ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI – INSTITUTE FOR PERSONALIZED MEDICINE BIOBANK DILI ALGORITHM IMPLEMENTATION **1**
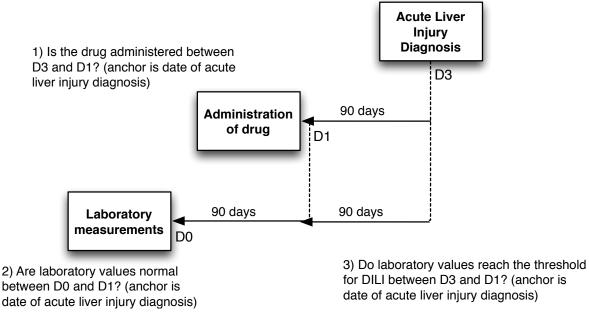
Icahn School of Medicine at Mount Sinai – Institute for Personalized Medicine Biobank DILI algorithm Implementation

Overview of implementation

1) Is the drug administered between D3 and D1? (anchor is date of acute liver injury diagnosis)

2) Are laboratory values normal between D0 and D1? (anchor is date of acute liver injury diagnosis)

3) Do laboratory values reach the threshold for DILI between D3 and D1? (anchor is date of acute liver injury diagnosis)

Baseline population
- Biobank clinical datamart population 2006-2013 (N=23,220)

Case Definition:

Acute liver injury diagnosis
- Structured data only (ICD-9 codes)
- Date of first instance of acute liver injury code, becomes D3.

Acute liver injury related diagnoses and procedures	ICD-9 codes
Disorders of bilirubin excretion	277.4
Acute and subacute necrosis of the liver	570*
Hepatic coma (hepatorenal syndrome)	572.2
Hepatorenal syndrome	572.4*
Other disorders of the liver, including chemical or drug induced	573*
Other specified disorders of biliary tract	576.8
Jaundice, unspecified, not of newborn	782.4
Hepatomegaly	789.1*
Nonspecific elevation of transaminase or lactic dehydrogenase levels	790.4*
Abnormal liver function test results	794.8*

Administration of drugs
- Structured data only (new medication orders)
- Any medication
- Date of a new medication order within 90 days prior to D3, becomes D1.

Laboratory measurements
- Upper limit of normal (ULN) is manufacturer specified.
- Threshold laboratory values for DILI
  - ALP (Alkaline Phosphatase) $\geq$ 2 x ULN
  - ALT (Alanine Aminotransferase) $\geq$ 3 x ULN
  - Bilirubin (Indirect or Unconjugated) $\geq$ 2 x ULN
- All laboratory values should be below thresholds for DILI (normal) between D0 and D1.
- Date laboratory values reach threshold for DILI between D3 and D1, becomes D2 (not shown)

Excluded diagnoses
- Structured data only (ICD-9 codes)

Chronic liver disease diagnosis description	ICD-9 code
Alcoholic fatty liver	571.0
Alcoholic cirrhosis of liver	571.2
Alcoholic liver damage	571.3
Chronic hepatitis	571.40
Chronic persistent hepatitis	571.41
Other chronic hepatitis	571.49
Cirrhosis of liver without mention of alcohol	571.5
Biliary cirrhosis	571.6
Other chronic nonalcoholic liver disease	571.8
Autoimmune hepatitis	571.42
Unspecified Chronic Liver Disease without Mention of Alcohol	571.9

Control Definition:
- NOT a case
- EVER taken ANY of the medications implicated in the algorithm-selected cases (D1)
- No exclusion codes (same as cases)

Validation steps
- Cases:
    - Manual chart review of all algorithm-selected DILI cases
    - 1 clinical reviewer
    - Expert decision, determination by DILI expert for questionable results
- Controls:
    - Manual chart review of a random sample of 50 algorithm-selected DILI controls (6354 controls total)
    - 1 clinical reviewer
    - Expert decision, determination by DILI expert for questionable results

Results
- Cases:
    - 24 algorithm-selected DILI cases
    - 5 out of 24 are definite cases
    - 2 out of 24 are possible cases
    - 17 out of 24 are not cases (false positives)
- Controls:
    - 50 controls randomly selected from a possible pool of 6354 algorithm-selected controls
    - 50 out of 50 are true controls
    - No false negative and no false positive controls