~22 hrs
    * CBD ~1-5 days

Zhu et al, 2019. *Canadian Liver Journal* 2 (3): 51–57.



	Time to first negative result (days)	*Duration (days)*	*Extended duration (days)*	*No. of negative gaps*	*Length of longest negative gap (days)*
All subjects (n = 86)					
EMIT-d.a.u.					
$\bar{X}$	16.0	27.1	32.0	2.6	3.4
SD	10.7	16.6	18.1	1.8	2.7
Range	3-46	3-77	6-81	0-8	0-10*

Ellis et al, 1985. *Clinical Pharmacology and Therapeutics* 38 (5): 572–78.

Urine Cannabinoid Metabolite Analysis

- Positive Test (usually 15-20 ng/mL)
  - Usually tests for primary metabolite THC-COOH (much longer detection time in urine)

- Dependent upon
  - Extent/duration of THC exposure/use
  - Time since last exposure
  - Hydration status (sample dilution)

  - **Effect of chronic liver disease?**

Connors et al, 2020. "*Journal of Medical Toxicology: 1*6 (2): 240–42.

Lucas et al, 2018. *British Journal of Clinical Pharmacology* 84 (11): 2477–82.

Urine Cannabinoid Metabolite Analysis

- Positive test - What does it mean?
  - THC has been present in the body
  - Does NOT indicate recent use or specific timing
  - CANNOT:
    - Indicate exposure route, source, dose, and intentional/accidental nature
    - Reliably identify synthetic cannabinoids or CBD
    - Determine clinical impairment

Connors et al, 2020. "*Journal of Medical Toxicology: 1*6 (2): 240–42.

Lucas et al, 2018. *British Journal of Clinical Pharmacology* 84 (11): 2477–82.

Urine Cannabinoid Metabolite Analysis

- Immunoassay
  - Poor specificity
    - Cross-reactivity of similar/same epitope can lead to false-positive
  - All positive results should be confirmed

- In liver transplantation tandem chromatography/mass spectroscopy is the gold standard

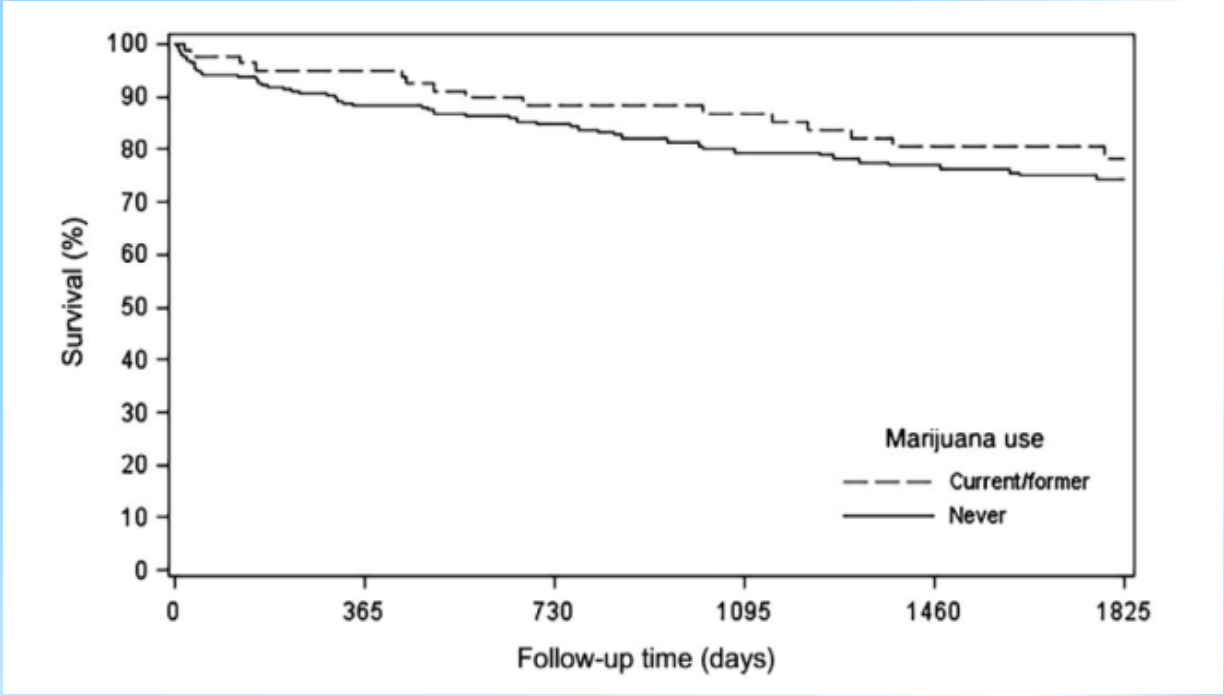
Connors et al, 2020. "*Journal of Medical Toxicology: 1*6 (2): 240–42.

Lucas et al, 2018. *British Journal of Clinical Pharmacology* 84 (11): 2477–82.

Marijuana Consumption in Liver Transplant Recipients

Pablo Serrano Rodriguez [1], Paula Diane Strassle,[1] Alfred Sidney Barritt IV [3], Randall Watkins,[2] David A. Gerber,[1] Paul Hideyo Hayashi,[3] and Chirag Sureshchandra Desai [1]

* Retrospective analysis of MJ use on posttransplant M&M and graft survival
  * 26% MJ smokers
  * 20% both marijuana and tobacco smokers
* No difference between MJ users (past/current) and never-users
* **Pre- LT MJ use, past or current, did not impact LT outcomes**



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Liver Transplantation 25 734–740 2019 AASLD.

History of marijuana use does not affect outcomes on the liver transplant waitlist

Prashant Kotwani, MD[1], Varun Saxena, MD[1], Jennifer L. Dodge, MPH[2], John Roberts, MD[2], Francis Yao, MD[1], and Bilal Hameed, MD[1]

* Retrospective cohort study at a large LT center
* Evaluated risk of waitlist mortality/de-listing, likelihood of LT among prior MJ users, prevalence/factors associated with MJ use
  * MJ use by self-report or positive UDS, ongoing use not permitted
* 48% used MJ (7% recent, 41% prior), often with alcoholic cirrhosis and Hep C
* MJ use not associated with worse outcomes on the LT waitlist (recent illicit drug use was)

Kotwani et. Al, Transplantation. 2018 May ; 102(5): 794–802.

What does this all mean?

* MJ use is increasingly common, and to a lesser degree accepted, in pre-LT patients
* Policies regarding MJ have become more flexible but remain highly variable among programs
* According to retrospective cohort studies, pre-LT MJ use (past or current) does not impact LT outcomes on the waitlist or post-transplant
* Pre-LT MJ use tends to be associated with longer waitlist times, alcohol-induced or HCV cirrhosis, and/or more psychosocial instability
* Prospective studies are needed!

Kotwani P et. Al; Transplantation. 2018 May;102(5):794-802.

OBJECTIVE 2

* Identify clinical circumstances in patients with ALD that may result in variable test results at different times after last alcohol or marijuana consumption in order to increase accuracy and effectiveness of drug testing in those undergoing LT evaluation

When Choosing a Test That's Right For You, Consider These 5 Factors:

1. Range of testing (drug panel)
2. Desired window of detection
3. Specimen type
4. Level of adulteration potential
5. Notice required before collection

Enter your search term

https://www.usdtl.com/media/peth-resourcesadd text

Alcohol Testing

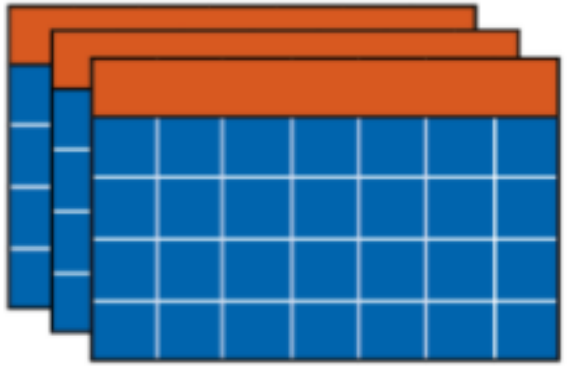
Think 3/3/3:

- 3 days
- 3 weeks
- 3 months

Nail & Hair

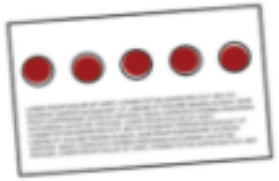
Indicates multiple occurences of high alcohol consumption within an average of 3 months of collection

3 Months

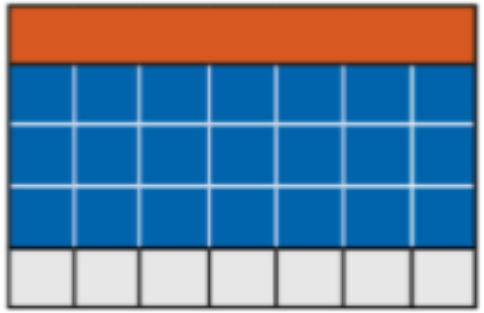


Blood

Indicates high alcohol consumption within an average of 3 weeks of collection



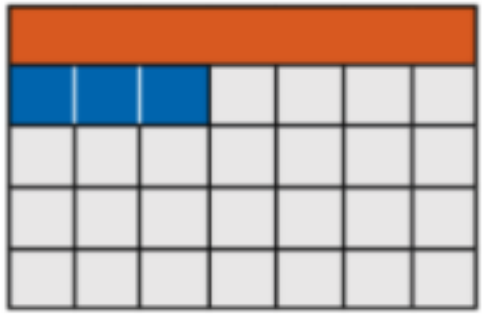
3 Weeks



Urine

Indicates alcohol consumption within an average of 3 days of collection

3 Days



https://www.usdtl.com/media/infographics/choosing-the-right-testto add

What is PeTH!

- an alcohol-derived phospholipid
- formed from phosphatidylcholine
- mainly in RBCs
- enzyme = phospholipase D
- requires alcohol to catalyze

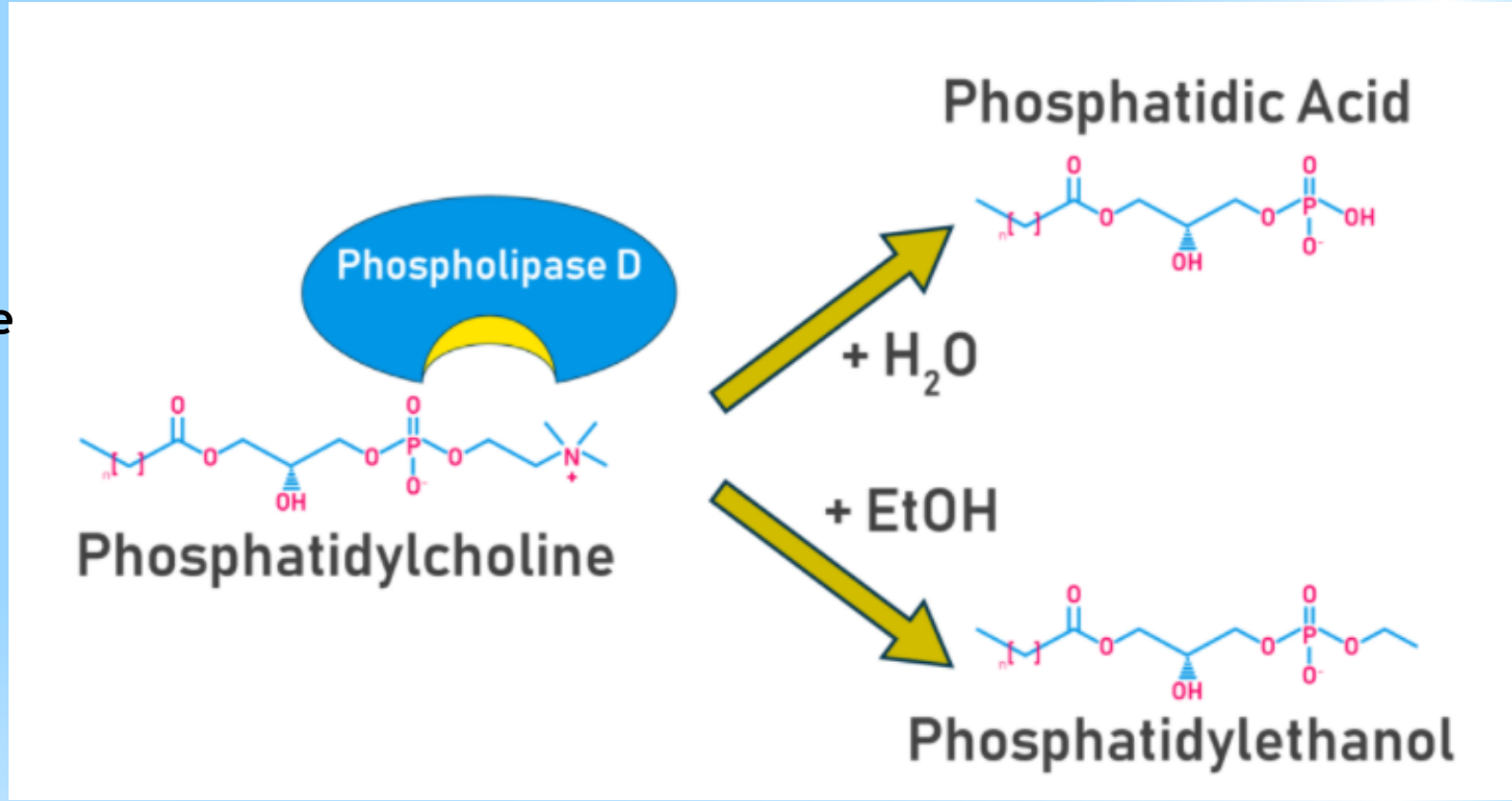


Figure 1: Schematic of the action of PLD on phosphatidylcholine. Phosphatic acid and phosphatidylethanol are alternately produced depending on the use of water or ethanol, respectively, in the reaction.

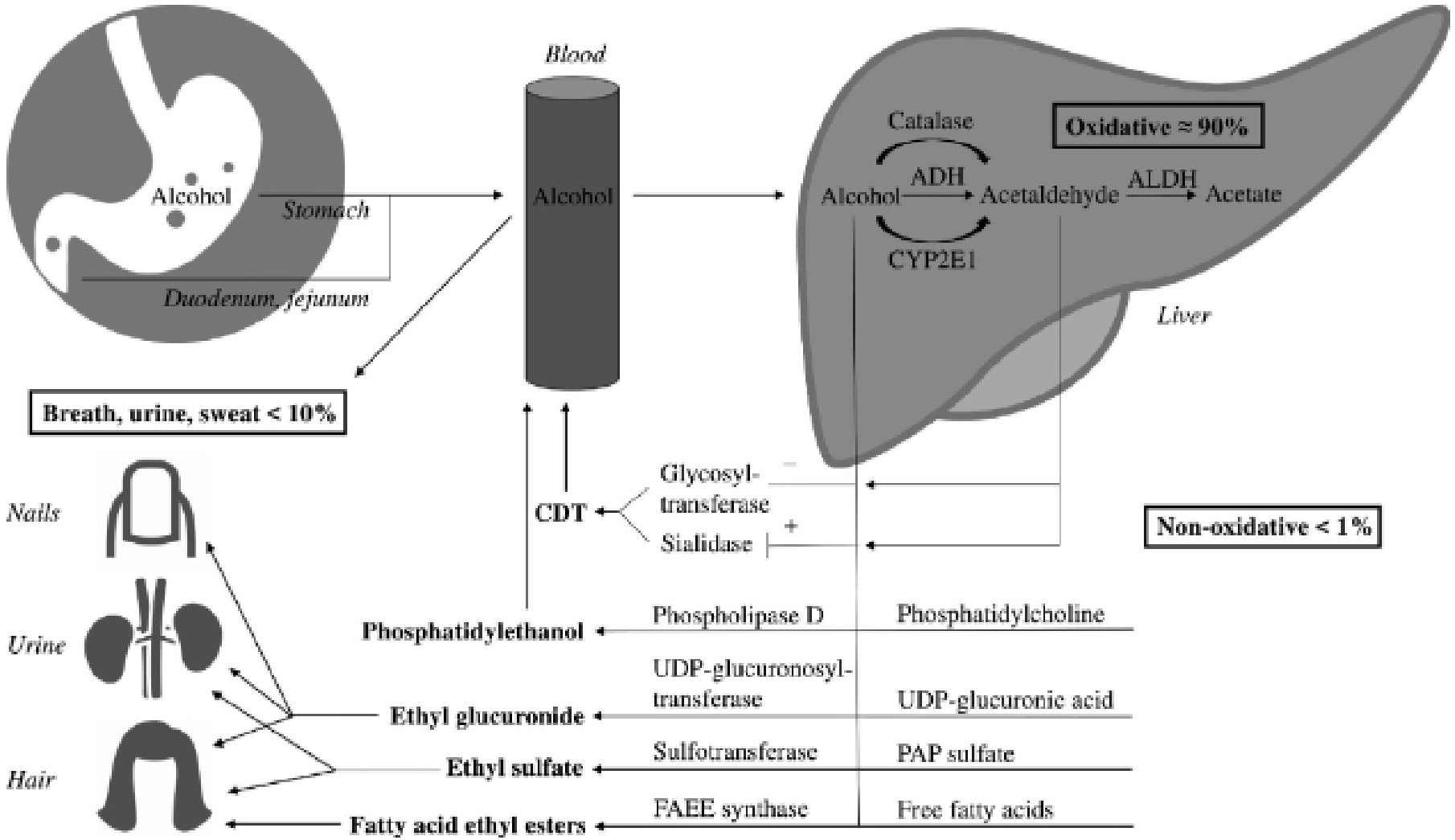


Fig. 1. Schematic overview of the oxidative and nonoxidative alcohol metabolism. ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1; FAEE, fatty acid ethyl ester; PAP sulfate, 3′-phosphoadenosine-5′-phosphosulfate; UDP-glucuronic acid, uridine 5′-diphosphoglucuronic acid; UDP-glucuronosyltransferase, uridine 5′-diphosphoglucuronosyltransferase (UGT).

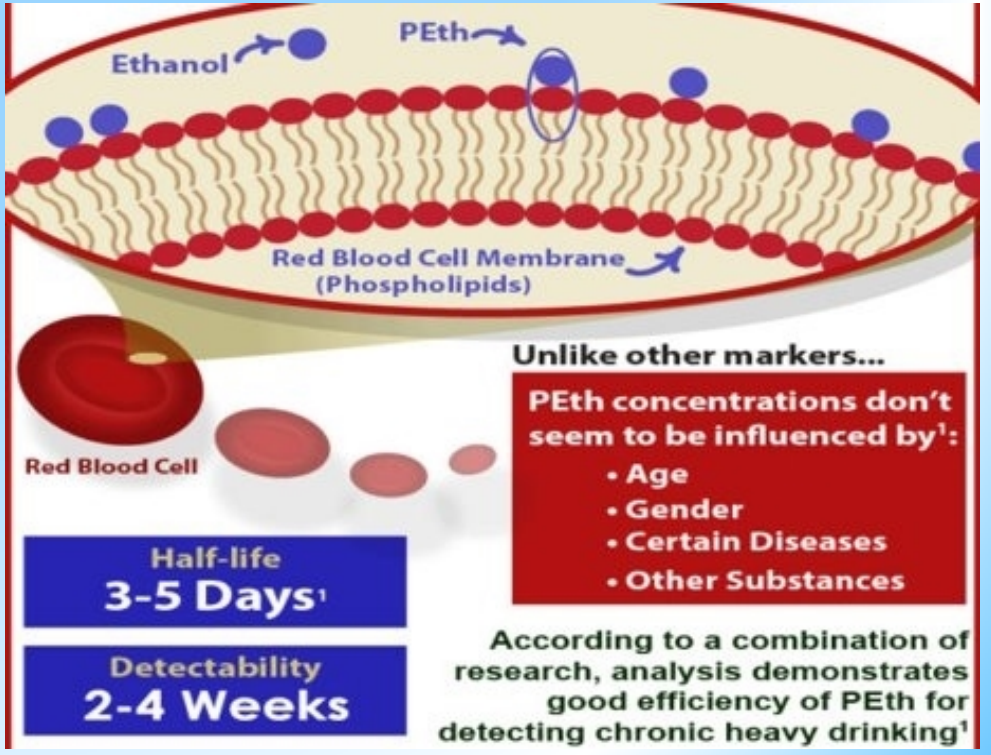
Pros and Cons of PeTH Testing

Strengths

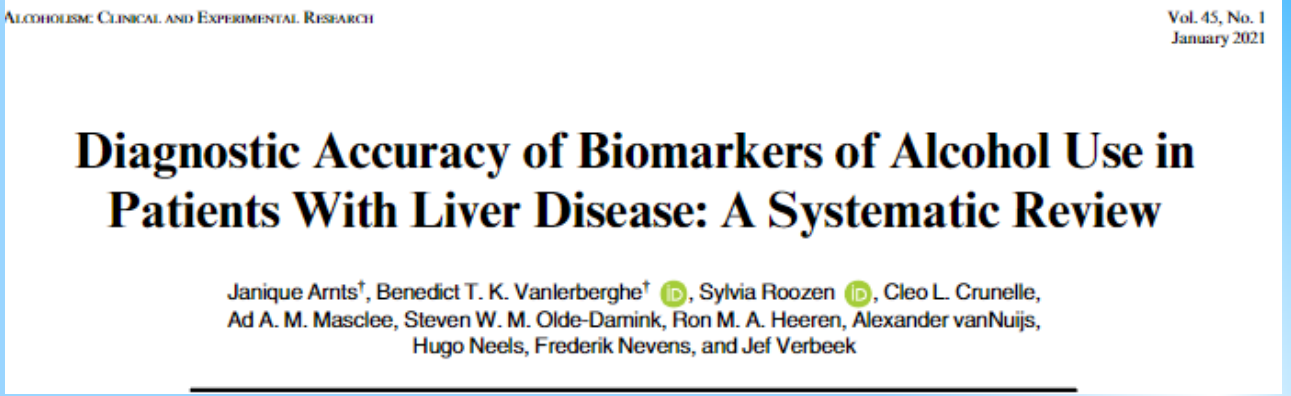
* Higher specificity compared to other tests
* Longer T ½ (4-12 days)
* Longer detection window (2-4 wks) but 8 week upper limit

Limitations

* Subject to Internal Variability
* False elevations in ALD



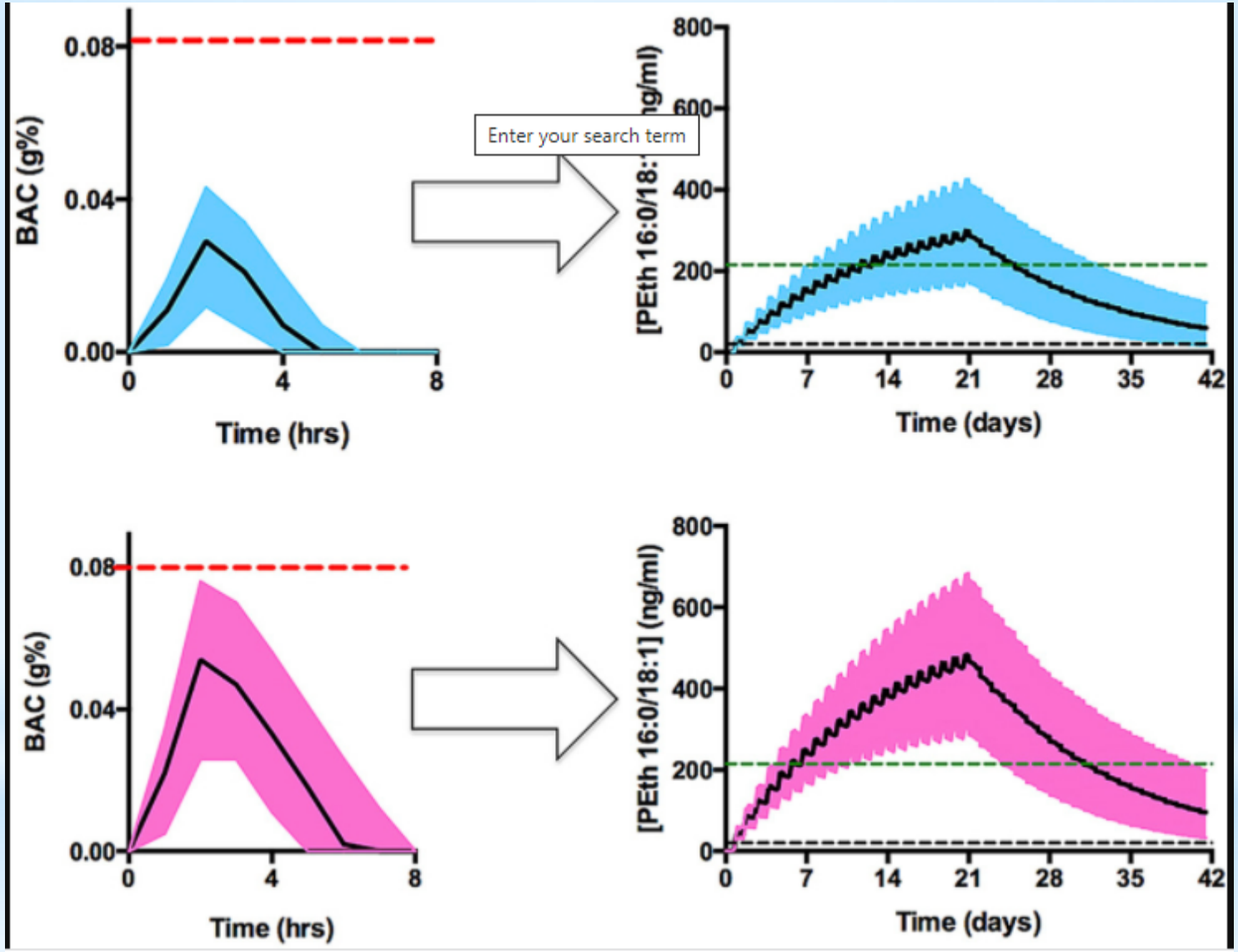
PeTH!Half-Life À


Alcoholism: Clinical and Experimental Research
Vol. 45, No. 1
January 2021

Diagnostic Accuracy of Biomarkers of Alcohol Use in Patients With Liver Disease: A Systematic Review

Janique Arnts†, Benedict T. K. Vanlerberghe†, Sylvia Roozen, Cleo L. Crunelle, Ad A. M. Masclee, Steven W. M. Olde-Damink, Ron M. A. Heeren, Alexander vanNuijs, Hugo Neels, Frederik Nevens, and Jef Verbeek

- can detect a single drinking event over the last 3-12 days (Schr€ock et al.,2017).
- After longer periods of drinking (5 subsequent days with BAC=1 g/l after 3 weeks of abstinence), T ½ = 4-10 days in healthy sub-jects (Gnann et al., 2012).
- Patients with chronic alcohol abuse might have shorter PeTHT 1/2 (4 days) Varga et al., 2000), but heavily drinking subjects can have a POS PeTH after 5-6 wks of abstinence (Stewart et al., 2014)



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Journal of *Clinical Medicine*

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Article

Phosphatidylethanol for Monitoring Alcohol Use in Liver Transplant Candidates: An Observational Study

Pablo Barrio [1,*], Antoni Gual [1], Anna Lligoña [1], Lidia Teixidor [1], Wolfgang Weinmann [2], Michel Yegles [3] and Friedrich M. Wurst [4]

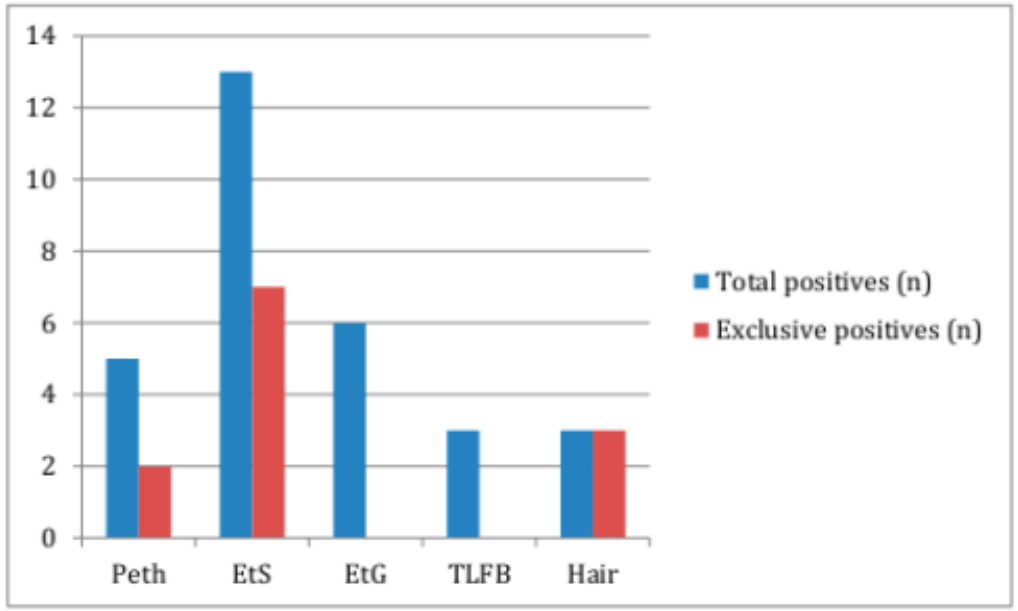
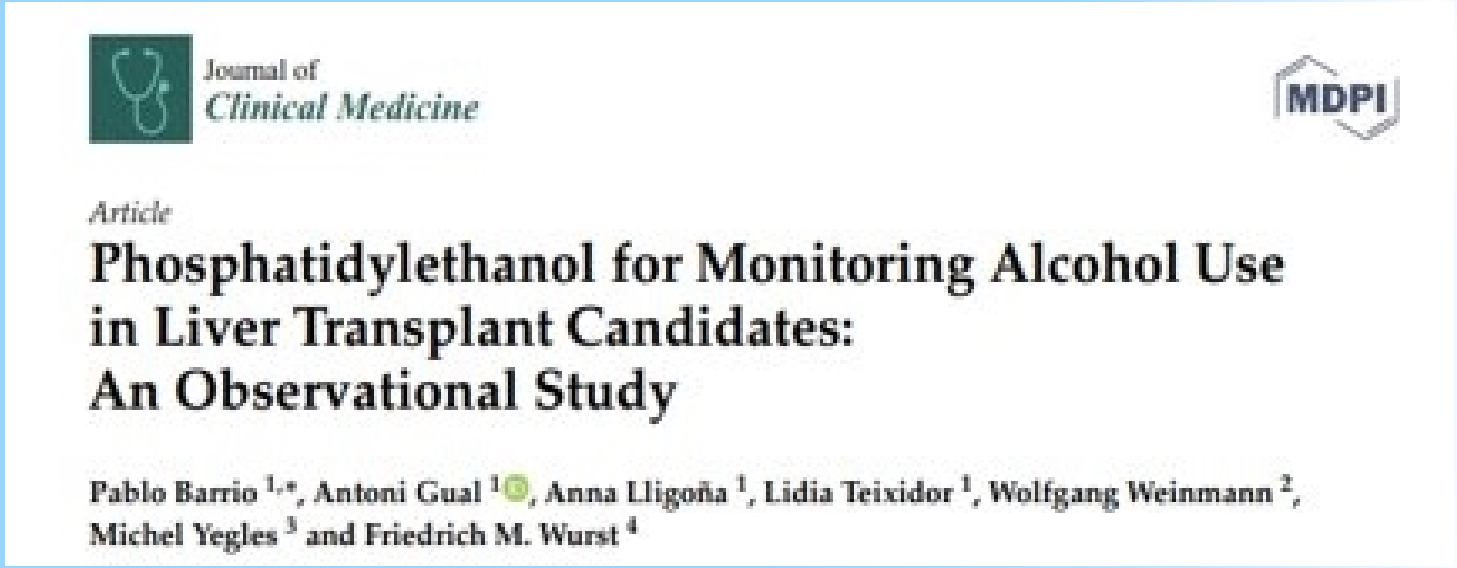


Figure 3. Barchart showing total and exclusive positives for each biomarker. EtG: ethylglucuronide; EtS: ethylsulfate; PeTH: phosphatydilethanol, HEtG: hair ethylglucuronide; TLFB: timeline follow back.

Review of Literature!

* 2 studies in ALD
* 2 studies including pre- and post-LT patients



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* overall, PeTH provides significant added value w/higher sensitivity in patients w/ALD

Alcohol Alcohol. 2009, 44, 464–467; Alcohol. Clin. Exp. Res. 2014, 38, 1706–1711
Transpl. Int. 2017, 30, 611–620.Alcohol. Clin. Exp. Res. 2017, 41, 857–862.

What To Do with Results

- Low sensitivity biomarkers may require several months to detect alcohol consumption
  - cut-off of 20 ng/mL is std
- vs
- Direct biomarkers like PeTH, a single point assessment may be enough
- PeTH testing should not be viewed as a decision rule to exclude pts from LT listing
  - a tool for early detection and treatment

New Alcohol Biomarkers. New challenges. Alcohol Alcohol. 2018, 53, 762–763.

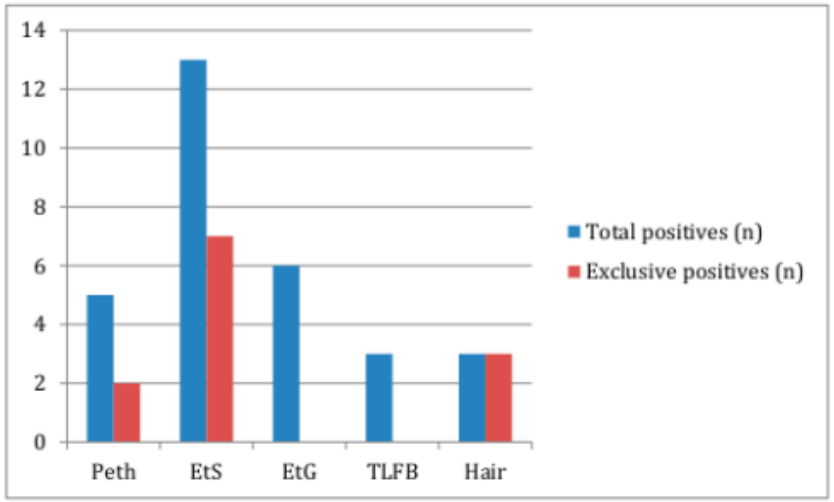


Figure 3. Barchart showing total and exclusive positives for each biomarker. EtG: ethylglucuronide; EtS: ethylsulfate; PeTH: phosphatydilethanol, HEtG: hair ethylglucuronide; TLFB: timeline follow back.

* Major findings:
  * Most frequently POS biomarker was EtS, followed by EtG and PEth.
  * Peth POS in 5 pts and 1 FALSE POS -> patient admitting drinking 1 week prior and POS EtG and EtS also
  * These results diverge from previous studies in same population ->
    * PEth was the **MOST Frequent POS biomarker.**
  * Fleming et. Al did not analyze any other biomarker besides PEth so unable to compare, but found 20% POS PEth samples
    * rates of positive self-report are similar (8 vs. 6%)
    * Alcohol in. Exp. Res. 2017, 41, 857–862.

Transpl. Int. 2017, 30, 611–620.

ASAM Appropriate Use of Drug testing

- “All physicians (and others) involved in drug testing should determine the questions the test are intended to answer before the testing is administered and should have a plan for what to do with the results"
- False accusations/interpretations regarding use
  - Delayed medical care, relapse
  - Disruption of the therapeutic rapport between patients and physicians
  - Highlight inequalities in healthcare systems

https://www.asam.org/quality-care/clinical-guidelines/drug-testing

ASAM Appropriate Use of Drug Testing

- Self reported substance use
  - Drug testing should be used in combination with a patient's self-reported information about substance use
    - In transplant: self-report or other subjective tools may not be reliable
      - Fear of stigmatization
      - Potential denial of a life-sustaining intervention.

https://www.asam.org/quality-care/clinical-guidelines/drug-testing

ASAM Appropriate Use of Drug Testing

- A positive drug test does not diagnose a SUD and a negative test result does not rule out a SUD
  - All tests have some rate of false-positive and false-negative outcomes
- Quantitative definitive tests
  - Use caution to draw conclusions about the amount or pattern of a patient's substance use
- When test results are unclear, communicate with the testing laboratory to properly interpret them

https://www.asam.org/quality-care/clinical-guidelines/drug-testing

AASLD PRACTICE GUIDELINE

Evaluation for Liver Transplantation in Adults: 2013 Practice Guideline by AASLD and AST

- A 6-mos min abstinence period is commonly enforced
  - Allows addiction issues to be addressed
  - With recent alcohol consumption or acute alcoholic hepatitis, may allow for spontaneous recovery and obviate the need for LT
  - May reduce the risk of AR
- Acute alcoholic hepatitis : No response or continued deterioration
  - Early LT (prior to abs. x 6 mos) is controversial but has been shown to improve survival
  - **Post-LT alcohol related aftercare and counseling may be considered**
- 6 mos abstinence w/out full assessment or treatment does not therapeutically address a potential AUD and abstinence alone may not meet LT listing criteria.

AASLD Practice Guideline. 2013

* **Address and Evaluate**
  * **Psychiatric Health**
  * **Substance Use Disorder**
  * **Social Support Network**

* While some programs exclude patients with active MJ use from LT, this remains controversial
  * Concerns re: AEs on the course of liver disease

ASAM Ethical Use of Drug Testing

- Recommended as a therapeutic tool as part of evidence-based addiction treatment.
  - Not a punitive measure
  - Screening vs definitive tests
- Used only when clinically necessary
  - Document rationale and clinical decision making
- Definitive testing when results are needed to inform clinical decisions and potentially alter care plan
  - Scope justified by the patient's clinical status and the need for information
- Providers should have knowledge and proficiency in drug testing
  - Consider using a toxicologist or clinician who is knowledgeable in toxicology

https://www.asam.org/docs/default-source/public-policy-statements/2019-ethical-use-of-drug-testing-in-the-practice-of-addiction-medicine.pdf?sfvrsn=75bb4bc2_4

Ethics of Alcohol/Substance Abstinence Criteria

- Establishing diagnosis
  - Severity
  - History, collateral
- Consider a combination of documentation of abstinence in addition to
  - Substance use disorder treatment
  - Transplant support groups
  - Evaluation of psychosocial factors and commitment to treatment/transplant
  - Risk of relapse
    - Prediction tools

Bramstedt, Katrina A. *Journal of medical ethics* 32.5 (2006): 263-265.

Beresford, Thomas P. *Alcohol and Alcoholism* 53.2 (2018): 135-144.

Predicting Low Risk for Sustained Alcohol Use After Early LT for Acute Alcoholic Hepatitis: The Sustained Alcohol Use Post–LT (SALT)

- Sustained Alcohol Use Post-LT **(SALT) score** (range: 0-11):
  - >10 drinks per day at initial hospitalization (+4 pts)
  - multiple prior rehabilitation attempts (+4 pts)
  - prior alcohol-related legal issues (+2 pts)
  - prior illicit substance abuse (+1 pt)

- SALT score ≥ 5 ---> 25% PPV (95% CI: 10%-47%) and
- SALT score < 5 ---> 95% NPV (95% CI: 89%-98%)

Lee et. Al, 2016

Topics for Debate & Discussion

- Topic #1: MJ use should NOT be permitted in patients with ALD who are undergoing LT evaluation

- Topic #2: MJ testing SHOULD be a component of the LT evalution process

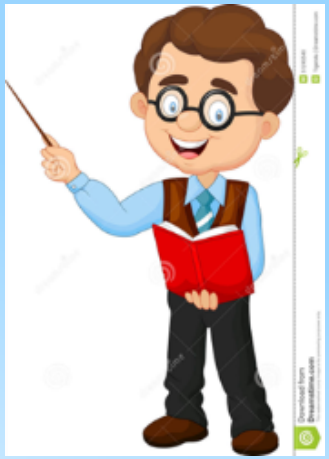
- Topic #3: Patients with ALD undergoing LT evaluation SHOULD be monitored for recent, ongoing or relapse to alcohol consumption and the best ways to monitor include drug testing

Debate RULES

1) *RESPECT* your fellow debaters
2) *NO* swearing
3) *IGNORE* or respond politely to trolls
4) Make *UNBIASED* picks
5) *NO* petty ratings or activity
6) *NO* repeat picks or forum topics
7) *HAVE FUN!* Learn something new ☺

*Topic #1:

*MJ use should NOT be permitted in patients with ALD who are undergoing LT evaluation?



Dr. Pueringer

Dr. Weiss

AFFIRMATIVE #1: Dr. Pueringer

* **Health Effects:**
  * MJ has known harmful effects and patients undergoing LT evaluation are particularly vulnerable
* **Prevalence:**
  * MJ users are more likely to use other illicit substances so in some sense it acts as a "gateway drug" to other substance use that we know can have problematic outcomes in pts undergoing LT evaluation

* **CONCLUSION:** Given the health effects and high prevalence of MJ use in this population, patients should be educated about these effects and encouraged to abstain from <u>all use pre and post LT</u>

REBUTTAL #1: Dr. Weiss

* **Possible Benefits to MJ Use:**
  * appetite stimulation
  * analgesia
  * nausea/vomiting

AUDIENCE RESPONSE #1

Topic #2

- MJ testing should be a routine component of the LT evaluation process in patients with ALD

AFFIRMATIVE #2: Dr. Weiss

* **Known Risks/Health Effects of MJ Use**
  * Respiratory, Cognitive, Stroke, and a few isolated cases of aspergillus (contaminated MJ)
  * Endogenous cannabinoids that bind to CB1 and CB2 receptors are upregulated in liver disease
* MJ use can be a gateway to other illicit substance use
* association between MJ smoking
* MJ testing is relatively easy and not costly to obtain thru urine drug testing, monitoring levels

REBUTTAL #2: Dr. Laes

* **Non-Maleficence, Health Care Justice and Informed Consent:**
  * Imposing an arbitrary period of abstinence before being listed for a LT can exacerbate the disease and thereby cause harm
  * It also discriminates against people based on a class of disease
  * Lack of understanding re: the use of CBD or CBD-cont. products that can cross-react with routine IA that test for MJ
  * POS screening test in the EHR that was collected by an outside lab or office may be flagged without confirmatory testing

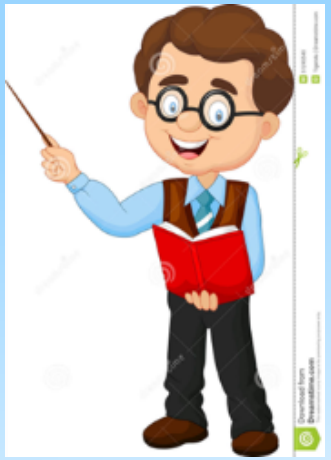
* **Cost and Resource Allocation:**
  * Users vs. Non-Users of MJ don't necessarily have worse outcomes post LT and vs. users of tobacco
  * Nuances of MJ testing, more availability of CBD products with possible health benefits, and legalization of MJ in most states suggests it maybe more cost-effective to reduce MJ testing in pre and post LT patients w/ALD- esp. those who do not have a history of tobacco or other illicit substance use

* **CONCLUSION:**
  * Isolating MJ testing in patients who are otherwise NEG for alcohol and all other substances violates principles of Informed Consent and may not be the most cost-effective use of drug testing
  * Withholding a LT listing in someone who is POS for MJ ONLY violates principles of Non-Maleficence, Health Care Justice

AUDIENCE RESPONSE #2

Topic #3:

- Patients with ALD undergoing LT evaluation should be monitored for recent, ongoing or relapse to alcohol consumption and drug testing is the most accurate way to predict post LT relapse



AFFIRMATIVE #3: Dr. Laes

- Recent alcohol use and post-LT alcohol use have clear associations with worse outcomes in patients awaiting LT or post-LT
- Testing for recent, chronic alcohol use can be easily done using PeTH testing and other alcohol biomarkers

REBUTTAL #3: Dr. Pueringer

- Evidence for a strong correlation between pre- LT abstinence duration and post LT risk for relapse is contradictory and inconclusive
  - ALD transplant recipients have been found to have the same patient and graft survival as non-ALD liver transplant recipients (Lucey, 2014.)
- Definitions of relapse vary and rates can range from 7-95%
- a single-center prospective study found that, by 8 years of follow-up, ~ 50% of ALD patients post-LT had at least 1 drink while only 6–7% fully relapsed in excessive harmful drinking (DiMartini et al., 2010).
- Dumortier et. Al, 2015 placed the recurrence of severe AR at 17% post- LT
  - 1/3 of these heavy drinkers developed rapidly recurrent alcohol-related cirrhosis in < 5 yrs with a poor prognosis and higher mortality

REBUTTAL #3:Dr. Pueringer (cont'd)

- **Conclusion:** Best practices for ALD patients mandates a thoughtful and thorough psychiatric and social evaluation to determine patient-specific factors that might increase risk of post LT relapse
  - goal of managing the AUD aggressively throughout the transplant process.

*SUMMARY

*CME QUESTIONS

1. Can drug testing alone be used to identify a substance use disorder during transplant evaluation

a. Yes, if it is a quantifiable definitive test such as gas chromatography mass spectroscopy .

b. Yes, regardless of whether it is a screening or definitive test

c. **No, drug testing should be used as part of a comprehensive evaluation**

d. No, drug testing has no role in transplant evaluation

2. Phosphatidylethanol (PeTH) is formed in the body by:

a. glucuronidation of alcohol catalyzed by uridine 5'-diphosphoglucuronosyltransferases

b. enzymatic sulfonation of alcohol by sulfotransferases

c. **A transphosphatidylation reaction catalyzed by phospholipase D in the presence of alcohol**

d. Alcohol related inhibition of glycosyltransferases and induction of sialidases

3. What is the main THC (delta 9 tetrahydrocannabinol)metabolite that urine drug testing measures?

a. **11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH)**

b. Cannabidiol (CBD)

c. 11-hydroxy-$^{\triangle 9}$-tetrahydrocannabinol (11-OH-THC)

d. delta 8 tetrahydrocannabinol

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