



Leveraging Information from Healthy Volunteers Placebo Data

Phuse EU Connect 2022

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Agenda

1. Introduction

2. Creation of a Pooled Database

3. R Shiny App

4. Future steps

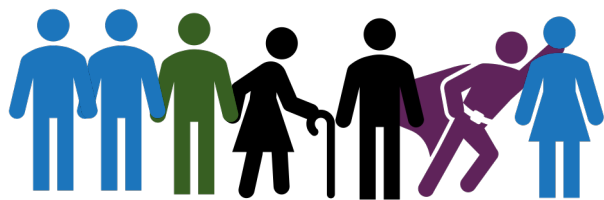
1. Introduction

PROBLEM?

The limited availability of placebo data in Healthy normal volunteers (HNV) clinical trials makes it difficult to put treatment-emergent abnormalities into context.

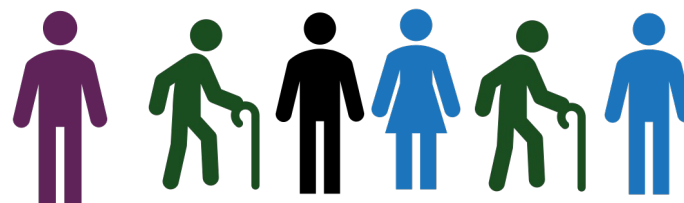
Trial A: Placebo

4 out of 8 (50%) with ALT abnormality



Trial A: Drug X

2 out of 6 (33.%) with ALT abnormality



WHAT?

To improve decision making on emerging safety signals in HNV, by allowing comparison with a matched HNV control group selected from pooled placebo data across our internal studies across therapeutic areas.

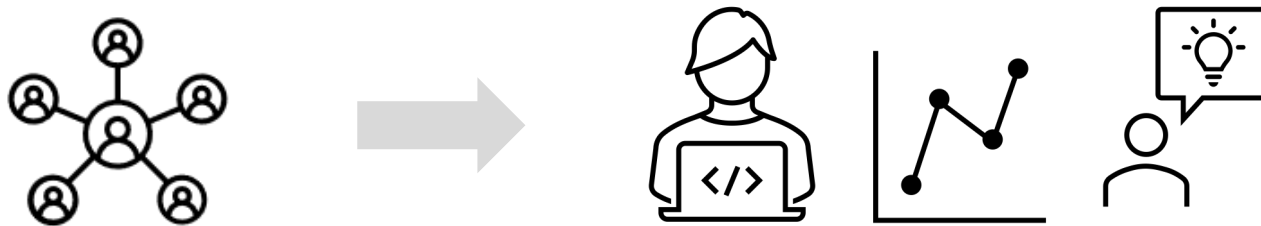
Trial A-Z: Placebo, matched to Trial A Drug X



1. Introduction (cont'd)

• HOW?

- A **pooled database** with available in-house data from HNV on placebo that can be queried through an interactive interface (**R-shiny app**).
- When a safety signal arises in a HNV trial, the app can generate statistics (e.g. expected incidence of such an event for placebo), taking potentially relevant subject characteristics into account



• OUTCOME?

To enable clinicians to compare the observed incidence of an event in a HNV trial with the historically observed incidence of the event on placebo.

Non-binding: to support the regular thinking process.

2. Creation of a pooled database



Placebo



Healthy Normal Volunteers
HNV



Fixed set of studies

studies in HNV conducted at the Janssen CPU in Belgium



Laboratory safety markers

(special focus on liver function tests ALT/AST)

2. Creation of pooled database (cont'd)

Creation of 3 analysis datasets

- **ADSLP:** demographics, original study information (1 line per subject)
- **ADLBP:** Lab dataset closely following LB structure
(1 line per subject, per lab parameter per visit)
- **ADCMP:** 1 dataset following CM structure, filtered on specific conmeds
(created to extract information on use of paracetamol and hormonal contraception)

Programs

- 1 SAS macro/study with 3 submacros (1 for each dataset)
 - Create variables needed, make sure each study has the same variables at the end (different SDTM versions to start from)
- 1 SAS program/dataset for the pooling and final touches
 - Eg. Labels, lab units,...

2. Creation of pooled database (cont'd)

Final dataset: 38 studies with lab data on 572 HNVs

Issues

- Older studies with different structures
- Lab parameters and units not the same across studies
- Different ULN/LLN (use Ratio for ALT, AST)
- Certain information not available
- Coding issues for medication

3. R shiny App

- Intuitive, simple & user-friendly
- Interactive features
- No time-consuming calculations
- Automated
(no/minimal updates to app when updating underlying database)



3. R Shiny App (cont'd)

At entry: overview of the demographics of all subjects.

 **HVsafety project**
App version: 0.0.4.1 | DB version: v3 | Updated: April 21, 2021

Overview Pooled Database | Subjects listing | Subject profiles | Liver function Inference

User Guide

Database last updated on: 2021-04-27 17:52:04

		Frequency	
Variable		N	
Studies		38	
Patients		572	

		Frequency	
Variable	Category	N	%
Study Duration	<= 1 month	15	39.5 %
	1-3 months	15	39.5 %
	> 3 months	8	21.1 %

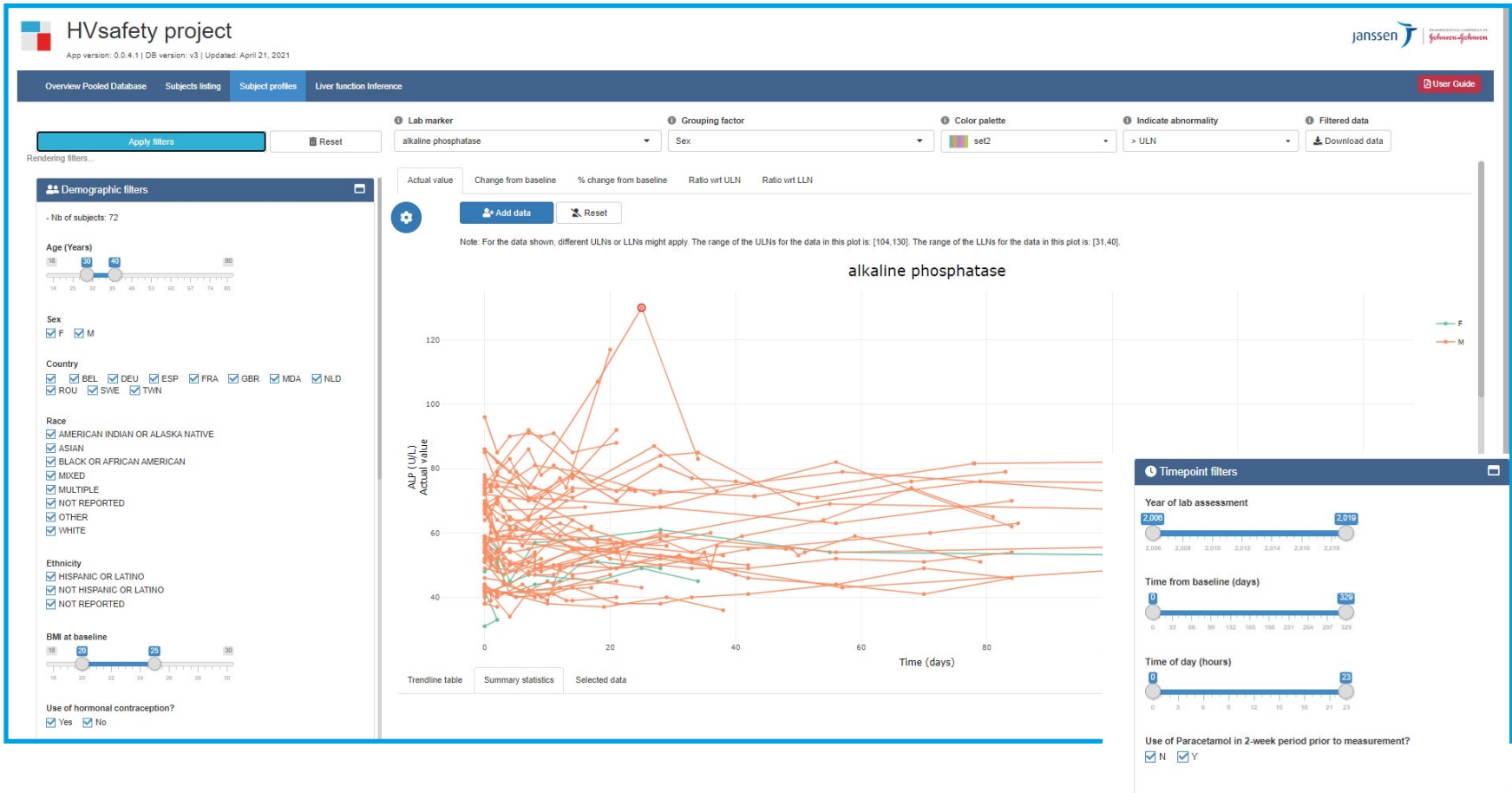
		Frequency	
Variable	Category	N	%
Sex	M	443	77.4 %
	F	129	22.6 %
Age	18-30	105	18.4 %
	31-40	129	22.6 %
	41-50	172	30.1 %
	51-60	117	20.5 %
	61-65	10	1.7 %
	> 65	39	6.8 %
Country	Belgium	381	66.6 %

3. R Shiny App (Cont'd)

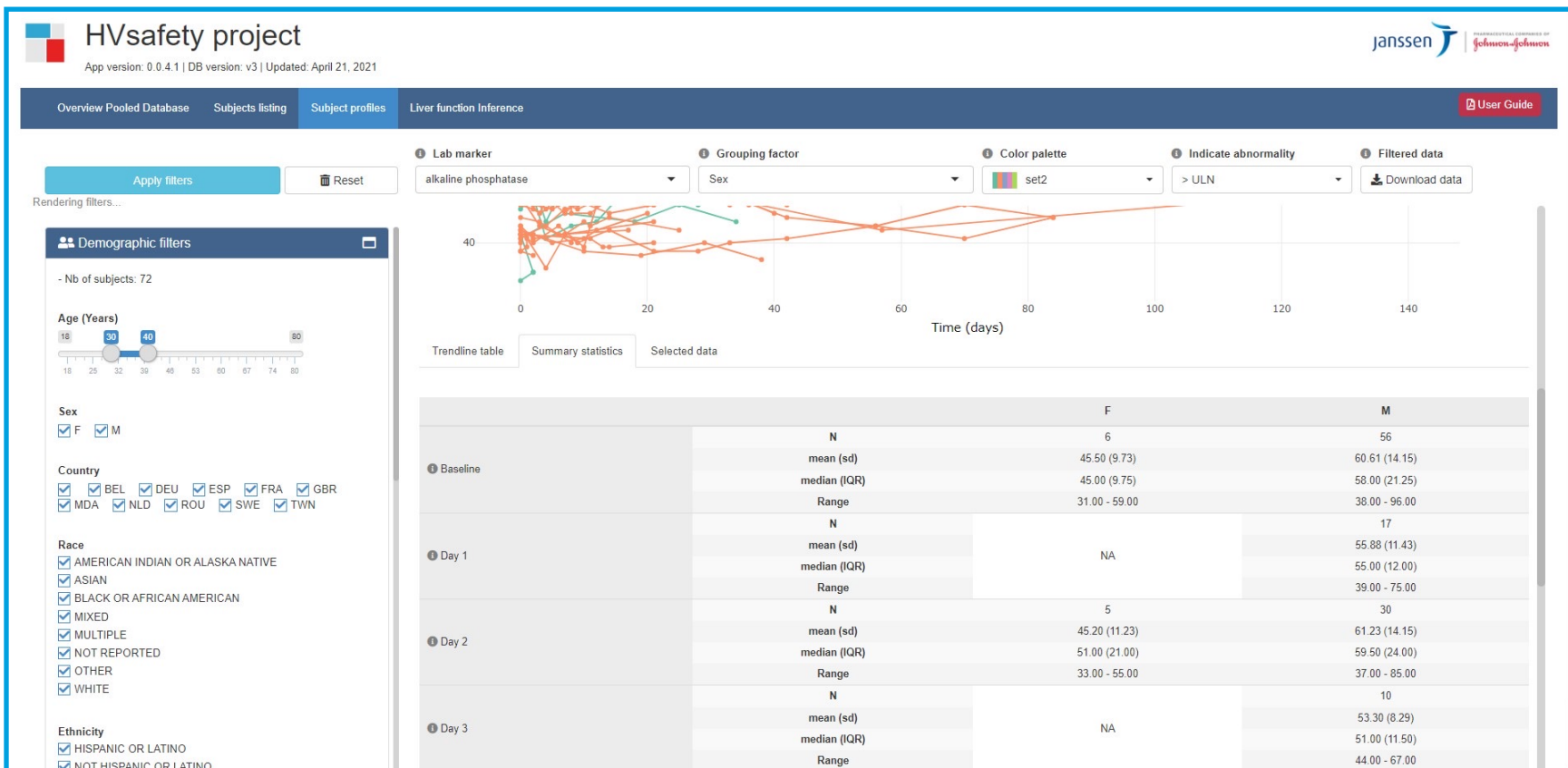
Make selections (demographic, timepoint, test, grouping factor)

Indicate abnormalities



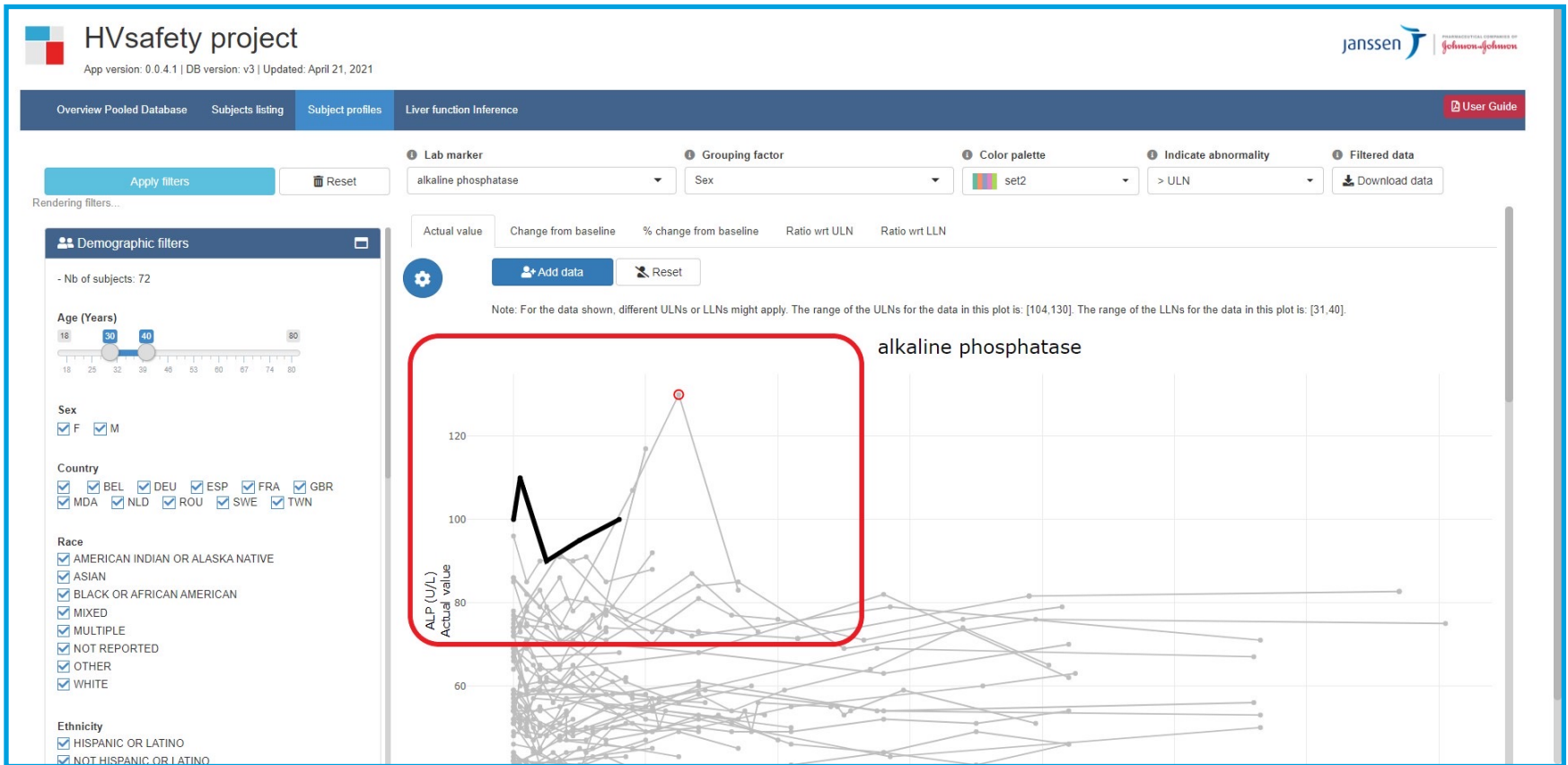
3. R Shiny App (Cont'd)

Summary statistics with same selections



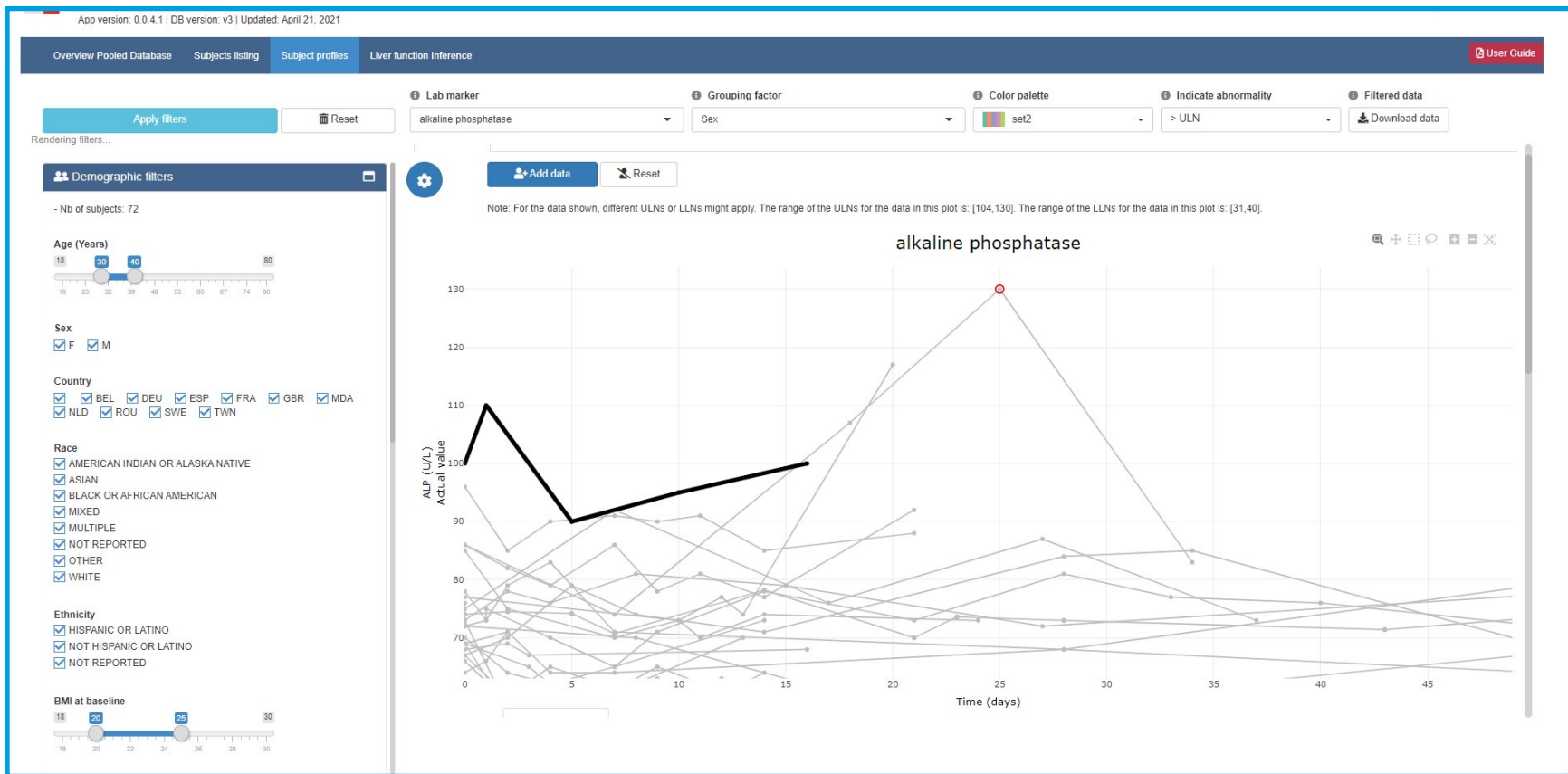
3. R Shiny App (Cont'd)

Add your own data



3. R Shiny App (Cont'd)

Select part of the graph



3. R Shiny App (Cont'd)

Predict incidence of liver function (ALT/AST) abnormality

For single subject or cohort, based on baseline info such as (ALT/AST value)/ULN ratio, age, BMI,...

**HVsafety project**
App version: 0.0.4.1 | DB version: v3 | Updated: April 21, 2021



Overview Pooled DatabaseSubjects listingSubject profilesLiver function Inference

User Guide

Choose overall settings

Liver function parameter

Toxicity criterion

Confidence interval coverage

ALT

> ULN

95%

Prediction for a single subject

Insert the subject characteristics and press the "Predict" button to obtain the probability of observing at least 1 abnormality for that subject

Subject	Age	Race	Ethnicity	1 BMI	1 Baseline value (ratio to ULN)	1 N samples	1 N subjects in database	1 Predicted Prob	1 95% CI
Subject	22	Non-Asian	NOT HISPANIC OR LATINO	23	0.5	6		5.95%	[2.89% ; 11.86%]

Predict

Prediction for entire cohort

1 Cohort size

1 Number of subjects with an abnormality

6

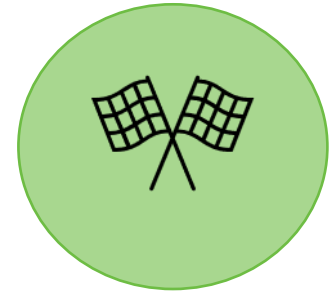
1

Insert the subjects characteristics for the entire cohort and press the 'Predict' button to obtain the probability of observing at least 1 subject(s) with an abnormality in this cohort. Predicted Probabilities per subject are also provided



4. Future steps

- Evaluation of R Shiny App and improving its content based on user-feedback
- Create template/job aids for study programmers
- Finetune the process flow
- Add ECG, AE and Vital Signs information



**THANK YOU
FOR YOUR
ATTENTION**



Questions now

Questions later



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