



U.S. Food and Drug Administration

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Use and limitations of the RUCAM

**James W. Freston, M.D., Ph.D.
University of Connecticut
Health Center**

Development of RUCAM

- **Council of International Organizations of Medical Scientists (CIOMS) proposed a consensus conference of experts to develop a hepatotoxicity causality assessment tool**
- **Sponsored by Roussel Uclaf Pharmaceuticals**
- **Meeting in 1989 in France**
JP Benhamou (France), J Bircher (Germany), G Danan (France), WC Maddrey (US), J Neuberger (UK), F Orlandi (Italy), N Tygstrup (Denmark), HJ Zimmerman (US)
- **Created scoring system: Roussel Uclaf Causality Assessment Method (RUCAM)**

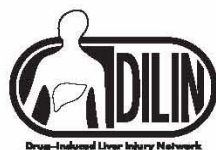
RUCAM

Domains and weightings

Temporal relationship	(0 to 2)
Course	(-2 to 3)
Risk factors	(0 to 2)
Concomitant drug	(0 to -3)
Non-drug causes	(-3 to 2)
Prior reports/ information	(0 to 2)
Rechallenge	(-2 to 3)

Range of scores possible -8 to 14

Highly probable >8	Possible 3-5	Excluded ≤ 0
Probable 6-8	Unlikely 1-2	



**Fax completed form to Duke Clinical Research Institute
(919) 668-7100**

Prospective Study

RUCAM

Site Number: _____ Participant ID Number: _____

RUCAM Causality Assessment of a Drug in a Case of Acute Liver Injury (continued)

Score

4 Concomitant drug(s):

- None or no information or concomitant drug with incompatible time to onset
- Concomitant drug with compatible or suggestive time to onset
- Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset
- Concomitant drug with evidence for its role in this case (*positive rechallenge or validated test*)

☐ 0

☐ -1

☐ -2

☐ -3

5 Search for nondrug causes:

Group I (6 causes):

RECENT VIRAL INFECTION WITH HAV (IgM anti-HAV antibody) or **HBV** (IgM anti-HBc antibody) or **HCV** (anti-HCV antibody and circumstantial arguments for non-A, non-B hepatitis); **BILIARY OBSTRUCTION** (ultrasonography); **ALCOHOLISM** (AST/ALT ≥ 2); **ACUTE RECENT HYPOTENSION HISTORY** (particularly if underlying heart disease).

Group II:

Complications of underlying disease(s); clinical and/or biological context suggesting CMV, EBV or herpes virus infection.

- All causes—groups I and II—reasonably ruled out
- The 6 causes of group I ruled out
- Five or 4 causes of group I ruled out
- Less than 4 causes of group I ruled out
- Non drug cause highly probable

☐ +2

☐ +1

☐ 0

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6 Previous information on hepatotoxicity of the drug:

- Reaction labeled in the product characteristics
- Reaction published but unlabeled
- Reaction unknown

☐ +2

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☐ 0

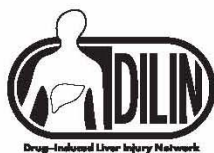
7 Response to readministration:

- | | | | |
|-------------------------------|--|---|-----------------------------|
| Positive | Doubling of ALT with the drug alone | Doubling of AP (or TB) with the drug alone | <input type="checkbox"/> +3 |
| Compatible | Doubling of ALT with the drugs already given at the time of the first reaction | Doubling of AP (or TB) with the drugs already given at the time of the first reaction | <input type="checkbox"/> +1 |
| Negative | Increase of ALT but less than N in the same conditions as for the first administration | Increase of AP (or TB) but less than N in the same conditions as for the first administration | <input type="checkbox"/> -2 |
| Not done or not interpretable | Other situations | Other situations | <input type="checkbox"/> 0 |

Investigator Signature

Investigator's signature: _____

Date signed: ____/____/____
day month year



Prospective Study

RUCAM

Site Number: _____ Participant ID Number: _____

Date completed: ____/____/____
day month yearReviewer Code: _____ ☐ Site investigator ☐ Reviewer A ☐ Reviewer B**RUCAM** Causality Assessment of a Drug in a Case of Acute Liver Injury

	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1 Time to onset:					
Incompatible	Reaction occurred before starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)		Reaction occurred before starting the drug or more than 30 days after stopping the drug (except for slowly metabolized drugs)		Unrelated
Unknown	When information is not available to calculate time to onset, then case is:				Insufficiently documented
	INITIAL TREATMENT	SUBSEQUENT TREATMENT	INITIAL TREATMENT	SUBSEQUENT TREATMENT	Score (check the results)
1a From the beginning of the drug:					
Suggestive	5-90 days	1-15 days	5-90 days	1-90 days	<input type="checkbox"/> +2
Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	<input type="checkbox"/> +1
1b From the cessation of the drug:					
Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	<input type="checkbox"/> +1
2 Course:	DIFFERENCE BETWEEN THE PEAK OF ALT (SGPT) AND UPPER LIMIT OF NORMAL VALUES		DIFFERENCE BETWEEN THE PEAK OF A.P. (OR TB) AND UPPER LIMIT OF NORMAL VALUES		
2a After cessation of the drug:					
Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		<input type="checkbox"/> +3
Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		<input type="checkbox"/> +2
Compatible	Not applicable		Decrease < 50% within 180 days		<input type="checkbox"/> +1
Inconclusive	No information OR Decrease ≥ 50%, after the 30 th day		Persistence or increase or no information No situation		<input type="checkbox"/> 0
OR	Against the role of the drug		Not applicable		<input type="checkbox"/> -2
2b If the drug is continued:					
Inconclusive	All situations		All situations		<input type="checkbox"/> 0
3 Risk factors:	ETHANOL		ETHANOL OR PREGNANCY		
Presence					<input type="checkbox"/> +1
Absence					<input type="checkbox"/> 0
Age of the patient ≥ 55 years					<input type="checkbox"/> +1
Age of the patient < 55 years					<input type="checkbox"/> 0

Development of RUCAM

- **Validation**
 - Application to 49 published DILI cases with positive rechallenge and 28 controls.
 - Cases scored without knowledge of rechallenge results
 - sensitivity 86%, specificity 89%
 - PPV 93%, NPV 78%

Danan, Benichou, J Clin Epidemiol 1993;46:1323

Comparison with another method: Clinical Diagnostic Scale (CDS) (M&V)

Domains and weightings

Temporal association

From initiation (1 to 3)

From cessation (-3 to 3)

Normalization (0 to 3)

Non-drug causes (-3 to 3)

Extrahepatic manifestations (0 to 3)

Rechallenge (0 to 3)

Prior reports (-3 to 2)

Range of scores possible - 9 to 20

Definite > 17

Possible 10-13

Excluded < 6

Probable 14-17

Unlikely 6-9

RUCAM vs CDS

215 cases of hepatotoxicity evaluated by 3 independent experts

Also assessed by both RUCAM and CDS

Absolute agreement in 42 cases (18%)

Disagreement of 1 level in 108 cases (47%)

Disagreement of 2 levels in 70 cases (31%)

Best agreement when injury suggested immunoallergy

Lowest agreement with cholestatic lesion

No agreement with fulminant hepatitis

Conclusion: RUCAM closer than CDS to experts' ratings

Lucena et al. Hepatology 2001;33:123

RUCAM limitations based on DILIN experience

- **Ambiguous instructions**
 - Definition of hepatocellular, cholestatic, mixed reactions
 - Unclear criteria for competing cause/drug
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- **Arbitrary weighting of factors; not based on data**
 - Overweighting of rechallenge
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 - Excessive penalty for competing hepatotoxic drug (RUCAM is drug-specific and DILI insensitive)
- **Limited risk factors: alcohol, pregnancy, age above 55**
- **Considerable variability among raters**



Prospective Study

RUCAM

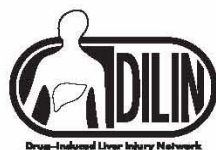
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Suggestive	5-90 days	1-15 days	5-90 days	1-90 days	<input type="checkbox"/> +2
Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	<input type="checkbox"/> +1
1b From the cessation of the drug:					
Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	<input type="checkbox"/> +1
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Compatible	Not applicable		Decrease < 50% within 180 days		<input type="checkbox"/> +1
Inconclusive	No information OR Decrease ≥ 50%, after the 30 th day		Persistence or increase or no information No situation		<input type="checkbox"/> 0
OR	Against the role of the drug		Not applicable		<input type="checkbox"/> -2
2b If the drug is continued:					
Inconclusive	All situations		All situations		<input type="checkbox"/> 0
3 Risk factors:	ETHANOL		ETHANOL OR PREGNANCY		
Presence					<input type="checkbox"/> +1
Absence					<input type="checkbox"/> 0
Age of the patient ≥ 55 years					<input type="checkbox"/> +1
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RUCAM limitations based on DILIN experience

- **Ambiguous instructions**
 - Definition of hepatocellular, cholestatic, mixed reactions
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RUCAM

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RUCAM Causality Assessment of a Drug in a Case of Acute Liver Injury (continued)

Score

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- None or no information or concomitant drug with incompatible time to onset
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- Concomitant drug with evidence for its role in this case (*positive rechallenge or validated test*)

☐ 0

☐ -1

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5 Search for nondrug causes:

Group I (6 causes):

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Group II:

Complications of underlying disease(s); clinical and/or biological context suggesting CMV, EBV or herpes virus infection.

- All causes—groups I and II—reasonably ruled out
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☐ +2

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| Negative | Increase of ALT but less than N in the same conditions as for the first administration | Increase of AP (or TB) but less than N in the same conditions as for the first administration | <input type="checkbox"/> -2 |
| Not done or not interpretable | Other situations | Other situations | <input type="checkbox"/> 0 |

Investigator Signature

Investigator's signature: _____

Date signed: ____/____/____
day month year

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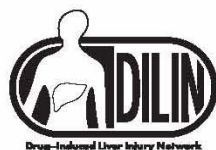
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Compatible	Not applicable		Decrease < 50% within 180 days		<input type="checkbox"/> +1
Inconclusive	No information OR Decrease ≥ 50%, after the 30 th day		Persistence or increase or no information No situation		<input type="checkbox"/> 0
OR	Against the role of the drug		Decrease < 50%, after the 30 th day OR Recurrent increase		<input type="checkbox"/> -2
2b If the drug is continued:					
Inconclusive	All situations		All situations		<input type="checkbox"/> 0
3 Risk factors:	ETHANOL		ETHANOL OR PREGNANCY		
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| Not done or not interpretable | Other situations | Other situations | <input type="checkbox"/> 0 |

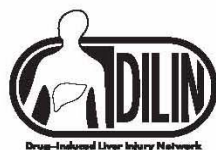
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Variability in RUCAM Assessment of 17 Prospective DILI Cases

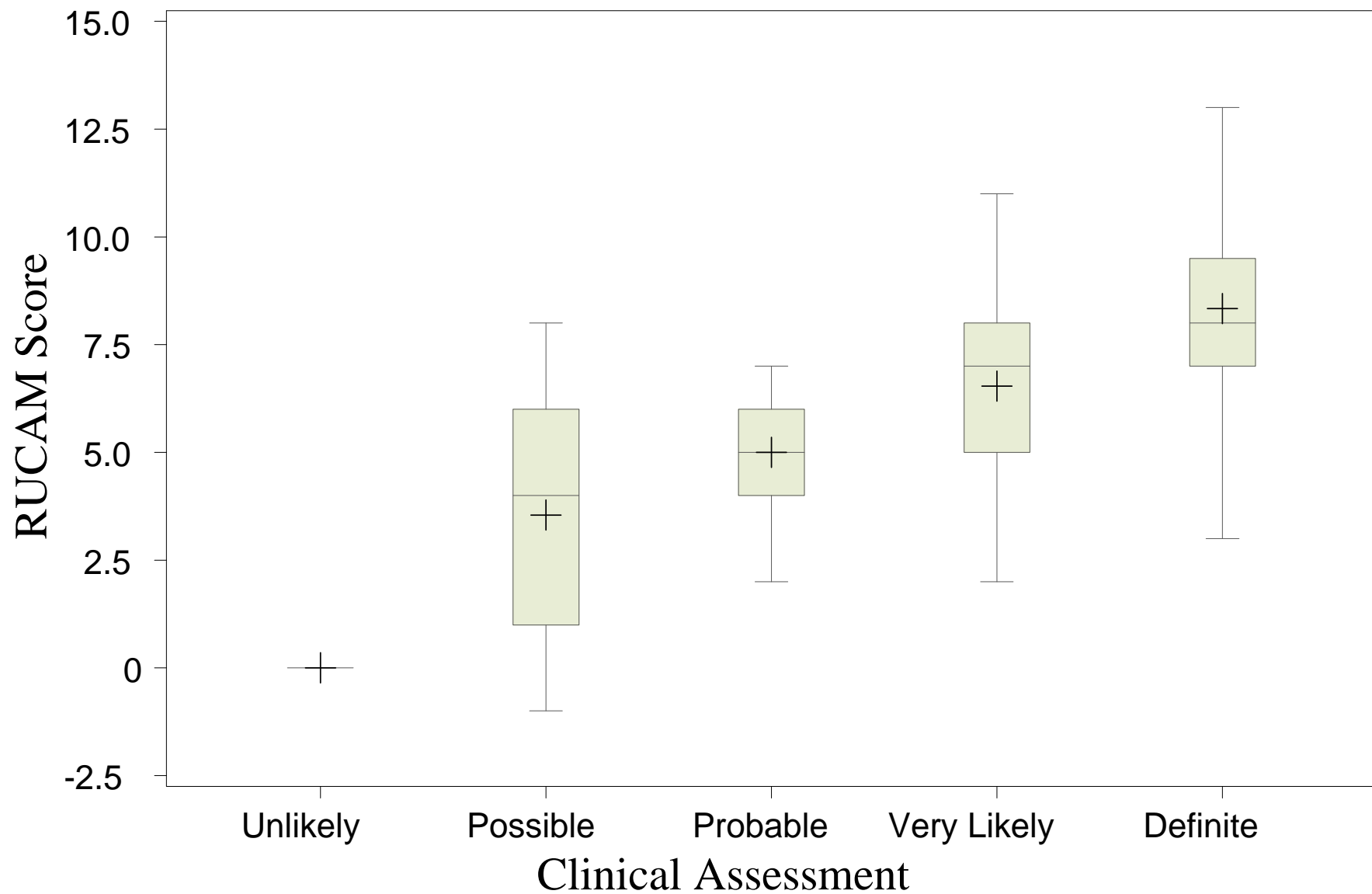
No. cases complete agreement	4
No. cases with score varying by 1	3
No. cases with score varying by >1	10

DILIN - Retrospective Study

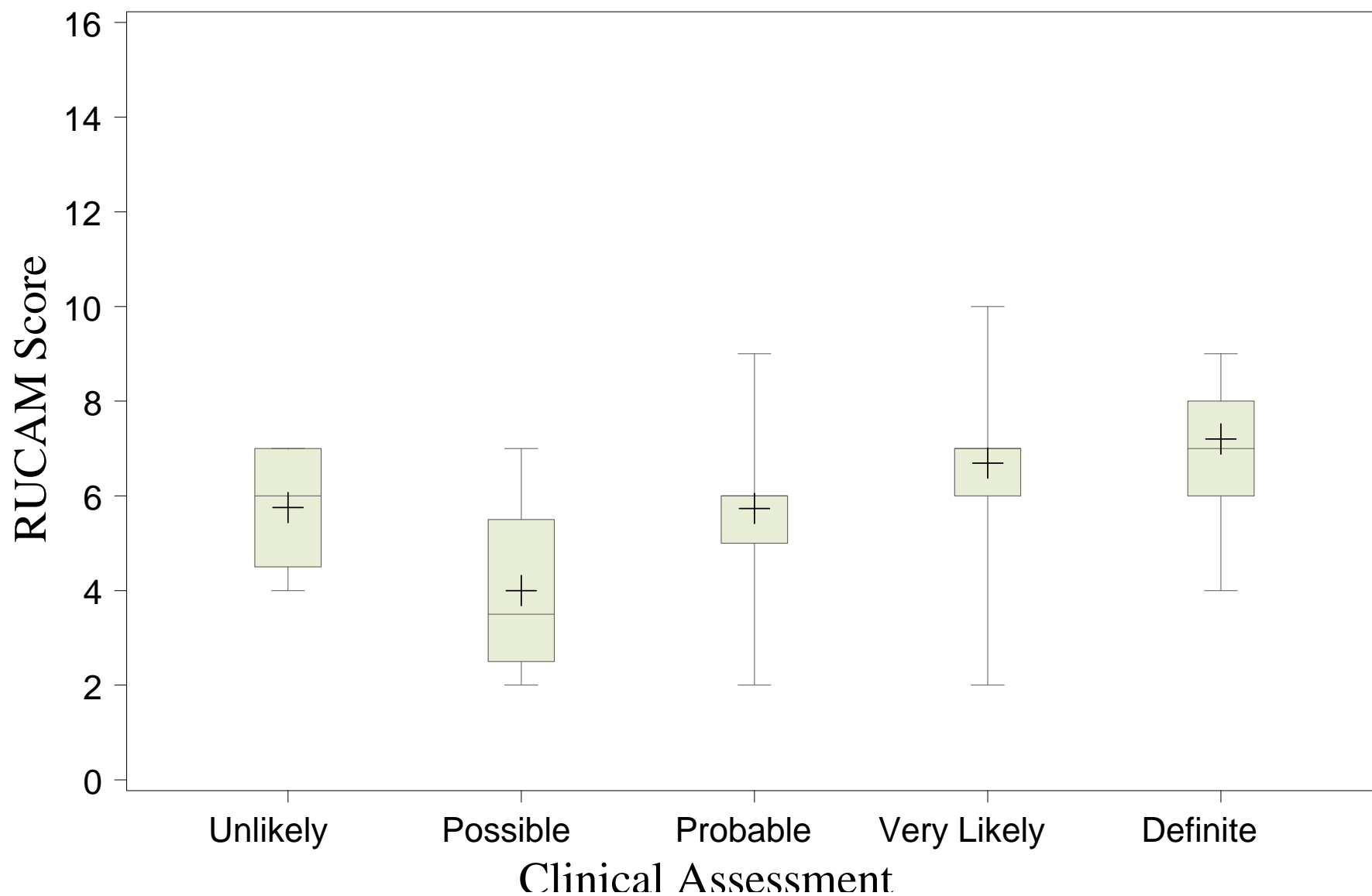
Figure 6

Correlation Between RUCAM and Clinical Assessment

Pearson Corr=0.62 (p=<.0001)



DILIN - Prospective Study
Figure 4
Correlation Between RUCAM and Clinical Assessment
Pearson Corr=0.39 (p=<.0001)



DILIN attempts to improve RUCAM consistency

- **Adoption of standard operating procedures**
 - **Definitions**
 - Hepatocellular vs. cholestatic vs. mixed reactions:
Use of “R ratio”
 - Time to onset: LFT abnormalities, symptoms or both
 - Calculating extent/time of decline in ALT and Alk P'tase
 - When to score as “inclusive”
 - Alcohol use: ≥ 14 drinks per week in men, ≥ 7 in women or clear-cut history of chronic alcoholism
- **Practice**

Defining the reaction type according to “R ratio”

$$R = (\text{ALT/ULN}) / (\text{Alk P'tase} / \text{ULN})$$

Hepatocellular: $R > 5$ and $\text{ALT} > 2 \times \text{ULN}$ or
baseline

Cholestatic: $R < 2$ and $\text{Alk P'tase} > \text{ULN}$

Mixed: $2 < R < 5$

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- Practice

DILIN attempts to improve RUCAM consistency

- Re-review of 18 cases
 - No significant difference on average between the two reviews but this masked individual scoring changes ranging from -4 to +7
 - Reliability among reviewers improved from first to second review
 - Preliminary conclusion: Application of RUCAM can be improved by use of standard operating procedures, practice, or both.
- A full re-review of cases is underway.