Can Study Protocols Protect Patients with Liver Diseases from Serious DILI?

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Disclosures

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Consultant-Advisor: Abbvie, BMS, Excalenz, Janssen, Genentech-Roche, Gilead, Globeimmune, HepQuant, HEPATIQ, Immuron, Intercept, Merck

NIH NIDDK: Member of DILIN DSMB and Executive Committee of LTCDS

Speakers' Bureaus (CME Only): Chronic Liver Disease Foundation (CLDF), Gastroenterology and Liver Association (GALA), ViralEd

Background

- Identification of drugs or biologics with potential to cause serious, life-threatening DILI requires causality assessment and comprehensive testing for alternative etiologies in each suspected case[1].
- Since idiosyncratic DILI is rare, prediction of the risk of serious DILI post-marketing relies on identification of cases of interest meeting Hy's Law criteria during phase II-III clinical trials[2].
- Subjects with pre-existing, chronic liver diseases (CLDs), with or without cirrhosis, are challenging because current FDA guidance is based largely on criteria for studies that exclude subjects with abnormal liver tests [3].
- CLDs do not increase overall susceptibility for DILI, but multiple exceptions suggest that additional examples will be identified in future clinical trials [2].
- DILI in subjects with CLD is worrisome because subjects with reduced hepatic functional reserve are less likely to recover and more likely to die[2,3].
- The probability of subjects with CLDs enrolling in clinical trials is increasing, especially in therapeutic trials targeting components of the metabolic syndrome (enriched for NAFLD), antimicrobials, specific CLDs, complications of cirrhosis and hepatocellular carcinoma.

[1]Avigan MI. Semin Liver Dis 2014; 34: 215-26
[2]http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174190.pdf
[3]Chalasonai N, et al Gastroenterology 2015; 148: 1340-52

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Key Questions:

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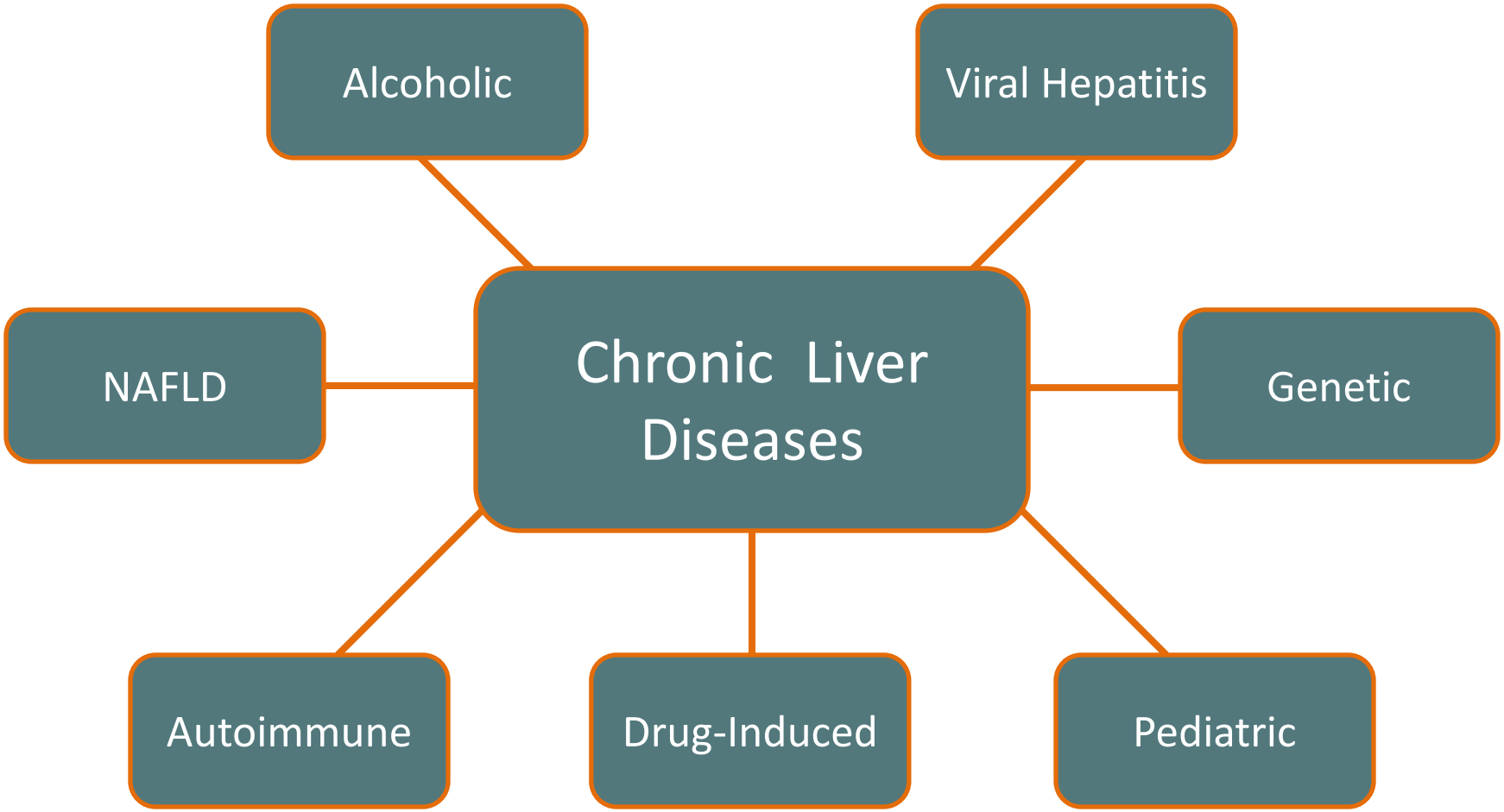
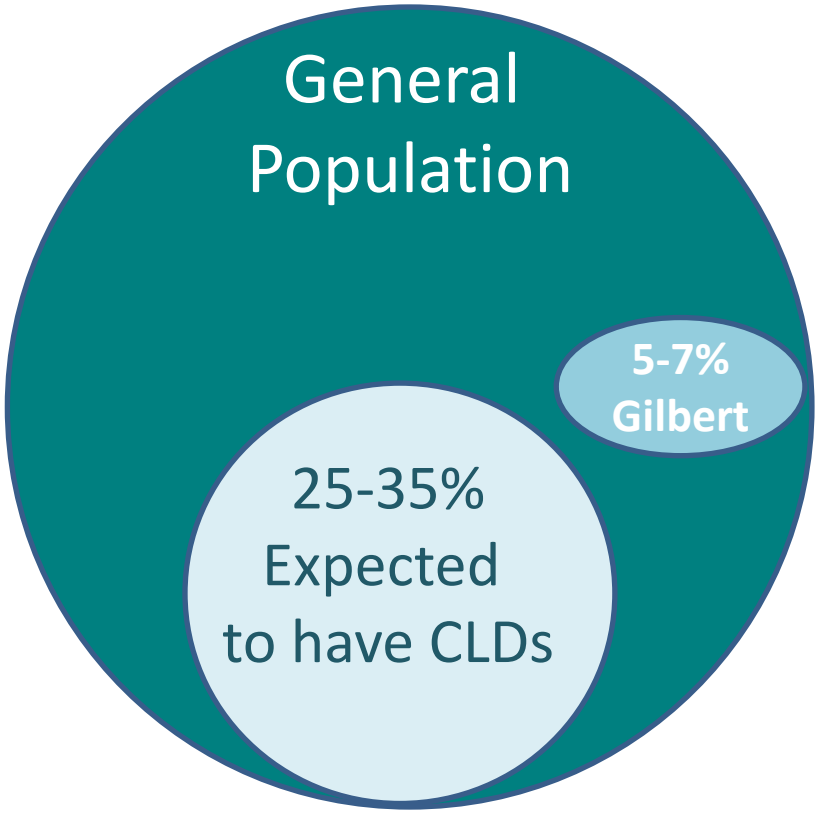
4. What improvements in protocols can provide greater protection from serious DILI in patients with CLD, including cirrhotics?
    a. Assessment pre-enrollment
    b. Monitoring on treatment
    c. Functional assessment of suspected DILI and stopping rules

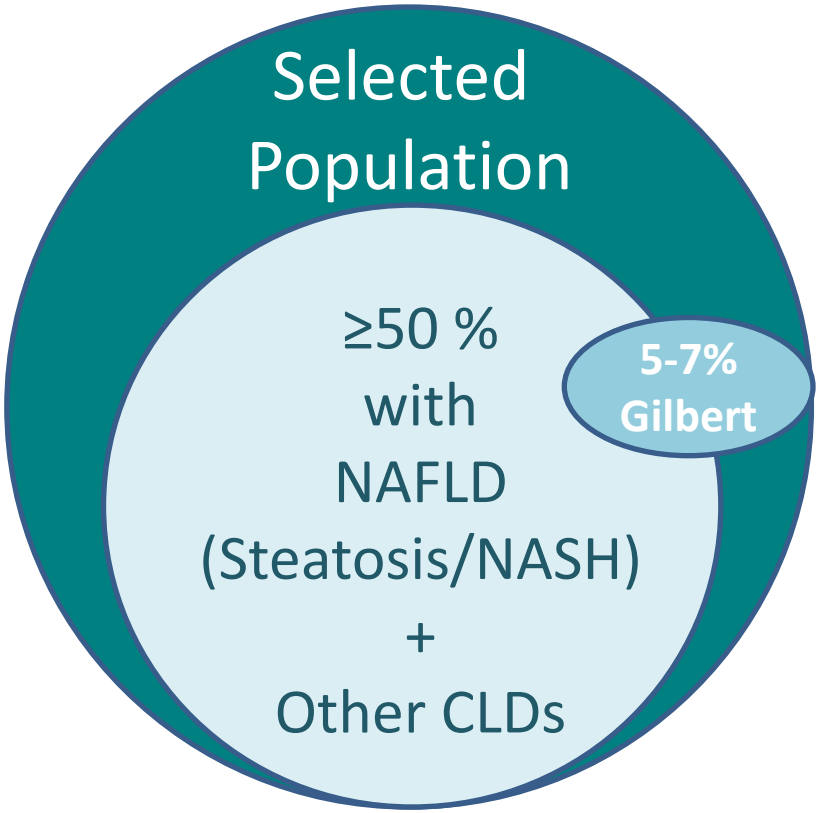
Etiologic Spectrum of Chronic Liver Diseases with Risk of Progression to Cirrhosis



Probability of Enrolling Americans with CLDs with or without Cirrhosis in Clinical Drug Trials



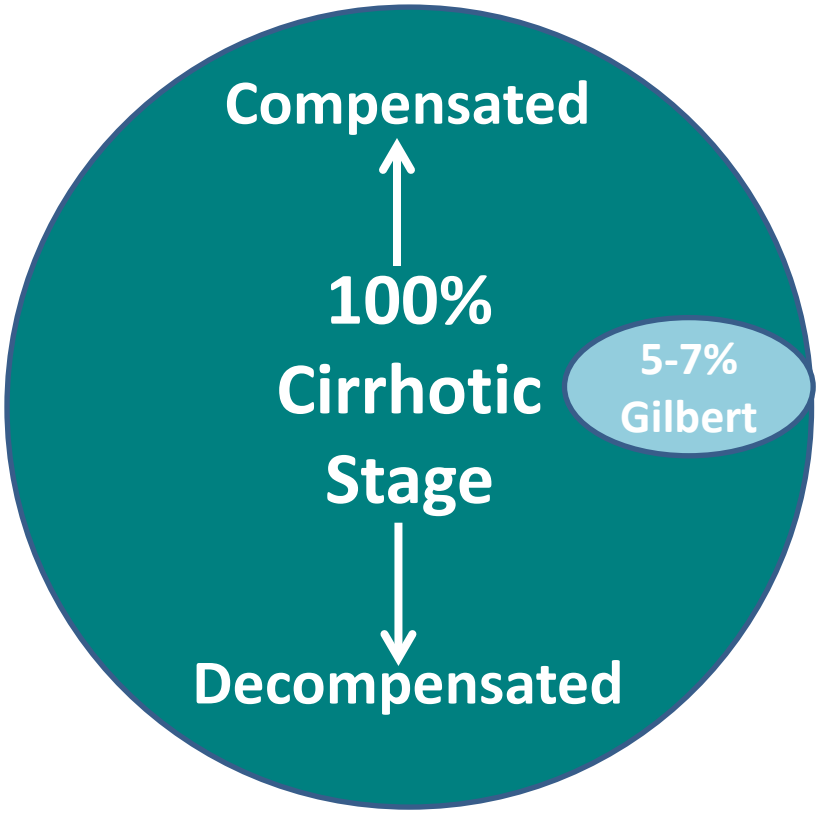
General Drug Development



Drug Development

- Obesity
- DM-2
- Hyperlipidemia
- Hypertension
- Gout

Certainty of Enrolling Americans with CLDs with or without Cirrhosis in Clinical Drug Trials



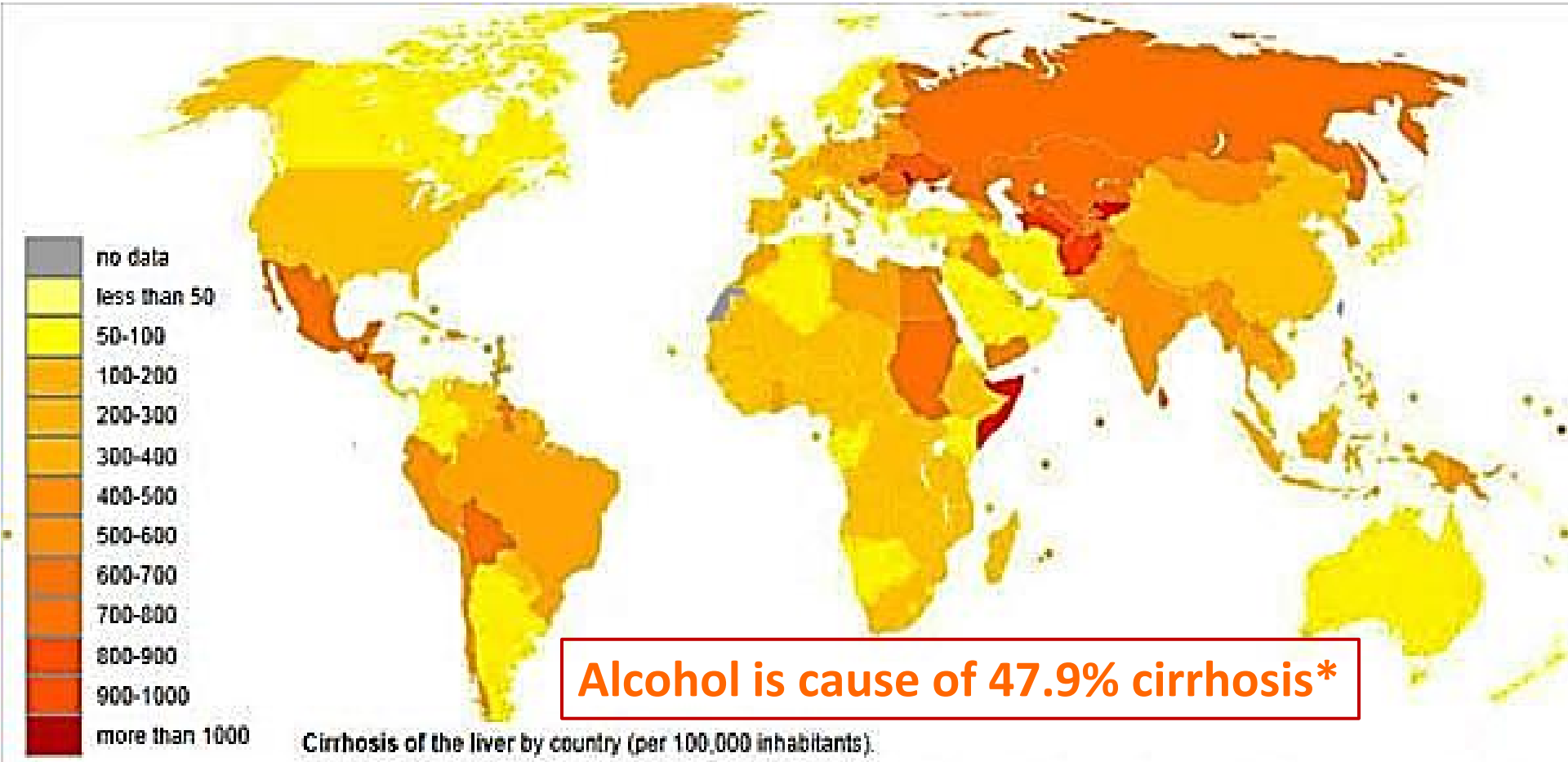
Drugs for specific CLDs

- HBV±HDV, HCV±HIV, HEV
- NAFLD/NASH
- AIH, PBC, PSC
- Genetic

Drugs for Cirrhosis/Complications

- Cirrhosis
- PVHTN
- Varices
- HE
- HCC
- Antifibrotics

Cirrhosis: Global Prevalence per 100,000 Persons



Alcohol is cause of 47.9% cirrhosis*

* Rehn H, et al J Hepatol 2013; 59:160-68

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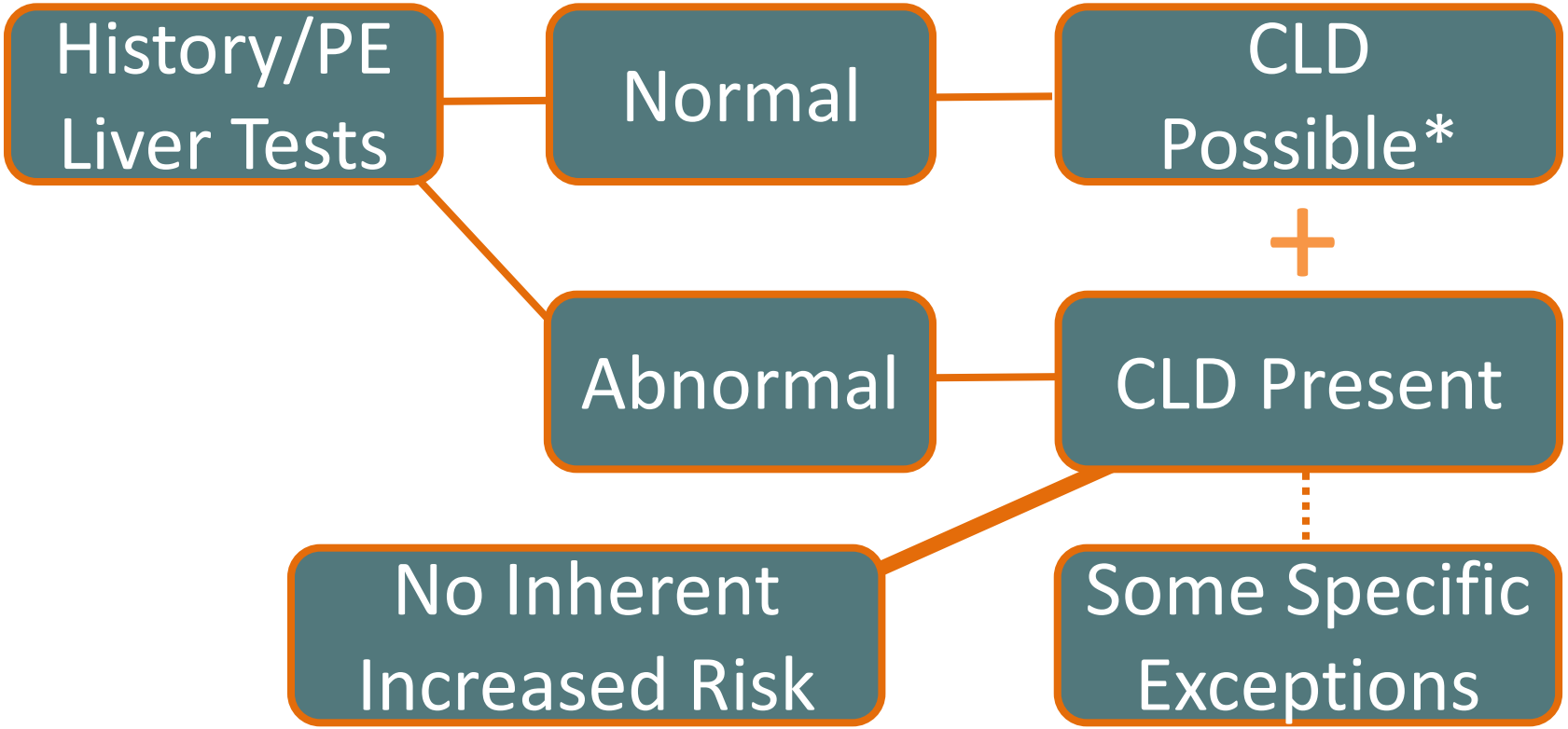
Risk of DILI in Subjects with CLDs?
Increased Susceptibility?



*CLDs with potential for Liver Tests WNL: HBV, HCV, NAFLD, AIH,PBC, PSC, burned out cirrhosis (e.g. ETOH, HBV)

Gupta NK, Lewis JH Aliment Pharmacol Ther 2008; 28: 1021-41
Watkins PB, et al. Hepatology 2008; 48: 1680-89

Increased Risk of DILI in CLDs?

Disease-Specific and Non-Specific Susceptibility

Chronic Viral Hepatitis

- HAART: HCV-HIV
- Anti-TB Rx:
  - HBV
  - HCV ± HIV
  - UGT1A1*27/*28

NAFLD

(OR 3.95; 95% CI 1.4-11.5)

- Antihypertensive
- Anti-Platelet agents
- Antimicrobials
- OTC: NSAIDs, PPI, APAP

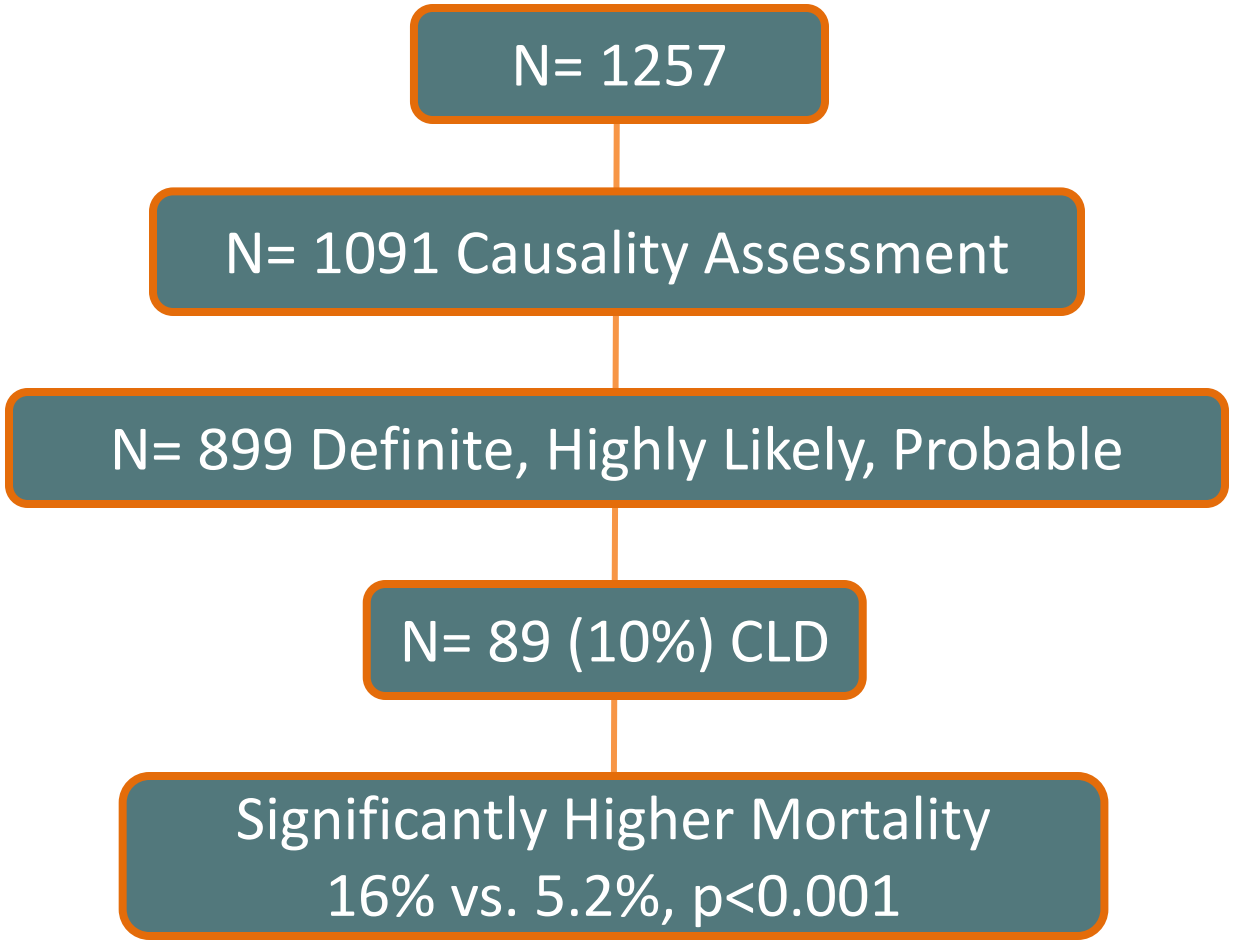
Unspecified CLDs

- Anti-TB Rx: UGT1A1*27/*28
- Azole Antifungals
- Azithromycin
- Tacrolimus

Hoffman CJ, et al AIDS 2007; 19: 1301-8; Fernandez-Villar A, et al Infection 2007; 35: 295-7; Tarantino G, et al Hepatol Res 2007; 37: 410-5; Chang JC, et al Int J Tuberc Lung Dis 2012; 16: 376-8; Pais R, et al. Clin Liver Dis 2014; 18: 165-78; Ko MS, et al Int J Clin Pharmacol Ther 2015; 53: 363-71; Lo Re V, eta l Am J Med 2015 Nov 17 Epub; Chalasani N, et al Gastroenterology 2015; 148: 1540-52

Increased Risk of Serious DILI in CLD

NIDDK DILIN



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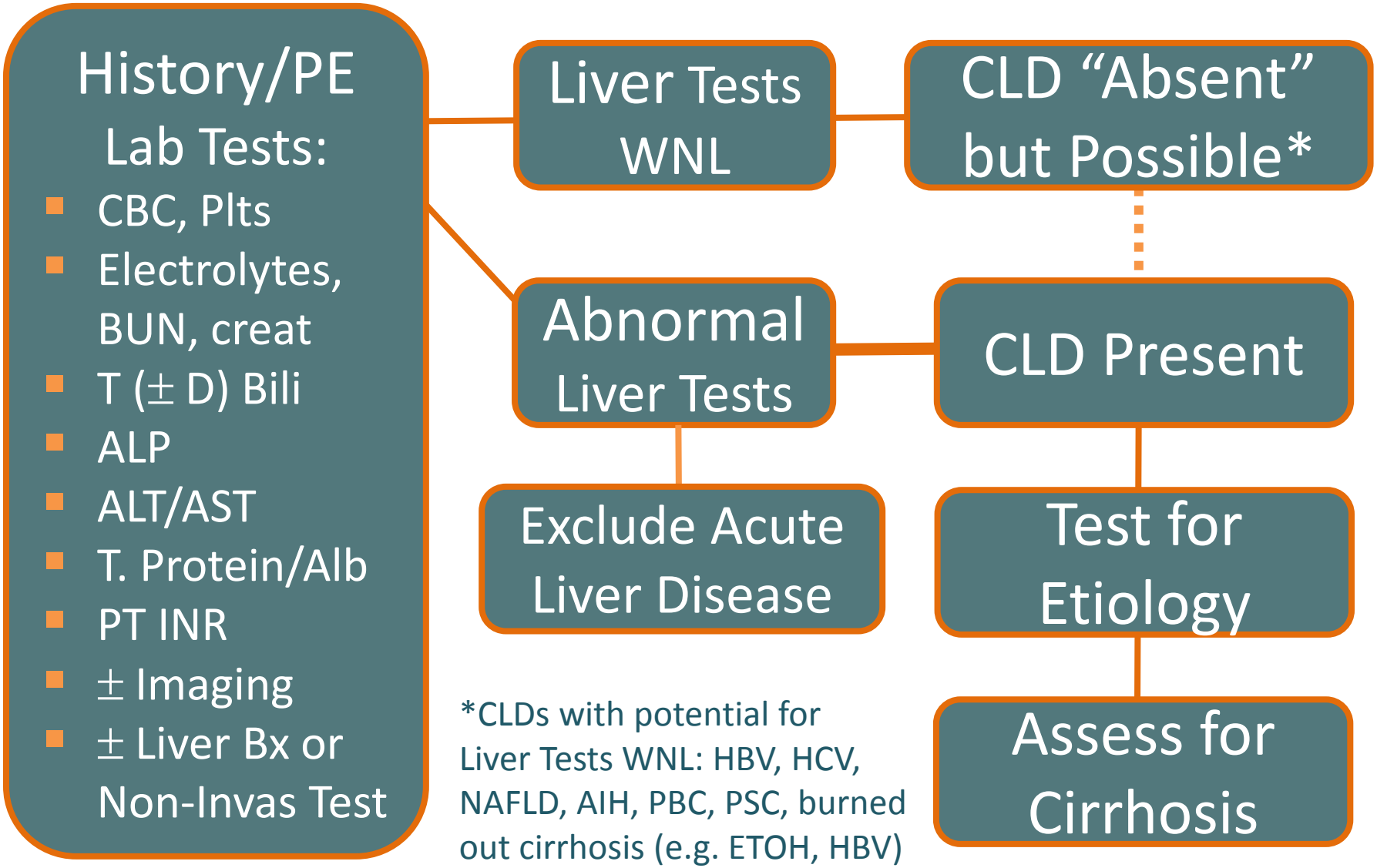
Identification of Study Subjects with CLDs

Current Inclusion and Exclusion Criteria



Identification of Study Subjects with Cirrhosis

Non-Invasive Detection Methods

Test	Parameters
FibroTest / FibroSure	Bili, GGT, g-globulin, haptoglobin, α2 M, apolipoprotein
FibroSpect	Hyaluronic acid, TIMP-1, α2 M
ELF	HA, Procollagen III amino terminal peptide (PIIINP), TIMP1
HepaScore	Hyaluronic acid, GGT, α2 M
Forns	GGT, cholesterol, platelets, age
APRI	AST /ULN X 100 / platelets (10^9/ L)
SHASTA; (HIV/HCV)	AST, HA, albumin
FIB-4	AST, ALT, platelets, age

Imaging Methods
Transient Elastography: ▪ Fibroscan (FDA-approved) ▪ Ultrasonic elastrography
Magnetic Resonance Elastography (MRE) FDA-approved No CPT Billing Code

Most accurate differentiating F0-1 from F4 cirrhosis

Hy's Law
Derivation and Current Definition

"Drug-induced hepatocellular jaundice is a serious entity. The mortality rate ranges from 10% to 50%."

Zimmerman, Hyman. Hepatotoxicity; 2nd edition, pp 432-3, 1999

Hy's Law as defined by FDA[1]:

- ALT or AST >3 X ULN (good sensitivity; poor specificity)
- Total bilirubin >2 X ULN (improved specificity)
- No "initial findings of cholestasis (elevated ALP)
- No alternative cause of liver test abnormalities

NIDDK DILIN[2]:

- ALT >3X ULN
- Total bilirubin >2X ULN
- ALP <2X ULN

Caveats:

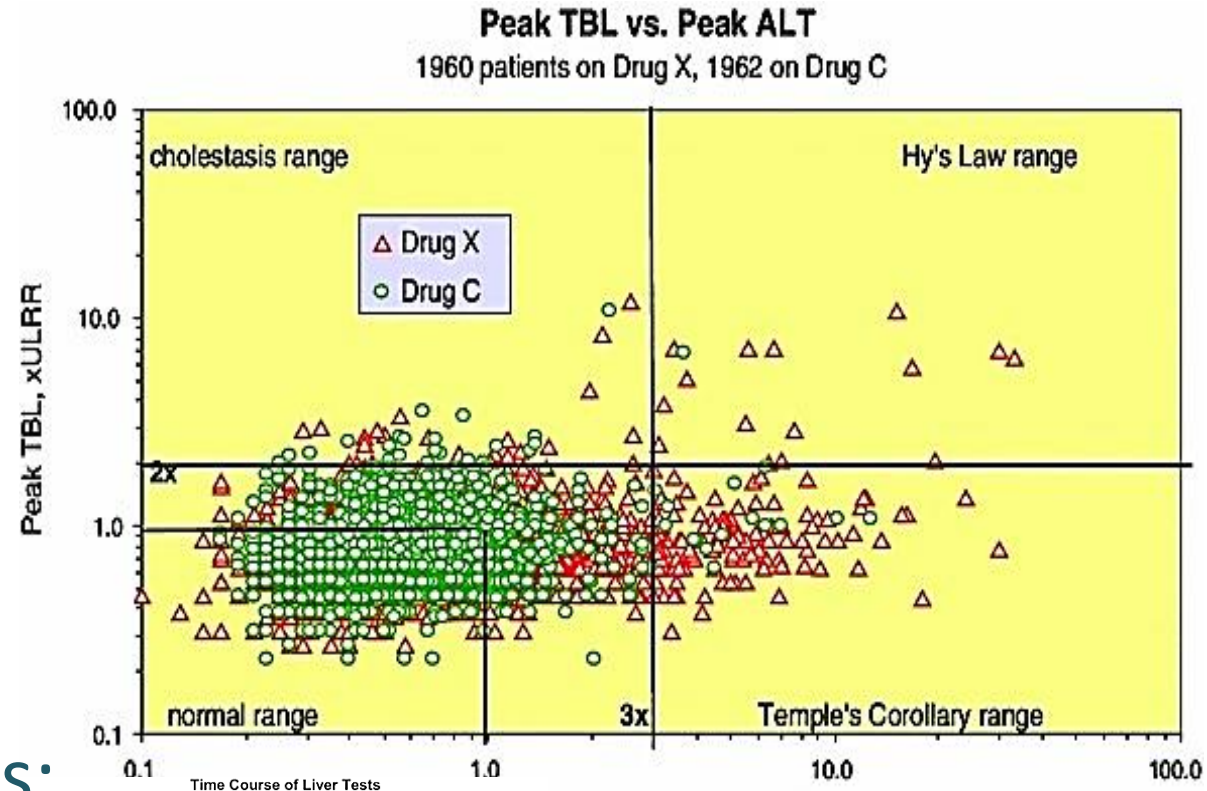
- Not a Law but a clinically useful tool!
- Calls for urgent assessment and adjudication
- 2 Case Rule: Finding 2 Hy's Law cases in a clinical trial is highly predictive of ALF[3]

[1]http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174190.pdf
[2]Fontana RJ, et al Gastroenterology 2014; 147: 96-52
[3]Avigan MI. Semin Liver Dis 2014; 34: 215-26

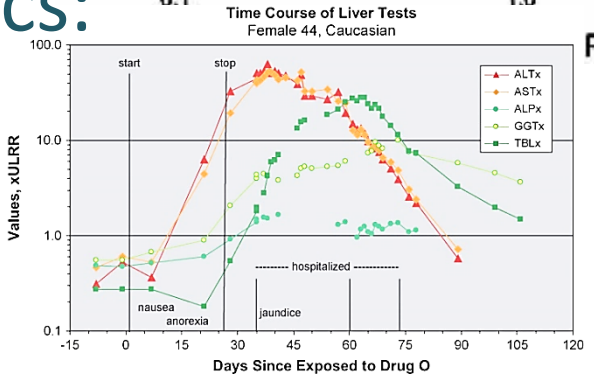
Identification of DILI in Subjects with CLDs

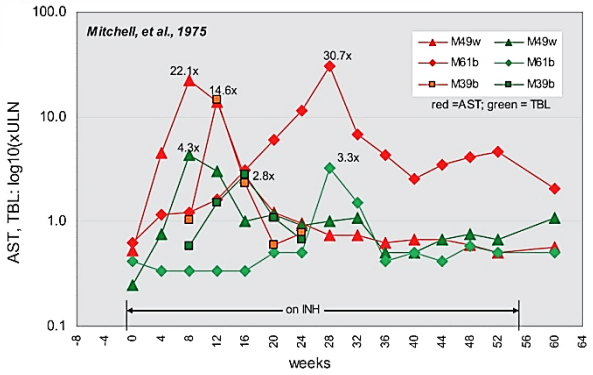
Importance of eDISH and Kinetic Analyses

eDISH:



Kinetics:





Watkins PB, et al. Hepatology 2008; 48: 1680-89

Serious DILI in Subjects with or without CLDs

Stopping Rules for Aminotransferases Alone or in Combination with Elevated Bilirubin or PT INR

Baseline ALT or AST	Stop if post-randomization values are:
Patients with normal ALT or AST	>8X ULN
	>5X ULN in 2 consecutive visits
	>3x ULN & (TBL >2xULN or PT INR >1.5)
	Any of the above
All patients (Regardless of baseline ALT, AST)	>8 ULN
	>5X ULN in 2 consecutive visits
	>3x ULN & (TBL >2xULN or PT INR >1.5)
	Any of the above

TBL, total bilirubin

FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009.: http://www.fda.gov/Biologics/BloodVaccinesGuidanceComplianceRegulatoryInformation/Guidance/default.htm

Biochemical Stopping Rules
Subjects with Decompensated Cirrhosis

Baseline ALT or AST	Stop if post randomization values are:	Patients Meeting Rule (GPB)	Patients Meeting Rule (Placebo)
		N=53	**N=51**
Patients with normal ALT or AST	>8 ULN	0	1
	>5X ULN in 2 consecutive visits	0	2
	>3xULN & (TBL >2xULN or PT INR >1.5)	7	6
	Any of the above	7	6
		N=90	**N=88**
All patients (Regardless of baseline ALT, AST)	>8 ULN	4	1
	>5X ULN in 2 consecutive visits	5	3
	>3xULN & (TBL >2xULN or PT INR >1.5)	18	13
	Any of the above	**21**	**14**

TBL, total bilirubin

Jurek M, et al. Pharm Med 2016 Epub 11 Jan 2016
Rockey DC, et al. Hepatology 2014; 59: 1073-83
FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009.:
http://www.fda.gov/Biologics/BloodVaccinesGuidanceComplianceRegulatoryInformation/Guidance/default.htm

Confounding Variation of Liver Biochemical Results in Decompensated Cirrhosis

Baseline Biochemical Tests:

Biochemical Test	Normal (%)	Abnormal (%)
ALT	58	42
AST	29	71
T Bili	33	67
PT INR	38	62

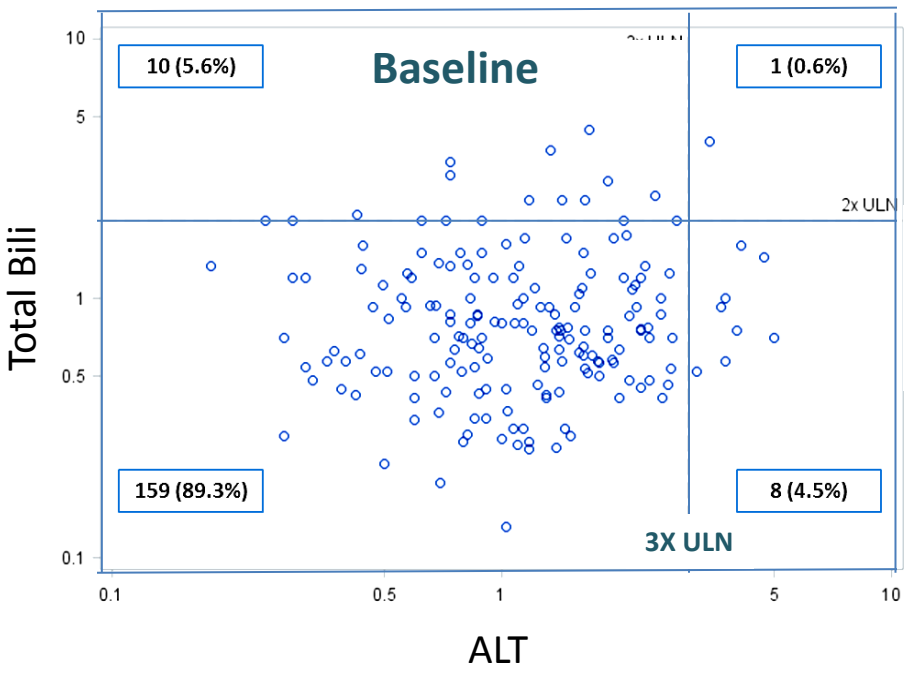
Baseline MELD (SD):

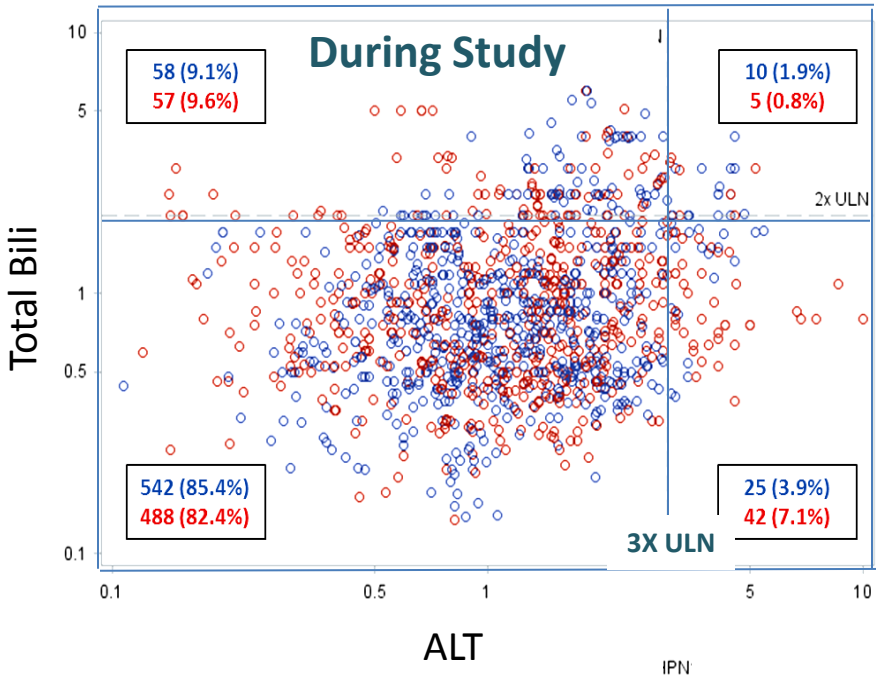
- Range: 5-26
- Mean: PL, 12.3 (3.8);GPB, 12.3 (3.7)

Baseline CTP Class (%):

- A (37); B (46); C (16)

eDISH Plots:





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Serious DILI in Subjects with or without CLDs

Grading of Liver Enzymes and Total Bilirubin

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
ALT	>ULN-3xULN	>3-5X ULN	>5X-20X ULN	>20X ULN
AST	>ULN-3xULN	>3-5X ULN	>5X-20X ULN	>20X ULN
Alkaline Phosphatase (ALP)	>ULN-2.5x ULN	>2.5-5X ULN	>5X-20X ULN	>20X ULN
Total Bilirubin	>ULN-1.5x ULN	>2.5-3X ULN	>3-10X ULN	>10X ULN

CTCAE v4.03 June 14, 2010; http://evs.nci.nih.gov/ftp1/CTCAE/About.hrml

Variability of "Stopping Rules" in Current CLD Trials

Disease	Sponsor	F4?	Evaluation and Stopping Rules
HCV	Abbvie DAAs	Yes	Post-baseline ALT >5X ULN AND >2X baseline: comprehensive evaluation DC: ALT ≥20 X ULN w/o alternative etiology; Increasing Direct bili or PT INR
	Gilead DAAs	Yes	ALT and/or AST > ULN and >5X Day 1 or Nadir; ALT >15X ULN; Hy's Law
	Merck DAAs	Yes	ALT or AST >500 IU/L; ALT or AST >3X baseline (>110 IU/L) + T bili >2X ULN; and/or PT INR >1.5 X baseline; ALT or AST >3X nadir (>100 IU/L) with new eosinophilia (.5%); Onset of moderate/severe TEAEs, including N/V, RUQ pain or tenderness
PBC	Intercept OCA	Yes	ALT and/or AST >3X ULN and 2X baseline OR 2 consecutive tests of T bili >ULN and >2X baseline in absence of biliary obstruction
	NGM FGF19	Yes	ALT and T bili >2X baseline; ALT >2X baseline may be observed with repeat PT INR
PSC	Intercept OCA	Yes	ALT and/or AST >3X ULN and 2X baseline OR 2 consecutive tests of T bili >ULN and >2X baseline in absence of biliary obstruction
	NGM FGF19	Yes	ALT and T bili >2X baseline; ALT >2X baseline may be observed with repeat PT INR
	Gilead Simtuzumab	Yes	2X baseline ALP, ALT, AST, ggt, T bili with level TEAE grade 3
NASH	BMS PEG-FGF21	No	ALT 2x baseline and >5X ULN + either T bili >2x ULN or PT INR >2;
	Immuron Anti-LPS	No	TEAEs grade 3 if related; DC for grade 4
	Gilead Simtuzumab	No	ALT or AST >2X baseline→repeat H&P, labs; ALT >3X ULN or T bili→repeat H&P, labs; Hy's Law and/or PT INR >1.5;
	Intercept OCA	No	ALT or AST >8X ULN; ALT or AST >5X ULN for >2 weeks; ALT or AST >3X ULN with new onset fatigue, N/V, RUQ pain/tenderness, fever, rash and/or eosinophilia (>5%); Hy's Law
	Genfit PPARα/δ	No	Normal Baseline ALT/AST: <3X ULN, monitor; >3X-<5X ULN, monitor; >5X ULN D/C; Abnormal Baseline ALT/AST: <3X, monitor; >3X baseline & <10X ULN, closer monitoring; >5X baseline or >10 X ULN, D/C; Hy's Law; ALT or AST >3X baseline or ULN + PT INR >1.5

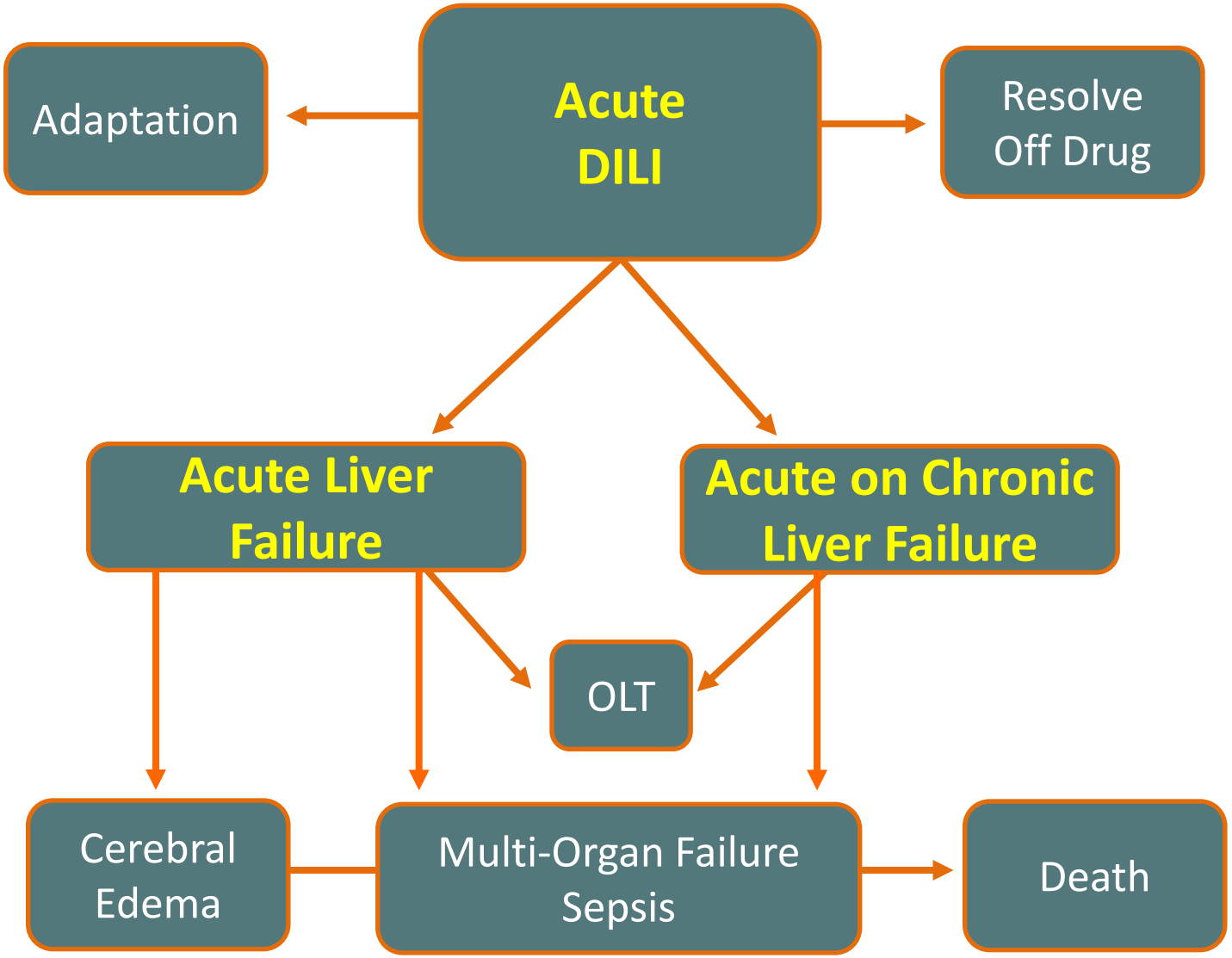
Assessment of DILI Severity
DILIN Severity Index Score

Stage	Description	Criteria
1	Mild	↑ ALT/AST or ALP; T Bili <2.5; INR <1.5
2	Moderate	↑ ALT/AST or ALP; T Bili >2.5 or INR ≥1.5
3	Moderate Hospitalized*	↑ ALT/AST or ALP; T Bili >2.5 or INR ≥1.5 and hospitalized or admission prolonged
4	Severe*	↑ ALT/AST or ALP; T Bili ≥2.5 and 1 of following: decompensation (INR ≥1.5, ascites, HE) or other organ failure associated with DILI event
5	Fatal*	Death or OLT due to DILI

*SAE in Clinical Trials

DILI Severity and Outcome

Acute Liver Failure vs. Acute on Chronic Liver Failure



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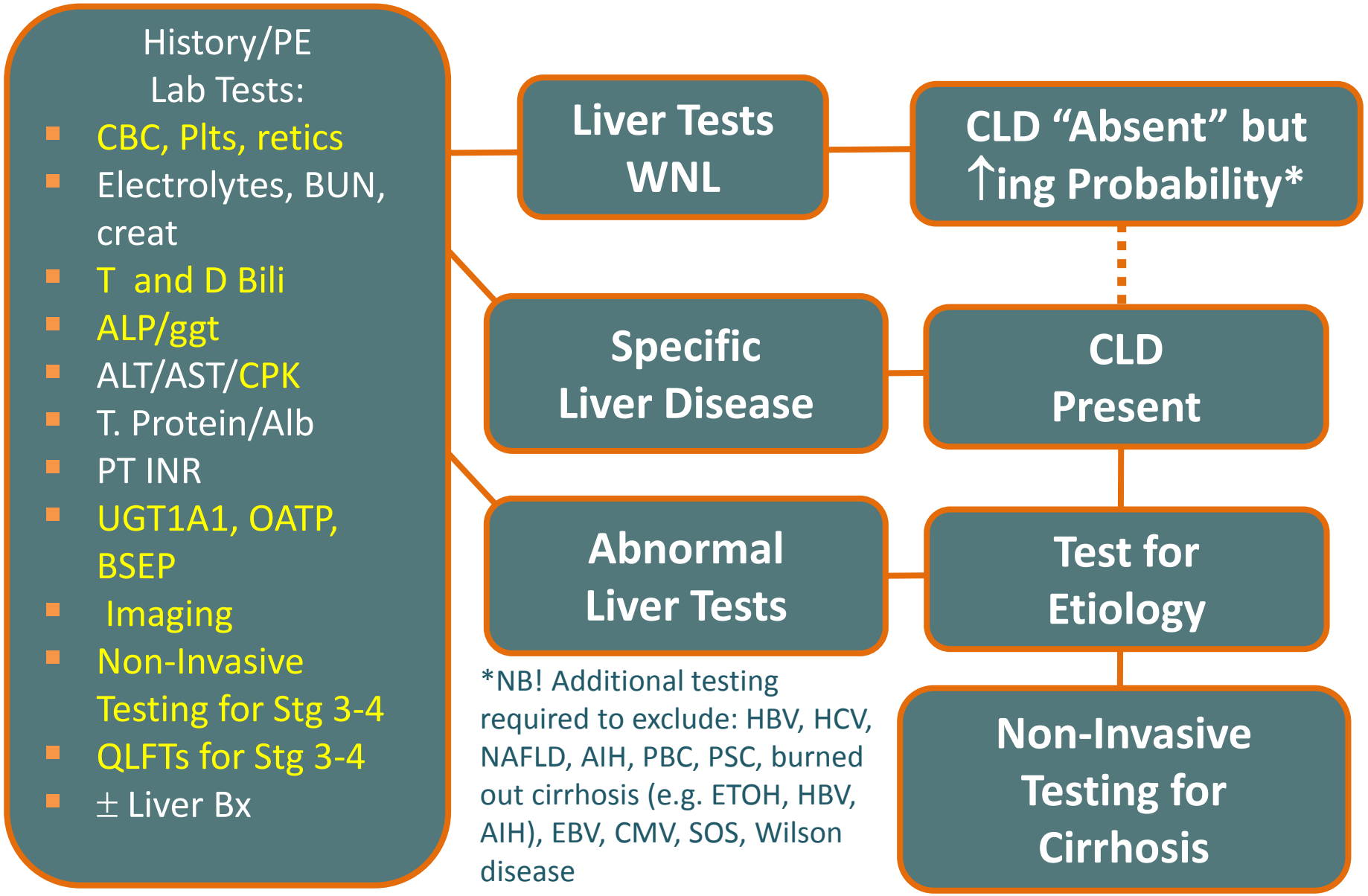
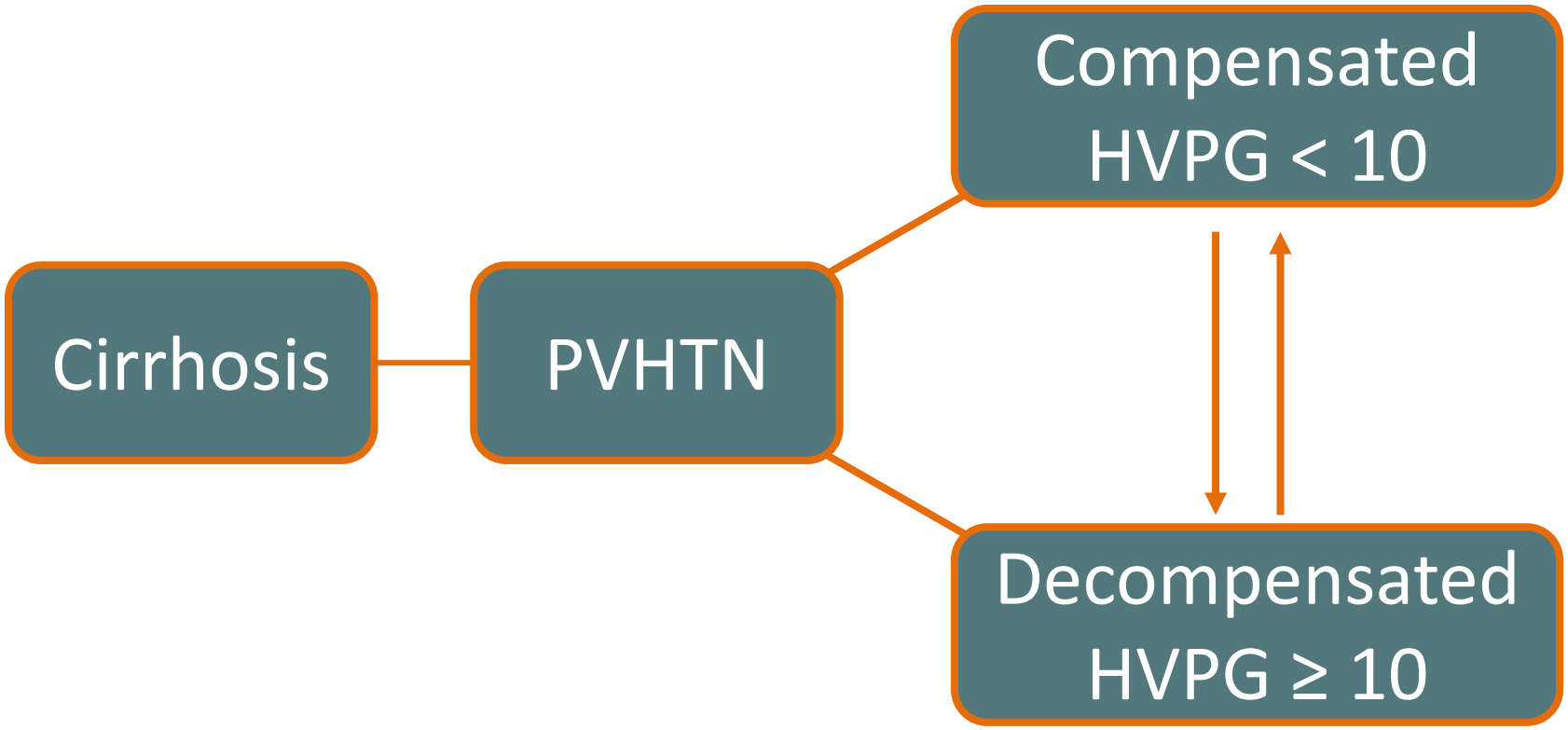
    c. Functional assessments
    d. Stopping rules

Identification of Study Subjects with CLDs

Expand Testing to Enhance Exclusion or Inclusion

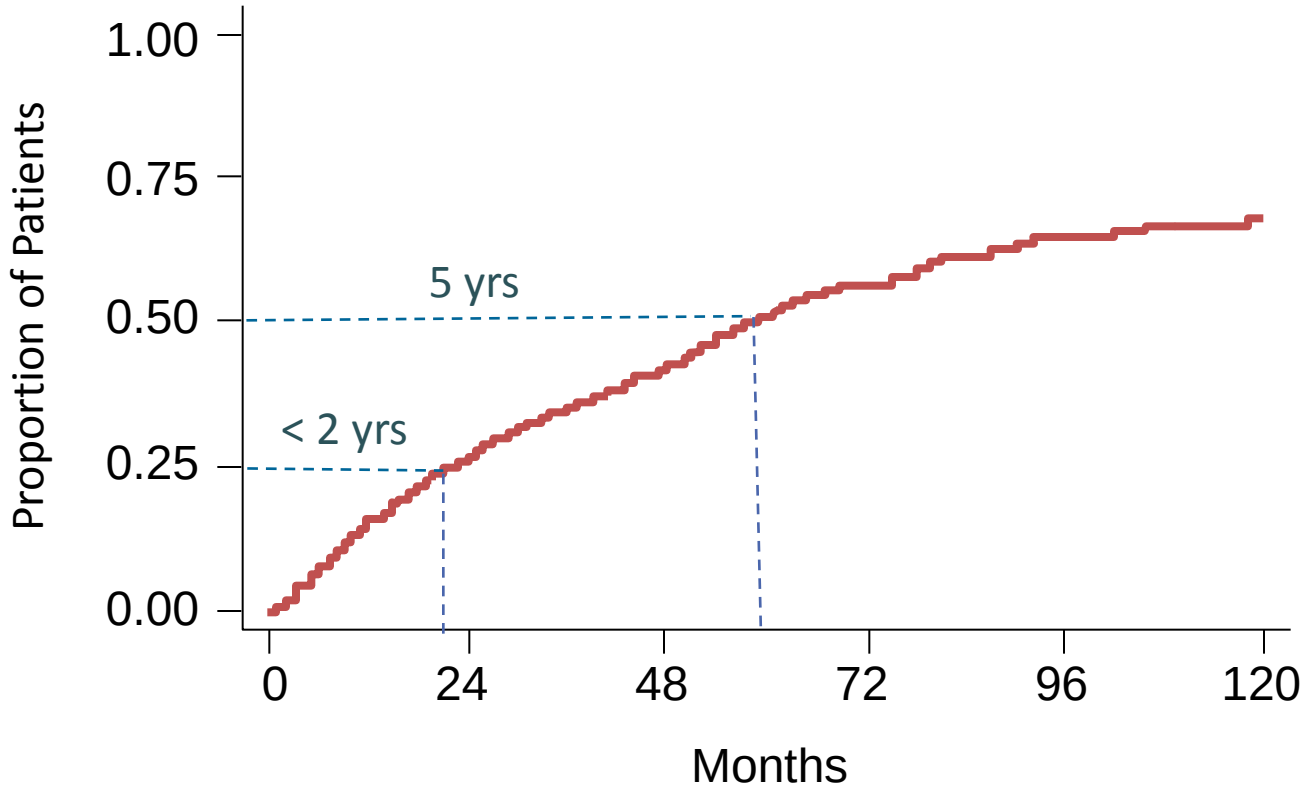


Risk of Decompensation of Cirrhosis
Gold Standard Fasting HVPG ≥ 10 mm Hg



Hepatic Venous Pressure Gradient (HVPG)=Wedged HV Pressure – Free HV Pressure

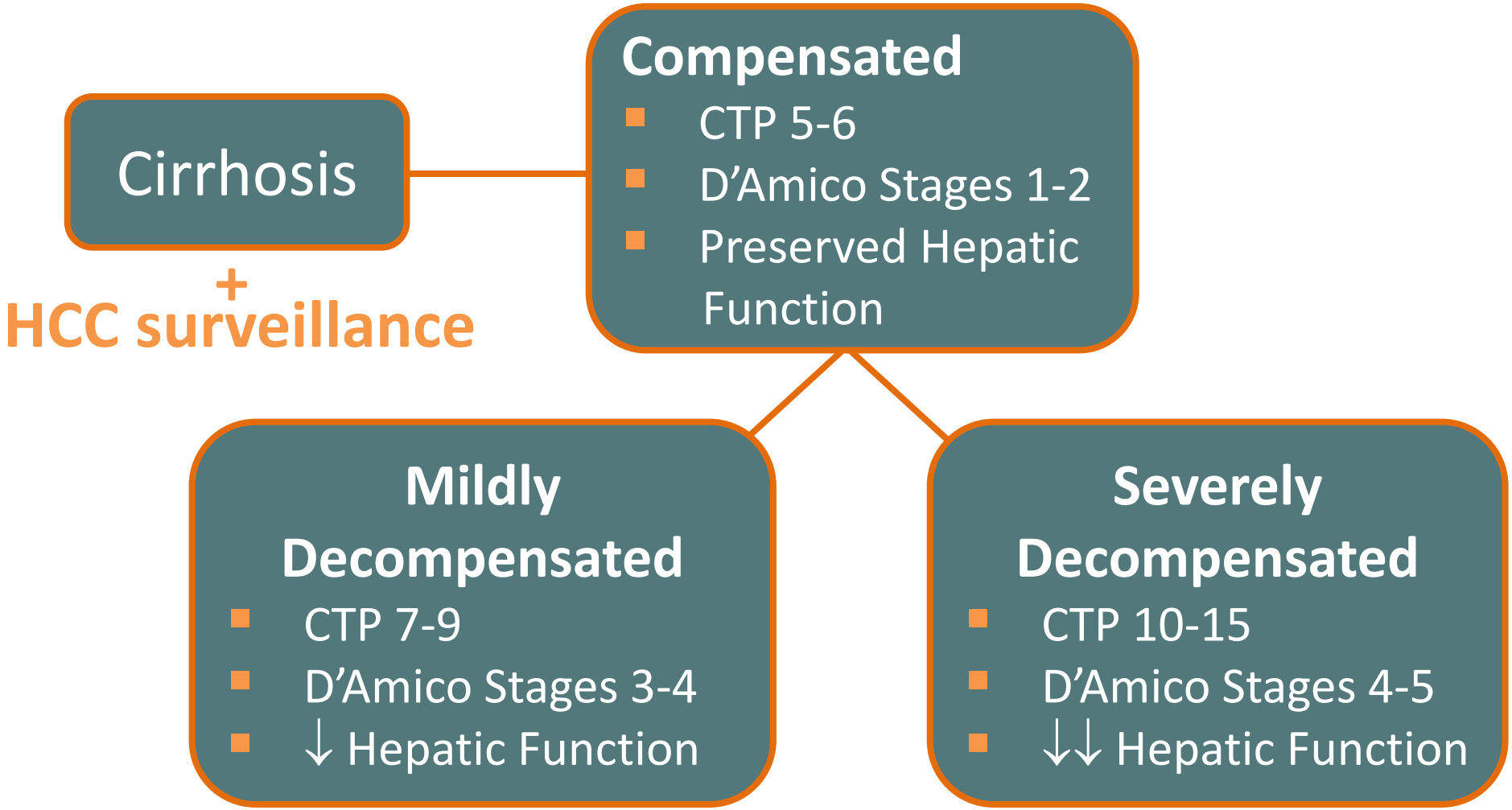
Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Cirrhosis



D'Amico G et al. J Hepatol. 2006.

Classification of Study Subjects with Cirrhosis

Surrogate Measures of Hepatic Functional Reserve



Quantitative Liver Function Testing

Non-Disease Specific Assessments of Function

HEPATIQ

- FDA approved
- ^{99m}Tc-Liver-Spleen Scan
- Software analysis calculates Perfused Hepatic Mass (PHM)

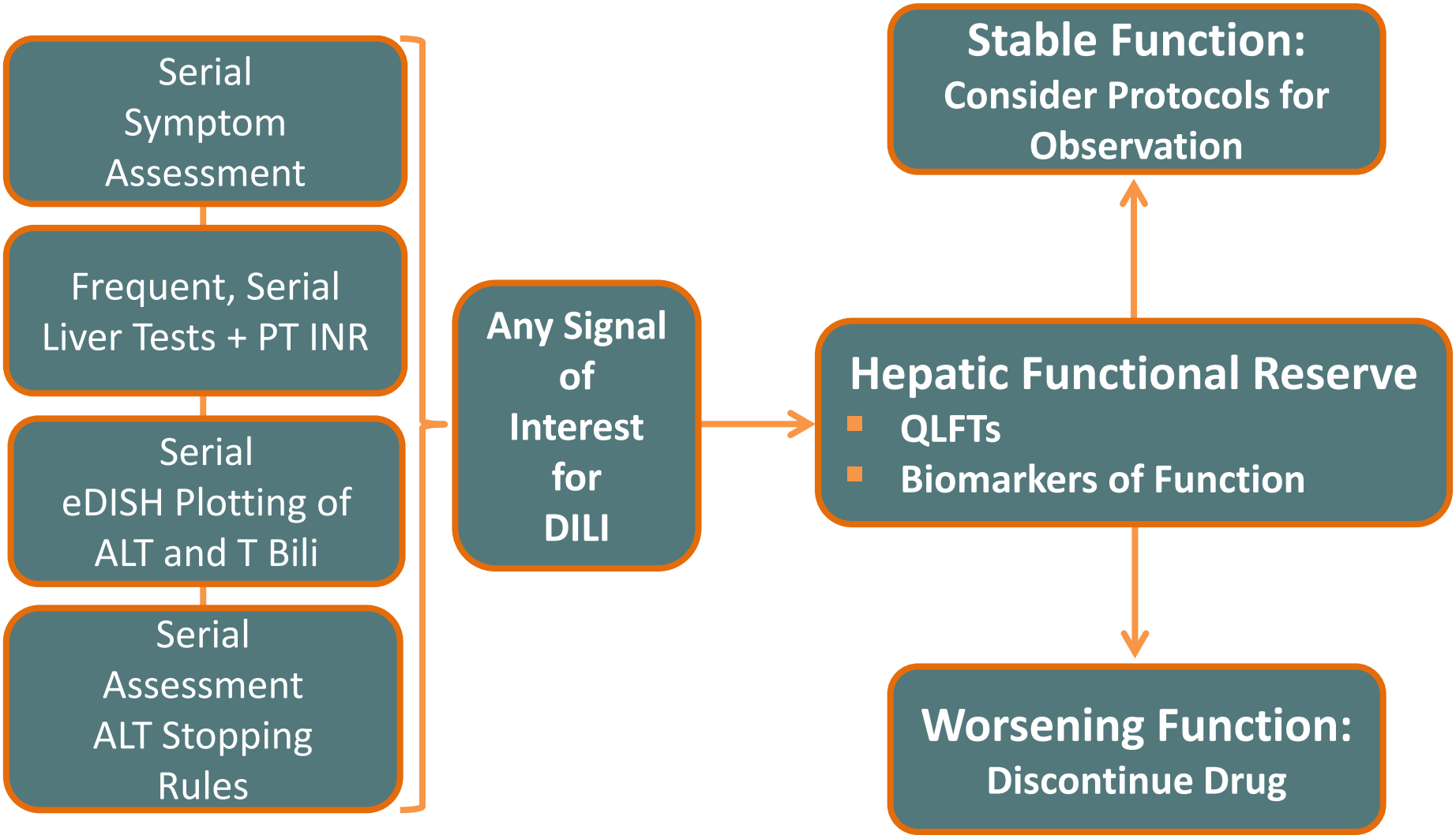
HepQuant

- Not FDA approved
- Analyses of oral and/or iv cholate clearance
- Calculation of Disease Severity Index (DSI) or STAT score

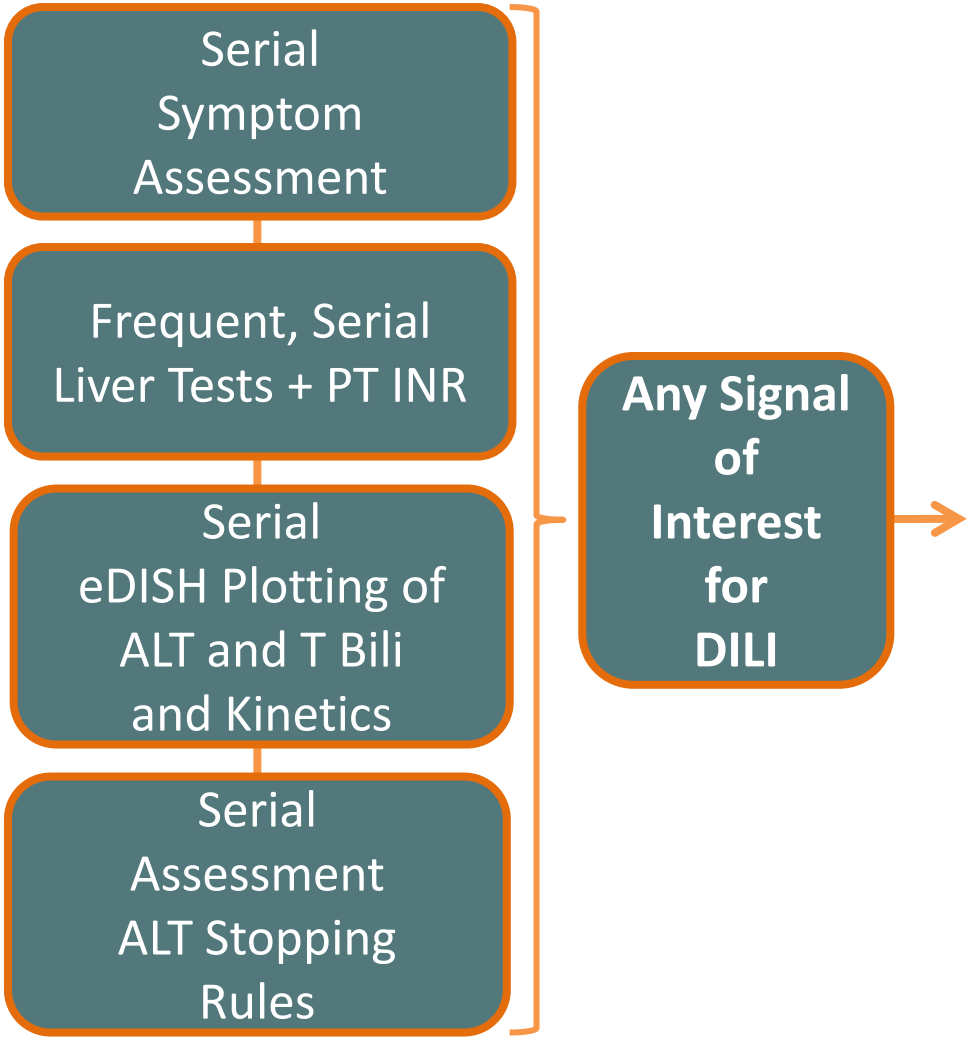
Excalenz

- Not FDA approved
- ^{13}C-Methacetin breath
- test of ^{13}C-M to APAP
- Generates PK/PD of
- $^{13}CO_2$

Stopping Rules Using Functional Monitoring for Severe DILI in CLD with or without Cirrhosis



Concern About DILI in CLD with or without Cirrhosis: A Call to Clinical Action



Urgent Need for:

1. Repeat history and PE
2. Repeat testing to verify
3. Comprehensive testing for etiologies other than DILI
4. Calculate MELD/Na, CTP
5. Repeat QLFTs to detect change in hepatic function
6. More frequent F/U visits, liver tests and QLFTs
7. Adherence to stopping rules

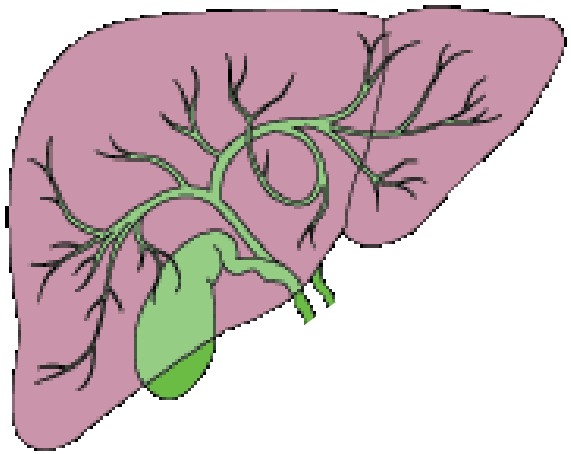
Future Investigative Opportunities in DILI

Host Factors and Drug Properties

Genetics
Polymorphisms
Proteomics
Metabolomics

Hepatic
Function
Testing

DILI
Pathogenetic
Mechanism(s)



Epidemiology
of
CLDs in Trials

Host-Drug
Transporters
Metabolism

Biomarkers
- DILI
- DILI Severity

PK/PD for
Hepatic Dosing
- Stages 0-3
- Cirrhosis

Microbiome
Drug
Metabolism

Summary

- Enrollment of patients with CLDs, with and without cirrhosis, in trials of drug development is increasing due to the rising prevalence of CLDs and cirrhosis:
  - general drug development
  - disease-specific therapies for all major classes of CLDs
  - cirrhosis (antifibrotics) and complications of PVHTN and HCC
- In general, CLDs do not increase susceptibility for DILI, but exceptions exist, and more are likely to be discovered.
- Subjects with CLDs and low hepatic functional reserves have increased risks of serious DILI and death.
- Currently, study protocols provide protection for subjects with CLD from serious DILI by alerting investigators to the need for urgent, comprehensive evaluation of cases meeting Hy's Law or other criteria and/or exhibiting evidence of decompensated cirrhosis.
- Future study protocols should provide additional protection for subjects with CLD by direct quantitative testing of hepatic functional reserve at baseline and during any suspected DILI event, applying biomarkers of DILI and its severity, testing for polymorphisms of UGT1A1, OATP and BSEP to aid in interpretation of abnormal bilirubin and cholestasis and utilizing advanced imaging techniques with the goal of producing better evidence-based stopping rules for patients with CLDs.