

BASELINE LIVER LABORATORY TESTS ACROSS CLINICAL TRIAL POPULATIONS

Bereket Tesfaldet, Tejas Patel, Lilliam Rosario, Eileen Navarro Almario
CDER/OTS/OCS



Introduction

Drug-induced liver injury (DILI) is a major cause of non-approval of new drugs as well as withdrawal of approved drugs from the market. Peak on-treatment elevations in liver lab tests relative to upper limit of normal (ULN) reference values from healthy population are used to identifying potential DILI cases in a clinical trial. Due to prevalent background elevations of liver tests, this method of identifying DILI cases is limiting in clinical trials involving subjects with liver disease. Hence, we explored variations in baseline liver tests across clinical trial populations as an important first step in developing tools that predict DILI in subjects with underlying liver disease.

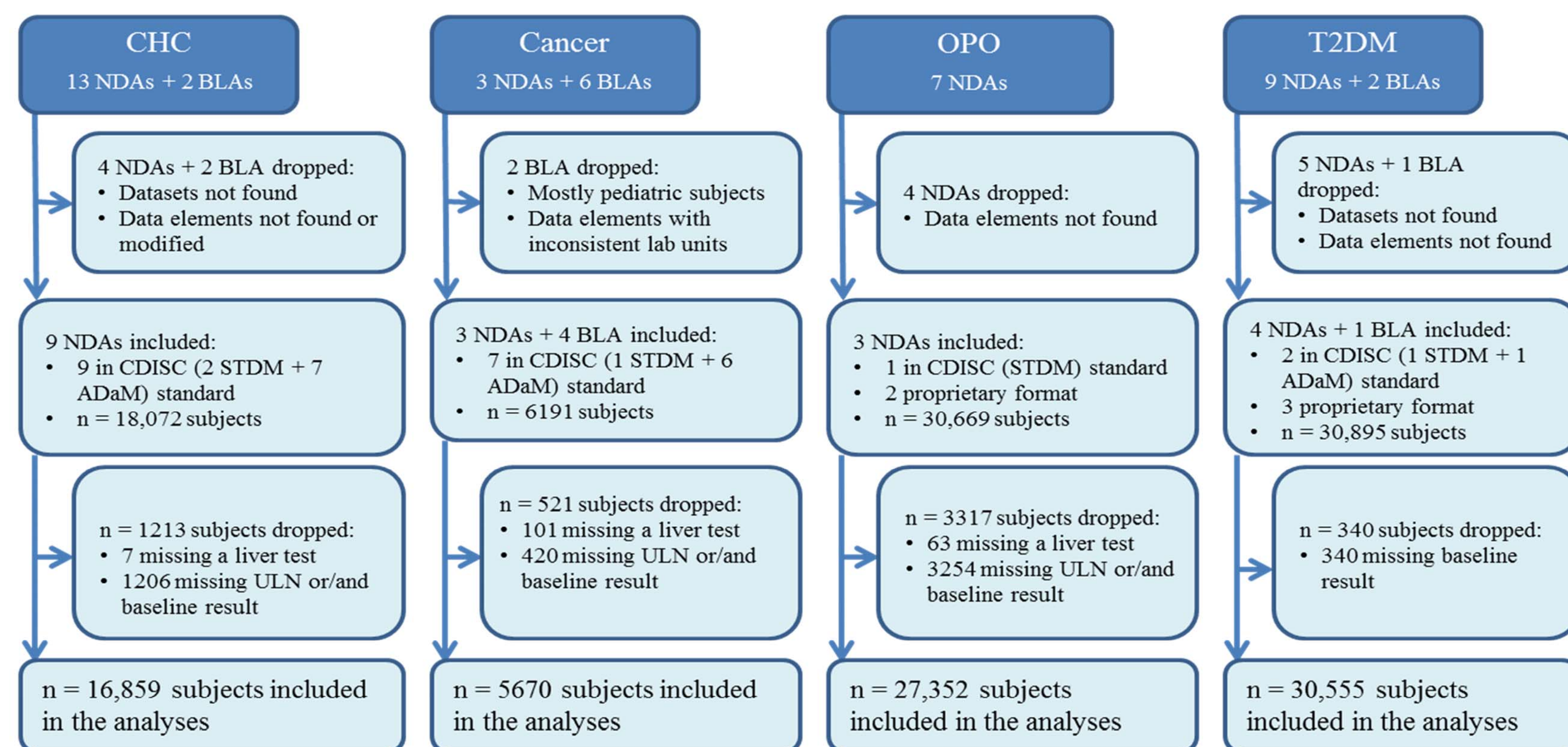
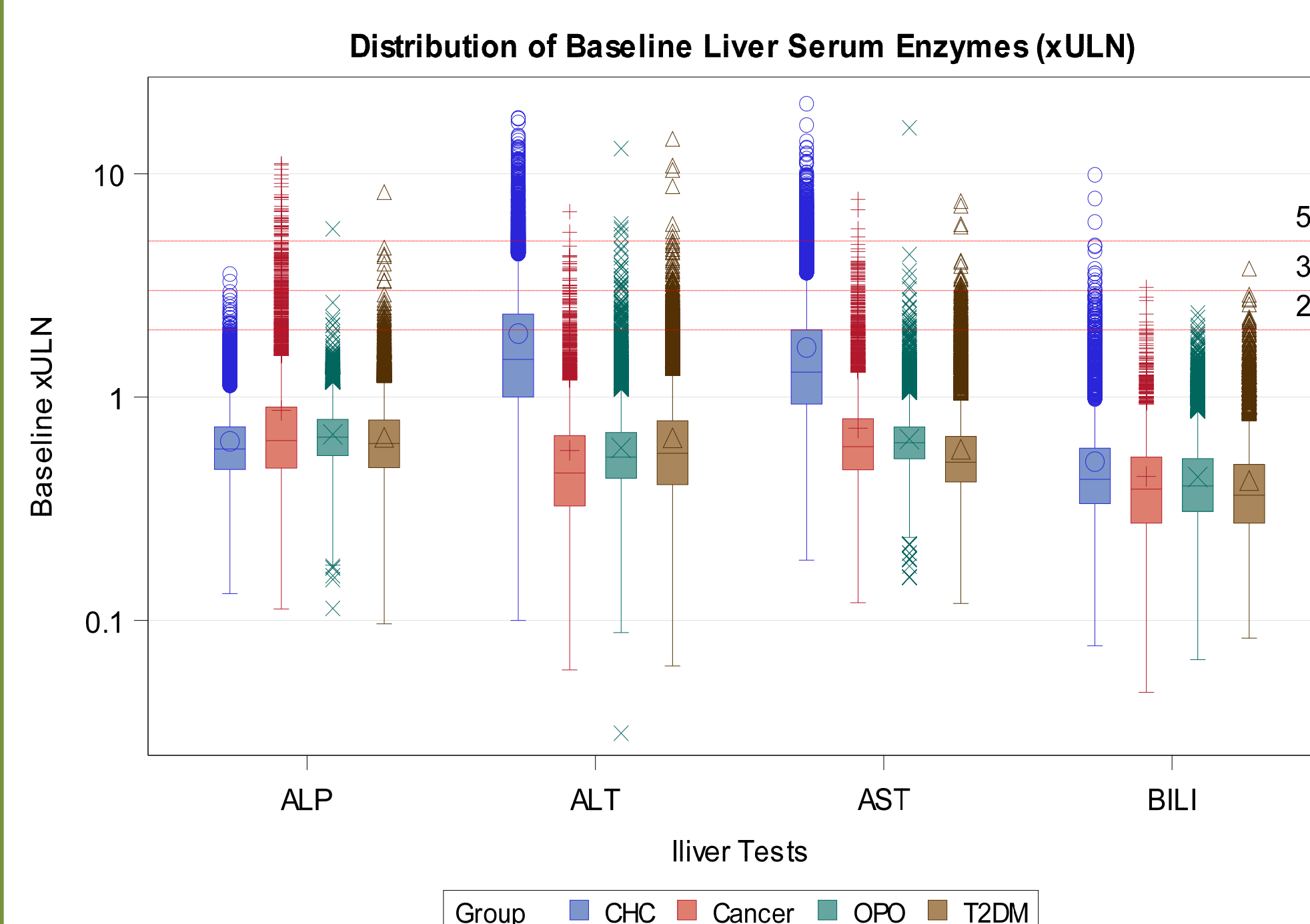
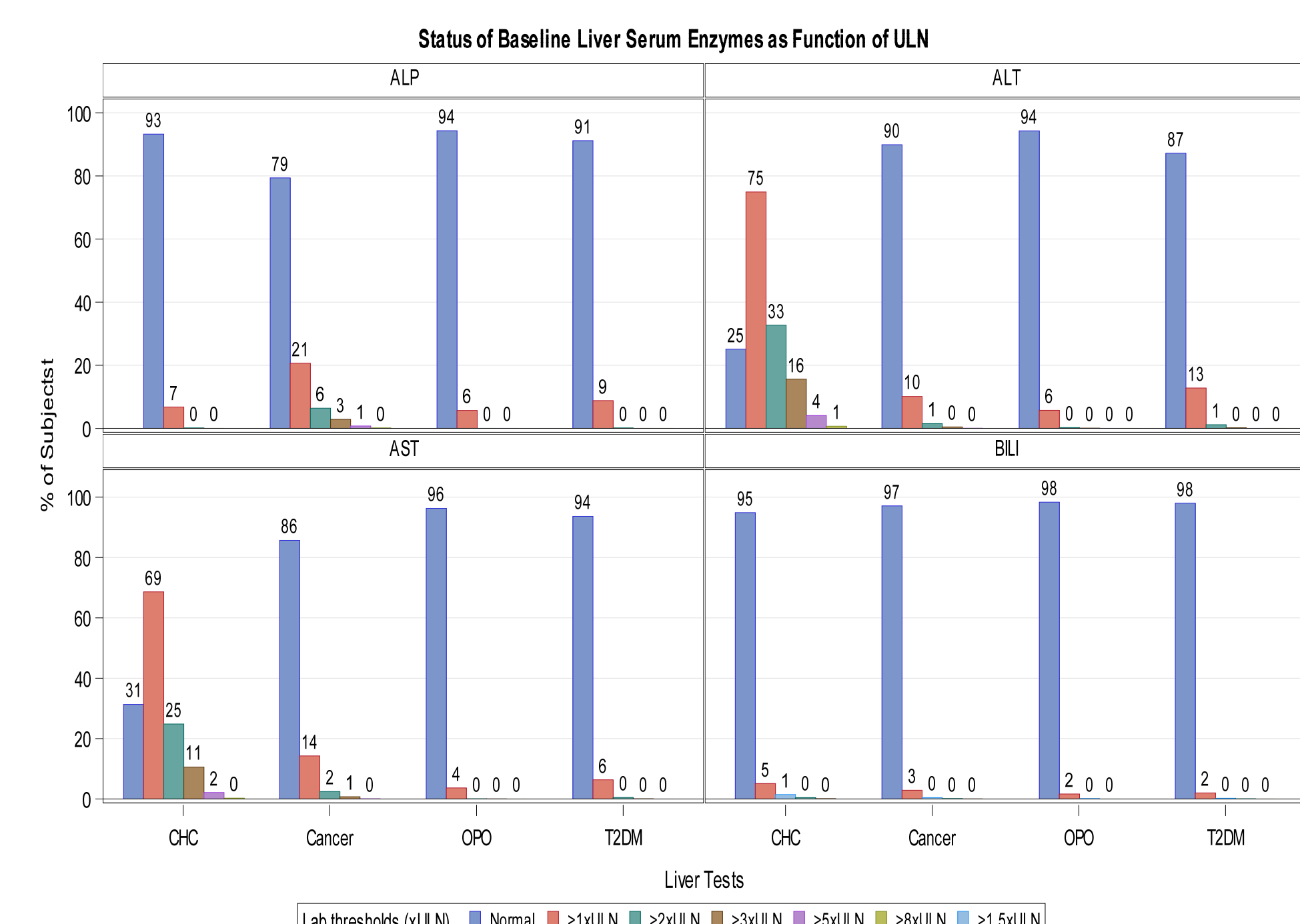
Methods

- Pretreatment liver test results of 145 clinical trials enrolling four distinct clinical trial populations: cancer, type 2 diabetes mellitus (T2DM), chronic hepatitis C (CHC), and osteoporosis (OPO) were aggregated and analyzed.
- The liver test of interest were alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (BILI)
- Tables and charts are used to examine the prevalence of background liver test elevations.

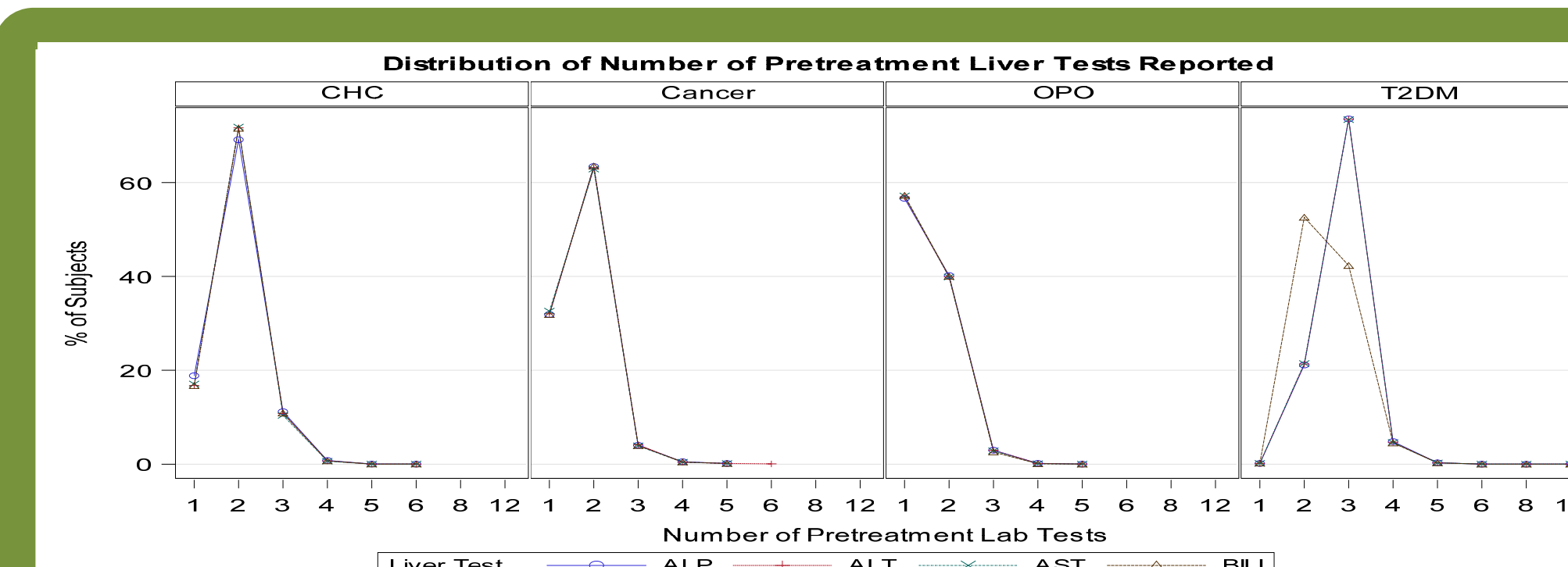
Conclusions

- Background elevations of liver tests in subjects with underlying liver disease is prevalent.
- Unexpected elevations of these tests in T2DM subjects were observed suggesting the presence of underlying liver disease, such as NASH.
- Tools designed around the ULN reference values may not be sufficiently predictive for these patients population.
- Assessment of the change from pretreatment lab values may be useful.

Results



		ALT	BILI	
		> 1xULN	>1.5xULN	> 2xULN
CHC (N=16859)	> 1xULN	707 (4.19)	188 (1.12)	68 (0.4)
	> 2xULN	346 (2.05)	76 (0.45)	25 (0.15)
	> 3xULN	162 (0.96)	23 (0.14)	4 (0.02)
Cancer (N=5670)	> 1xULN	34 (0.6)	3 (0.05)	1 (0.02)
	> 2xULN	6 (0.11)		
	> 3xULN	4 (0.07)		
OPO (N=27352)	> 1xULN	22 (0.08)	5 (0.02)	1 (<0.01)
	> 2xULN	2 (0.01)		
	> 3xULN			
T2DM (N=30555)	> 1xULN	104 (0.34)	9 (0.03)	2 (0.01)
	> 2xULN	9 (0.03)	1 (<0.01)	1 (<0.01)
	> 3xULN	4 (0.01)	1 (<0.01)	1 (<0.01)



- Majority of the subjects with cancer, T2D and CHC were White, male, and younger than 65 years of age.
- For CHC:
 - About 70% of the subjects had abnormal serum aminotransferases .
 - The prevalence of baseline ALT >3xULN was 15.59%, and BILI>1.5xULN was 1.36%.
 - The prevalence of baseline ALT >2xULN and BILI >1.5xULN was 0.45% and baseline ALT >3xULN and BILI >2xULN was 0.02%.
- The number of pretreatment tests per subject was variable (range 1-12 tests, mean 2.25 tests, median 2 tests per subject).

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