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Interactive Monitoring of Hepatotoxicity

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Abstract

Problems

- Drug development research is highly regulated and notoriously slow moving.
- Manual review of huge data listings is still common.
- Existing analysis tools are expensive, difficult to customize and tend to use proprietary formats, limiting reproducibility.

Solutions:

Create interactive tools that are

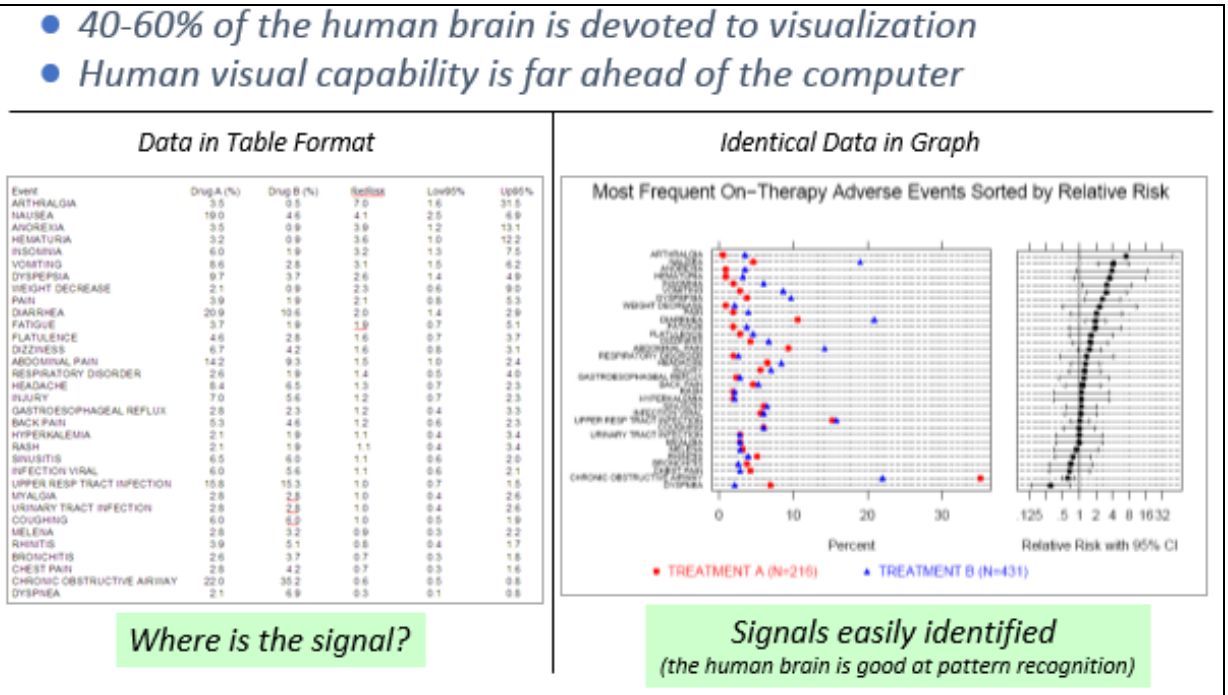
- Open Source - Transparent. Customizable. Free!
- Interactive - Users can explore their data.
- Easy to Use - Just open up a webpage.
- Easy to Configure - Streamlined configuration with R.
- Compliant with Data Standards - Support ADaM and SDTM by default.
- Highly Collaborative – Clinicians, Statisticians, and Programmers working together.
- Agile - Frequent releases with GitHub.
- Engaging - Regular Feedback from users. Pilot testing. Open issue tracking.

ASA Biopharm-DIA Safety WG is an interdisciplinary effort with a Taskforce on Interactive Safety Graphics. A primary feature of the Taskforce's efforts is the pairing of a clinical safety monitoring/review workflow for use during clinical development of a medicine with an interactive, graphical data display. Our first deliverable is for hepatotoxicity. The tool, released in the safetyGraphics R package, builds upon the existing evaluation of drug-induced serious hepatotoxicity (eDish) application, clarifying safety clinician practice based on established science. The interactive features of the tool reflect this workflow, as a means for safety experts as they review the incoming clinical trial data at sponsor companies, and subsequent review at FDA/CDER. As of this writing, testing is underway to release the first version in early 2019. The step-by-step clinical guide demonstrates intended use of the tool to monitor different aspects of hepatotoxicity.

In the spirit of open source, the workflow and tool will be available to all upon release for an organization's internal safety review use.

Introduction

With the advent of CDISC data standards, the world of drug development is ripe for standardized tools and processes to interactively and graphically assess patient data, improving the capabilities of signal detection from human's superior abilities for scientific pattern recognition and saving invaluable time in comparison to the conventional use of voluminous tables and listings (Figure 1).



Signals are more easily identified in a well-designed graph than in a table.

Figure 1. When it comes to signal detection, seeing is believing

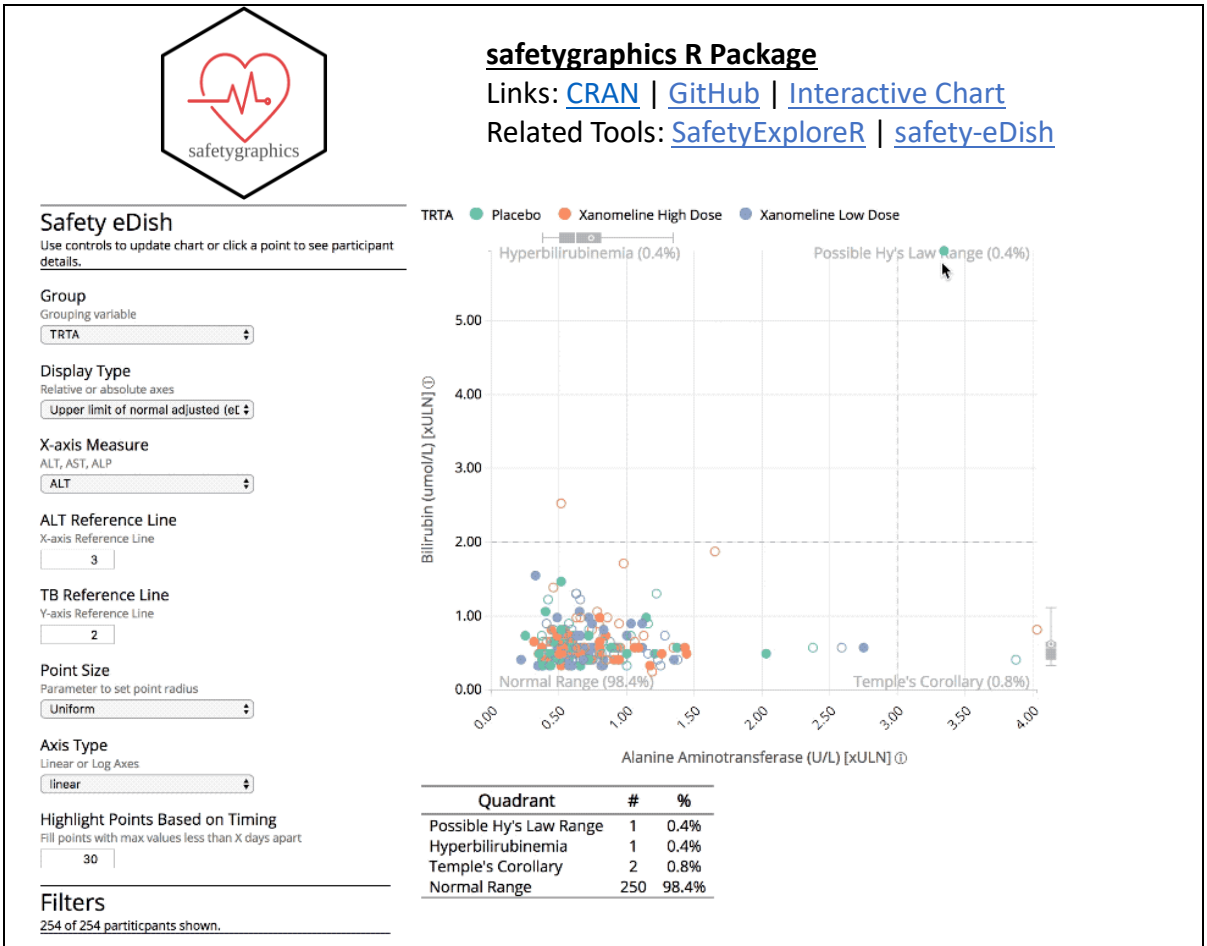
Why do we develop standardized interactive tools on an open source platform? The next step following data standardization in making clinical data readily interpretable is to create the lingua franca for answering those common safety questions of interest to most, if not all, clinical trials. When a community uses standardized ways to communicate about a commonly asked question, that promotes refinement and a deeper and more nuanced understanding of the topic.

Powerful new open source tools for creating interactive graphics, such as d3.js and the shiny package in R, have gained popularity in recent years and offer an intriguing platform upon which to develop and deliver tools across a large user base, developed by those who need it most.

With the community[1] of an interdisciplinary working group (safety clinicians, data scientists and statisticians), an agile software development platform with direct feedback from users themselves was an integral component of the agile development, resulting in a tool that safety clinicians and statisticians are seeking, based on a sound clinical and statistical foundation.

Another valued feature we developed is a standard workflow for clinicians to use in tandem with the tool, identifying a clinically sound pathway to answer common drug safety questions for signal detection and subsequent assessment of drugs under development, based on the literature, clinical expert opinion, and sound statistical and data science principles and design. Our team started its work on one of the most important drug safety topics, hepatotoxicity / drug-induced liver injury (DILI).

[1] This effort closely models two similar efforts with static graphs designed to answer common safety questions (Amit, Heiberger and Lane, 2008; CTSpedia Clinical Trials Safety Graphics Project, 2009-2011)




```
#Code to initialize shiny application
install.packages("safetyGraphics")
library("safetyGraphics")
safetyGraphicsApp()
```

Figure 2. eDISH Interactive Safety Graphics Features

Early specific indicators of drug-induced hepatic injury include elevations of hepatic transaminases and total bilirubin. However, the diagnosis of DILI is one of exclusion, having excluded other possible causes of the laboratory and clinical abnormalities. As first proposed by Dr. Hyman Zimmerman (1978) based on clinical presentation, and subsequently refined by FDA as an evaluation of biomarkers, the concept of "Hy's Law" became adopted to identify instances indicative of the potential for DILI. The predictive value of Hy's Law has been validated by studies in Sweden (Bjornsson & Olsson 2005) and Spain (Andrade et al. 2005). Dr. Ted Guo, a statistician at FDA, was the first to develop a graphical tool to screen laboratory datasets for elevations of transaminases and bilirubin that met the definition of possible Hy's Law cases; the application was called eDISH for evaluation of drug-induced serious hepatotoxicity (Senior 2014). This approach to the graphical display of hepatic laboratory data has subsequently been adopted by safety specialists in industry and academia.

Our Taskforce is interested in developing new interactive tools that expand upon the static nature of existing graphics, such as eDISH. Beyond just a tool for signal detection, the interactive tool would also provide data exploration capabilities to facilitate signal evaluation. This interactive safety graphic of the eDISH plot builds upon the traditional static eDISH graph to afford customization of the analysis and the ability to explore cases that appear in each of the quadrants of interest: potential Hy's Law cases,

Temple's corollary cases and isolated hyperbilirubinemia cases (Figure 2). For each such case of interest, the underlying data can be evaluated for evidence supporting or discounting a contributory role by the drug of interest. The companion user's manual provides not only instructions concerning the features of this tool, but also a suggested workflow for evaluating the characteristics of any cases meeting the conditions for a potential Hy's Law case, a case of Temple's Corollary or a case of hyperbilirubinemia. Each of the suggested evaluation steps is accompanied by information supported by the medical literature concerning how to interpret the findings of each evaluation. The user is also referred to the FDA's guidance document for a review of their approach to evaluating signals of potential DILI (FDA 2009).

Hepatotoxicity Evaluation Workflow

The diagnosis of drug-induced liver injury is one of ruling out other causes, where it is important to first identify possible confounding factors giving rise to elevations in transaminase and total bilirubin levels before concluding that exposure to the drug of interest has resulted in hepatotoxicity. A number of such evaluations can be conducted within the current version of the interactive eDISH graphic. The following flow diagram illustrates a proposed method of working through important analyses that will gather data that supports or discounts a causal role for the drug of interest. At the end of the workflow, and with the consideration of additional data elements, the user will be in a better position assessing the extent to which the drug of interest contributed to the observed laboratory abnormalities.

The workflow consists of several decision steps and suggested evaluations. For each evaluation, a discussion of the rationale and means of interpreting the results is provided based on the medical literature and best practices. Steps 1-3 describe how to assess a case for Hy's Law (upper right quadrant). Steps 4-6 describe a Temple's Corollary evaluation (lower right quadrant), and steps 7-9 describe a hyperbilirubinemia assessment (upper left quadrant). Steps 1-2 are shown in Figure 2 and are described for each element in the User's Manual.

We believe this is the first tool for hepatotoxicity signal detection that matches a software tool to a recommended case workflow based on a clinically referenced standard. The intended users are drug sponsor safety clinicians and statisticians monitoring for hepatotoxicity, and regulatory reviewer clinicians and statisticians. It may be useful for others as well, such as Data Monitoring Committees or others monitoring clinical trial hepatotoxicity.

Technical Framework

The eDish interactive graphic is available as part of the safetyGraphics R package, which is being developed on github and is available on CRAN. For instructions on how to download and use the package on your computer, please refer to: https://github.com/ASA-DIA-InteractiveSafetyGraphics/safetyGraphics/wiki/Vignette:-Shiny-User-Guide.

Discussion

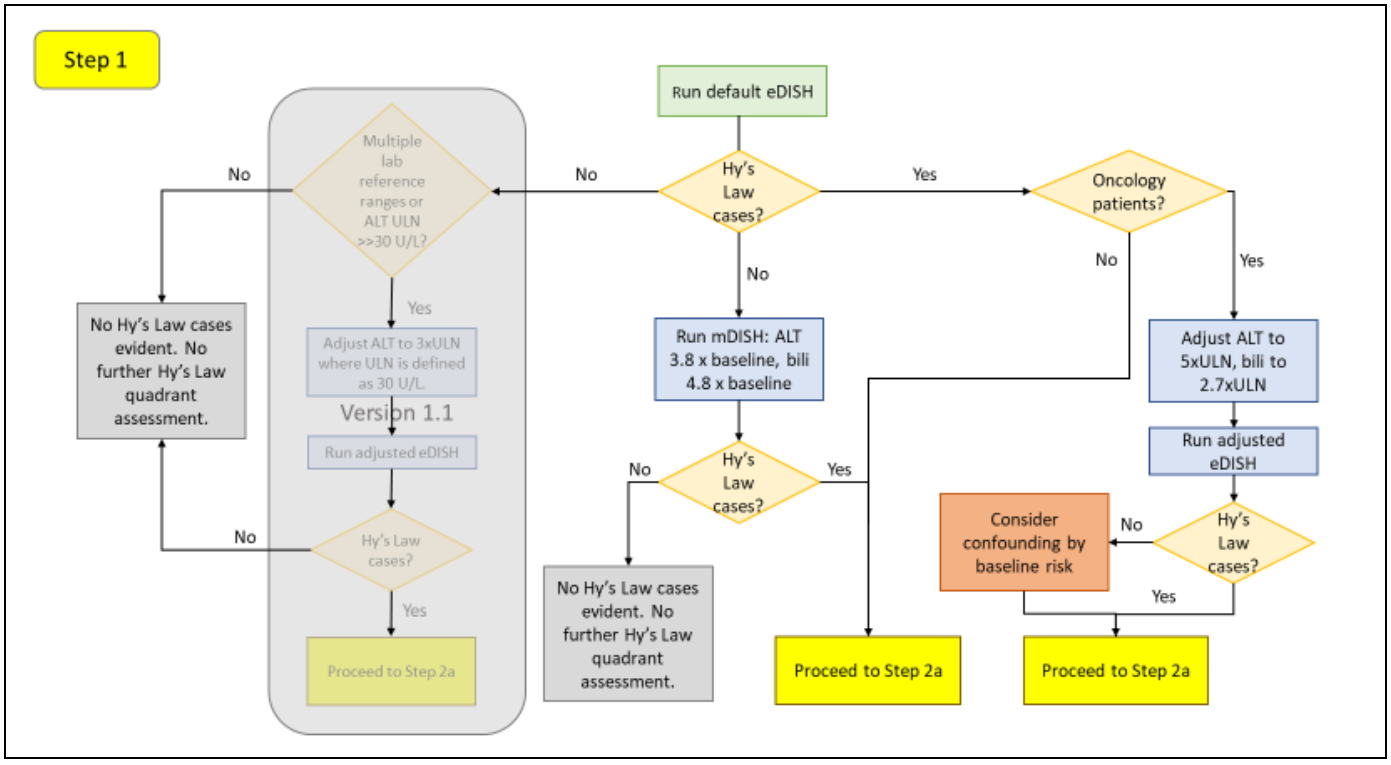
In the first year, this WG was established by ASA Biopharm statisticians so that we could better understand our role in aspects of patient safety during drug development. In our second year, we asked 20 thought leaders for their advice and predictions for the future – leaders in safety and statistics, leaders at FDA and statisticians already established in the discipline of safety statistics. To a person, every thought leader recommended that we expand the group to include clinicians. We followed that advice. This Taskforce is one of the results of doing so.

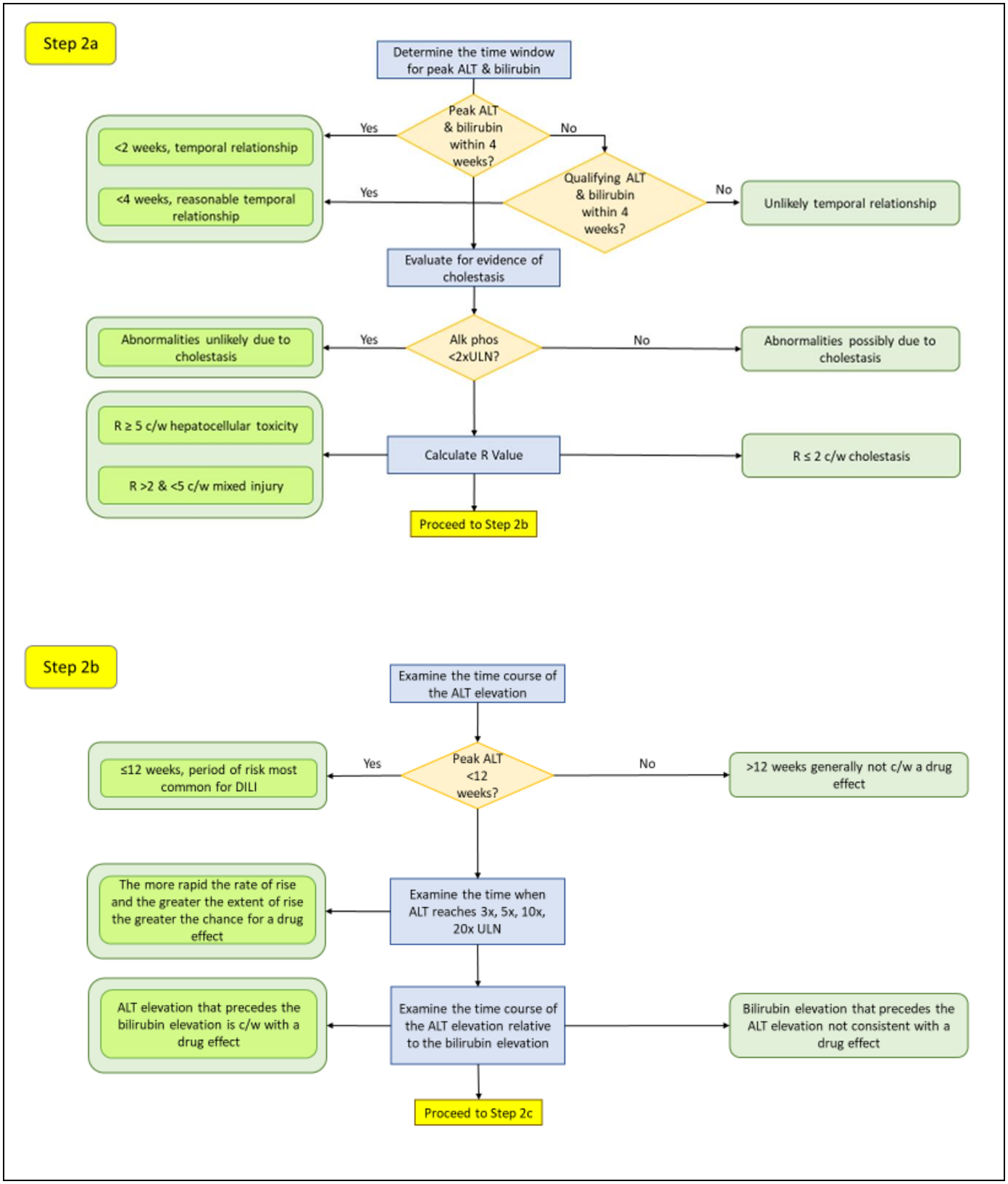
As co-leaders of this team,[2] we observed that the benefits of working across the appropriate disciplines

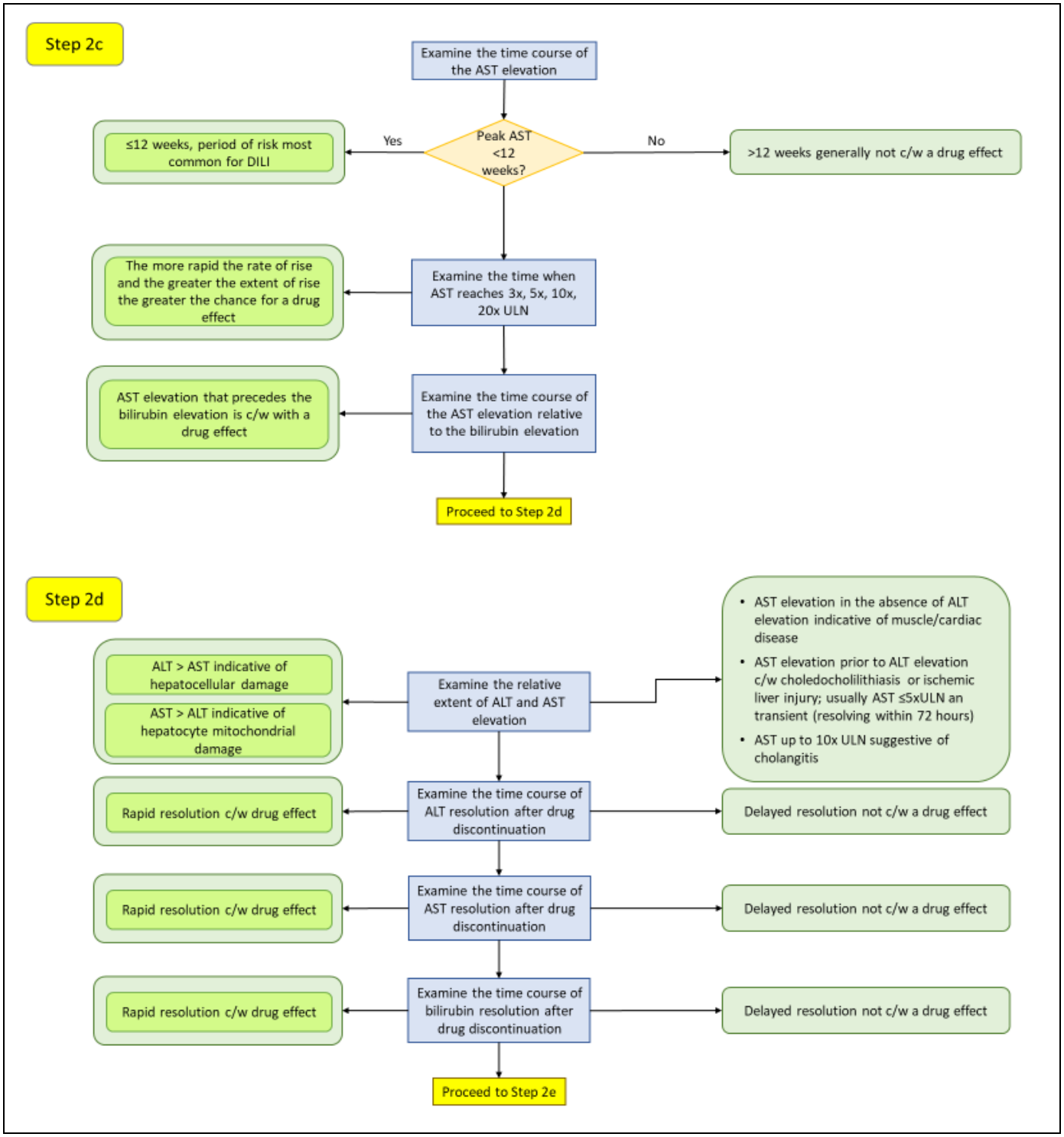
[2] Jim is a safety clinician, Jeremy is a statistician-turned-data scientist, Susan is a statistician

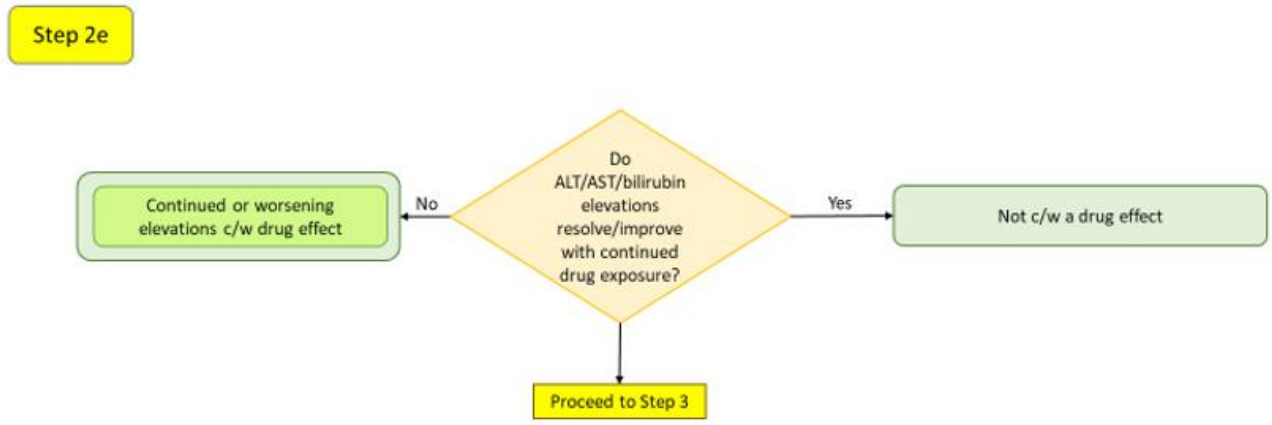
quickly created value and excitement in the tool and process we're endeavoring to create with our interdisciplinary team members (for membership, see acknowledgements below). For a WG to be successful, its members need to find it rewarding and enjoyable, and we're glad for that too.

Development of this open source hepatotoxicity tool and recommended clinical workflow for liver signals is our taskforce's first objective. Adverse events and EKG are the topics we will turn our attention to next.




Step 2a
Determine the time window for peak ALT & bilirubin
Peak ALT & bilirubin within 4 weeks?
Yes
No
<2 weeks, temporal relationship
<4 weeks, reasonable temporal relationship
Yes
Qualifying ALT & bilirubin within 4 weeks?
No
Unlikely temporal relationship
Evaluate for evidence of cholestasis
Abnormalities unlikely due to cholestasis
Yes
Alk phos <2xULN?
No
Abnormalities possibly due to cholestasis
R ≥ 5 c/w hepatocellular toxicity
R >2 & <5 c/w mixed injury
Calculate R Value
R ≤ 2 c/w cholestasis
Proceed to Step 2b
Step 2b
Examine the time course of the ALT elevation
≤12 weeks, period of risk most common for DILI
Yes
Peak ALT <12 weeks?
No
>12 weeks generally not c/w a drug effect
The more rapid the rate of rise and the greater the extent of rise the greater the chance for a drug effect
Examine the time when ALT reaches 3x, 5x, 10x, 20x ULN
ALT elevation that precedes the bilirubin elevation is c/w with a drug effect
Examine the time course of the ALT elevation relative to the bilirubin elevation
Bilirubin elevation that precedes the ALT elevation not consistent with a drug effect
Proceed to Step 2c


Step 2c
Examine the time course of the AST elevation
Peak AST <12 weeks?
Yes
No
≤12 weeks, period of risk most common for DILI
>12 weeks generally not c/w a drug effect
Examine the time when AST reaches 3x, 5x, 10x, 20x ULN
The more rapid the rate of rise and the greater the extent of rise the greater the chance for a drug effect
Examine the time course of the AST elevation relative to the bilirubin elevation
AST elevation that precedes the bilirubin elevation is c/w with a drug effect
Proceed to Step 2d
Step 2d
Examine the relative extent of ALT and AST elevation
ALT > AST indicative of hepatocellular damage
AST > ALT indicative of hepatocyte mitochondrial damage
AST elevation in the absence of ALT elevation indicative of muscle/cardiac disease
AST elevation prior to ALT elevation c/w choledocholilithiasis or ischemic liver injury; usually AST ≤5xULN an transient (resolving within 72 hours)
AST up to 10x ULN suggestive of cholangitis
Examine the time course of ALT resolution after drug discontinuation
Rapid resolution c/w drug effect
Delayed resolution not c/w a drug effect
Examine the time course of AST resolution after drug discontinuation
Rapid resolution c/w drug effect
Delayed resolution not c/w a drug effect
Examine the time course of bilirubin resolution after drug discontinuation
Rapid resolution c/w drug effect
Delayed resolution not c/w a drug effect
Proceed to Step 2e



Note: Grayed-out portions not available in Version 1.0 but is intended to be included in Version 1.1. Step 3 to be implemented in a future version.

Figure 3. eDISH clinical workflow.

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