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# The Story of eDISH (evaluation of Drug-Induced Serious Hepatotoxicity)

John Senior and Ted Guo

For DILI Conference XV

18 March 2015



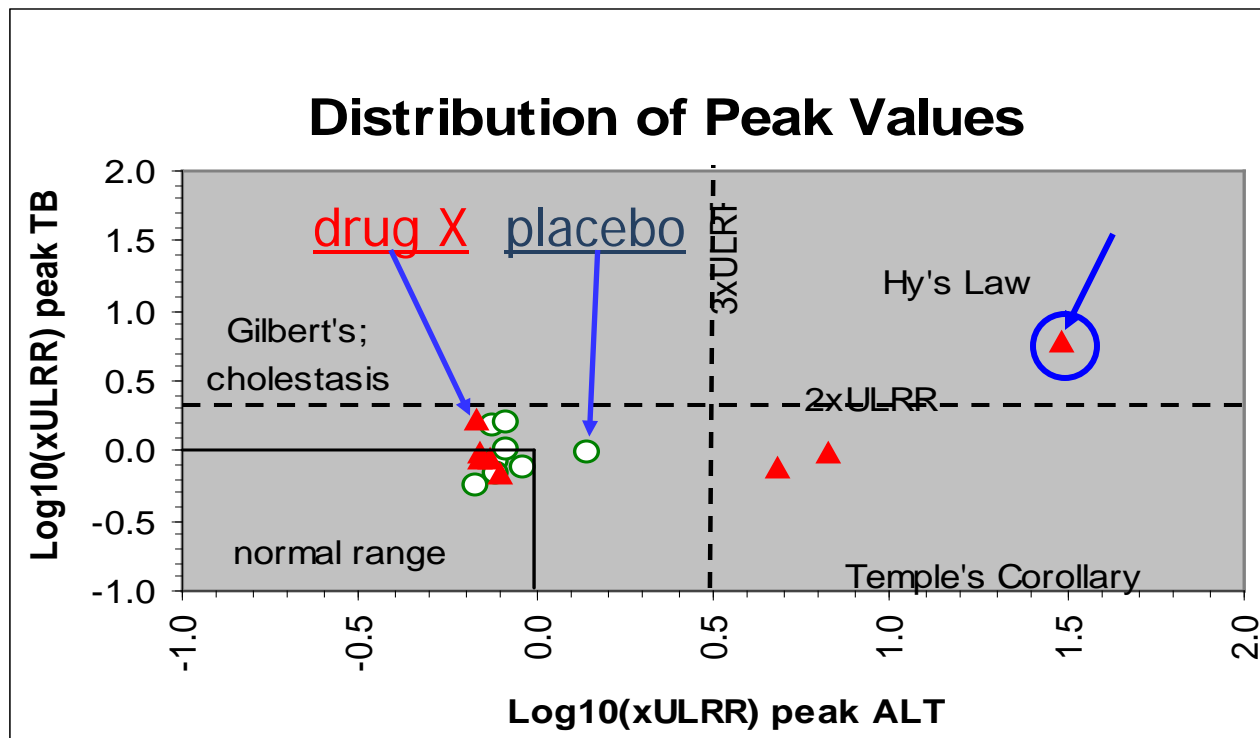
# A historical account of eDISH

- Met John Senior by chance – 2002, then to -09
  - RSR (Regulatory Science Review) enhancement program to aid reviewers at CDER
- He had an interesting idea and I was willing to get outside of the “box”
  - What is DILI? Can a biopsy determine DILI?
  - He taught me about differential diagnosis
  - We used powers of computers to search data, and of humans to recognize patterns at a glance



# The Concept

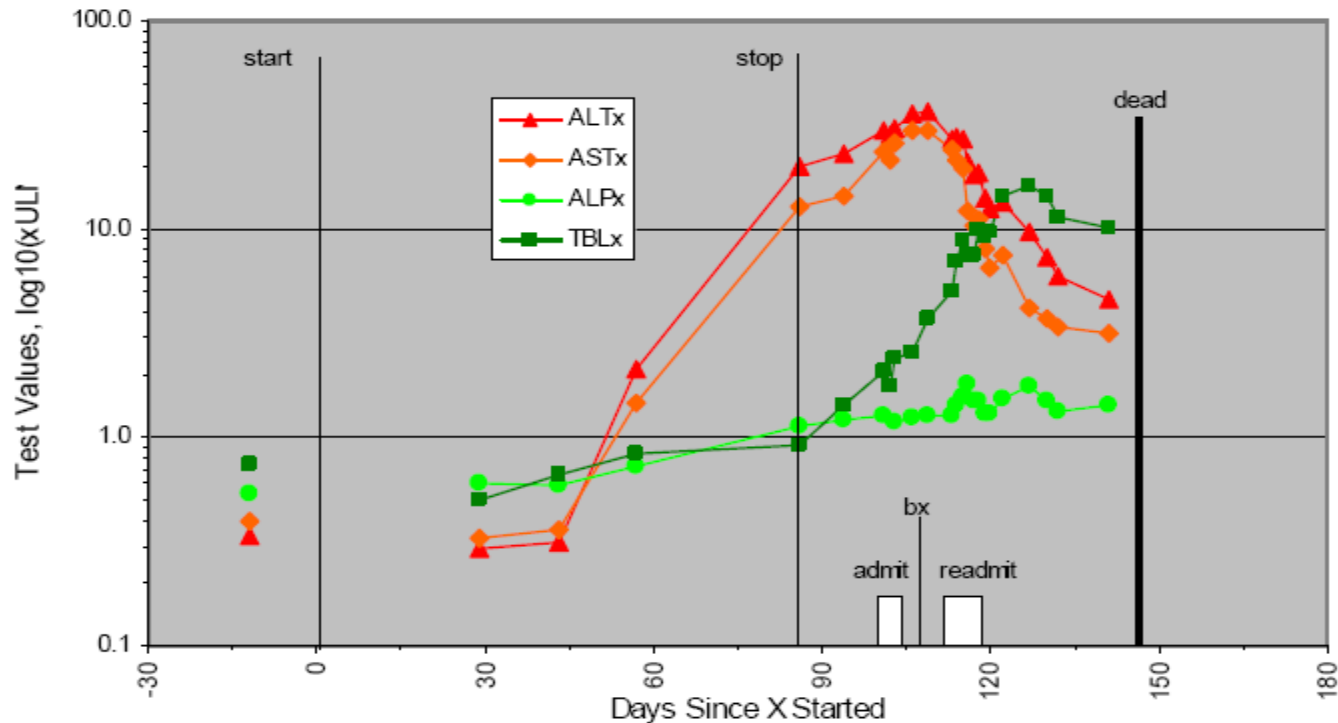
- How can we see all subjects in the study?
- And see all the data for a selected subject?





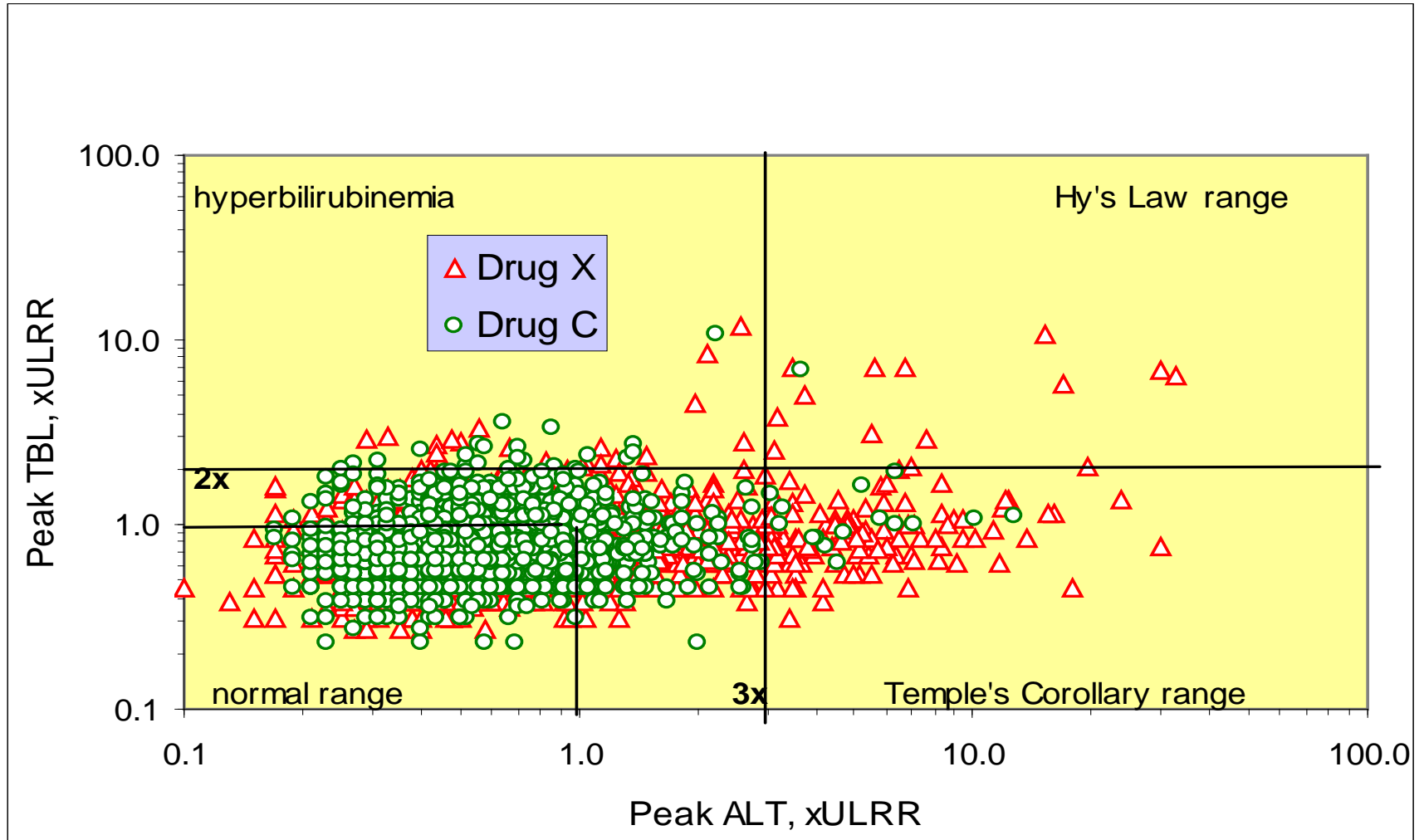
# The Concept (Con't)

- We wanted to see all the liver test data for a single selected subject over the time of study





# eDISH Graph 1 in SAS





# Visualization of a Concept – Step 1

- More than 3900 subjects on one graph
- Drug X showed 7 times as many ALT elevations  $>3x$  ULN, and 14 times as many in RUQ with both ALT  $>3x$ ULN and TBL  $>2x$ ULN
- Inspection showed that many were probably drug-induced; no other explanation
- Drug X was not approved – and later it was found that certain people were especially susceptible to X-induced liver injury



# Time Course of Liver Tests- Step 2

- When ALT rise (hepatocellular injury) precedes the rise in serum bilirubin (liver dysfunction), then it is likely that the injury caused the dysfunction; it may take a few days for bilirubin to accumulate in the circulation
- If bilirubin rise or fluctuating elevation precedes the ALT rise, look for some other cause, such as Gilbert's syndrome of genetically impaired conjugation with glucuronide, and not DILI
- Look at whether the AST rises more than ALT - ?muscle injury to heart or skeletal; is the ALP elevated, possible biliary obstruction



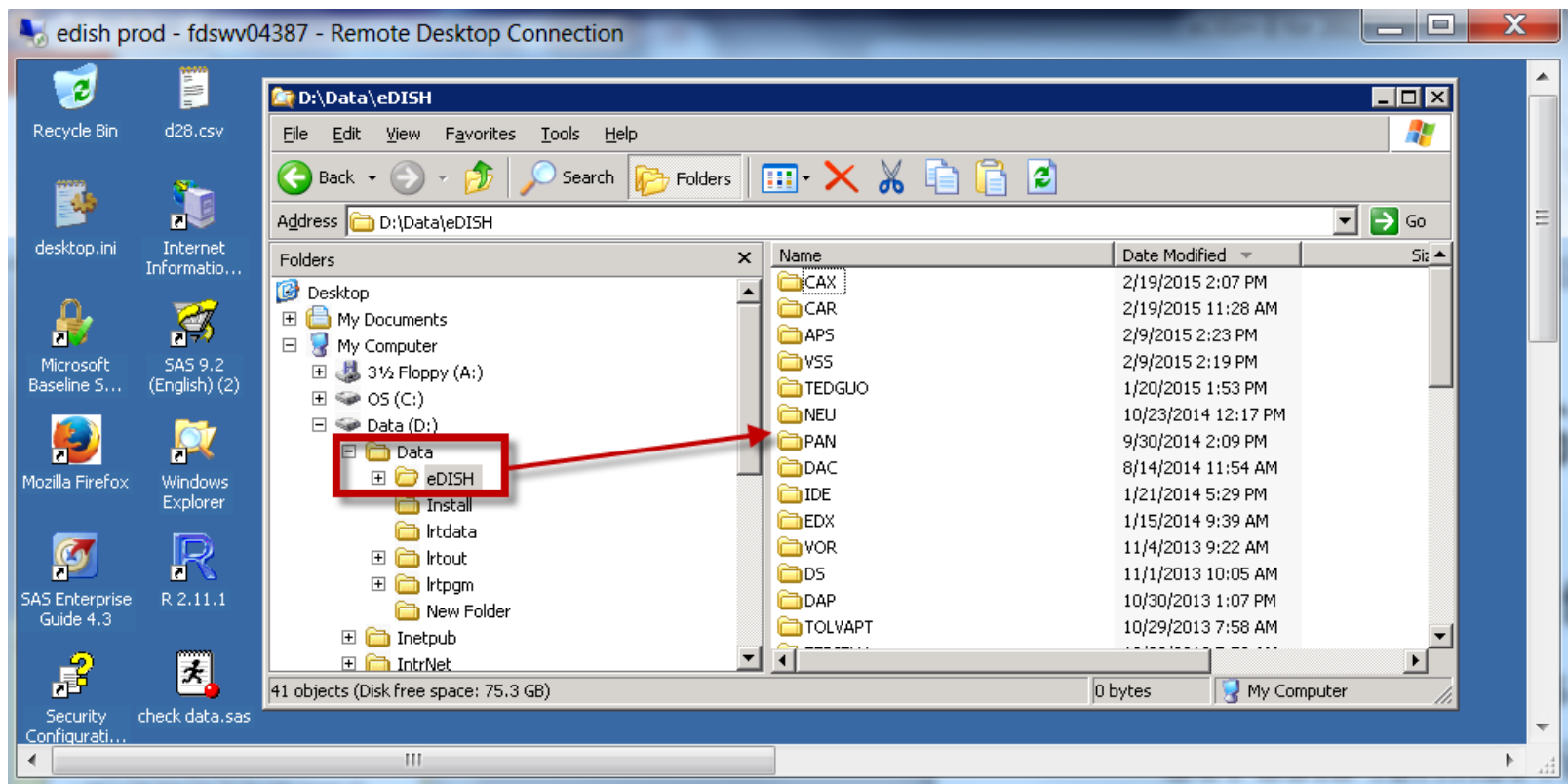


# Get a clinical narrative - Step 3

- The critical piece of the diagnostic puzzle:
- What is or should be in a narrative?
- Who should write it?
- What should the narrative include?
- *Not just a data dump from case reports*
- *Not by IT personnel, but by a physician*
- *Not a product of an automation process*
- *Protocols can't anticipate all AEs that occur*

# A growing database

- eDISH data from clinical trials in a uniform format and maintained in one place





# eDISH2 : Enhancement of eDISH

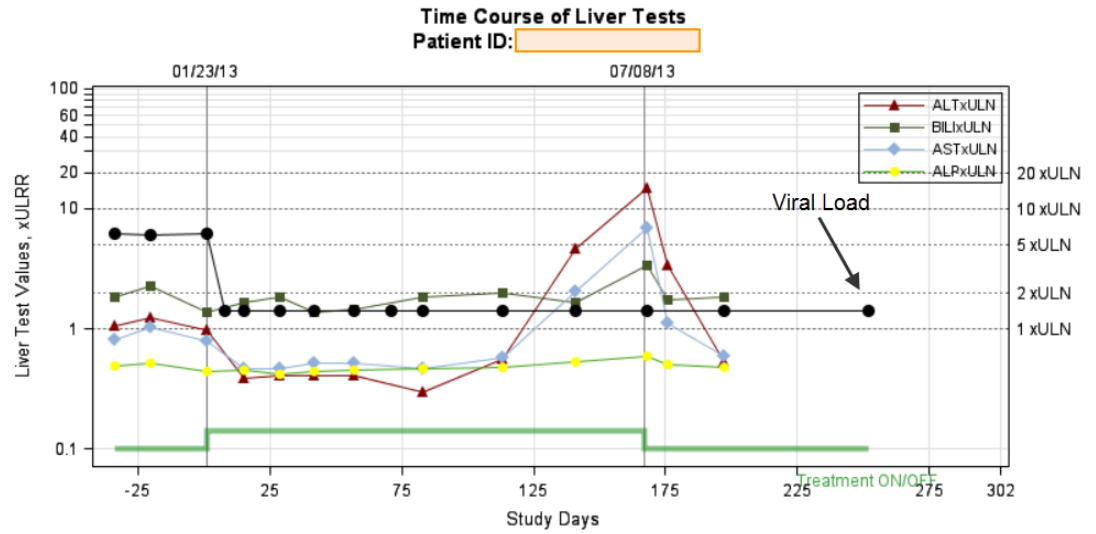
- More features, for research exploration
- More data to augment basic liver tests
- Clearer eDISH-data specifications, especially for the narratives
- The goal is to

***get it right, make the best possible  
diagnosis of what's causing the problem***



## More Data

- Viral-load data and other chemical enzyme data shown in the same graph
- Viral-load-data request as part of the eDISH Data Requirements



	A	B	C	D	E
1	<b>On-Demand Viral Load Data Requirement</b>				
2					
3	<b>Requirement</b>	<b>Standard variable</b>	<b>Variable means</b>	<b>Variable type</b>	
4	Required	STUDYID	Unique identifier for a study within the submission	Char	
5	Required	USUBJID	Unique subject identifier within the submission	Char	
6	Required	VLDC	Viral load Date of collected	Char (ISO 8601 YYYY-MM-DD)	
7	Required	VLSTRESN	Viral load Numeric Result in log10 IU/mL	Num	
8					
9		Note:	The viral load data are only needed for drugs used		
10			to treat chronic viral hepatitis C or B		
11					
12					
13					

Viral load data requested for  
drugs treating hepatitis C



# Get a clinical narrative - Step 3

- Dr. Senior will comment briefly about narratives



# Get a clinical narrative - Step 3.1

- eDISH is meant to be a clinical, medical diagnostic tool, not a statistical exercise of counting numbers;
- protocols cannot anticipate all possible adverse effects of a drug, especially if rare, so extra information is needed;
- physicians uniquely worry about causality, because they have responsibility to treat or prevent problems;
- ideally, narratives should be written by MD investigator at the site who can determine what extra information is needed to establish the probable cause of the problem;
- narratives should not be made by summarizing case records



# Get a clinical narrative - Step 3.2

- Hy's Law is NOT just elevated ALT and TBL, but requires a determination of probable cause; there is no such thing as "Hy's Law chemistries"
- Hy Zimmerman said "drug-induced hepatocellular jaundice is a serious lesion", with considerable mortality. The first requirement is that the drug caused the liver injury, and not something else. The second is that hepatocytes are injured and not biliary obstruction. Third, jaundice results because of the first two, indicating that enough hepatocytic injury has occurred that remaining cells cannot clear plasma bilirubin.
- How many times do we need to repeat this?



# Get a clinical narrative - Step 3.3

- Preparing narratives should not be an afterthought when clinical data are being summarized for NDA submission;
- DILI can be rapid and serious, even fatal, and not done in retrospect. The investigator at the site may have to act quickly and make the right decisions;
- There are many possible causes for elevations in ALT or AST, bilirubin, alkaline phosphatase. They are not simple biomarkers, but indications for close observation and very active diagnostic inquiry;
- Very high ALT levels do not measure severity of liver injury, but indicate the urgency to investigate!





# Get a clinical narrative - Step 3.4

- Clinical trials are not just data gathering exercises to get information to support approvals of new drugs, but are real world tests of drug effects, both good and bad in real people who may vary in how they respond;
- It is difficult to specify all the details needed for writing a good narrative. Go to medical school first, then practice a while, and you may begin to know what's needed;
- The purpose of eDISH is to assist reviewers to scan over all the subjects, learn which ones may need special attention and further investigation to understand the cause of their test abnormalities and clinical findings.