Harmonization of Clinical Immunogenicity Reporting

…An AAPS Initiative

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Janssen Research & Development, LLC

ONE TEAM Making the Difference for Patients WORLDWIDE

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Descriptions of immunogenicity in Drug Package Inserts are subjective and inconsistent

- **Antibody Incidence**
  - "…only based on higher titer results because the assay lacked sensitivity"
  - "…treatment emergent binding antibodies"
  - "…treatment induced antibodies…"

- **Magnitude (ADA levels)**

  "low titer" versus "high titer" antibodies

  "…equivocal titers"

  "…protocol specified high-titer"

  "…weakly positive"… "…low binding…"

  "…indeterminate" (low signal response)

- **Kinetics/Temporal Patterns**
  - Onset of ADA
    - "…median time to antibody formation"
    - "…median time to peak titer"
    - Early versus late onset
  - Duration of ADA
    - "short-lived"
    - "…transient"
    - "…persistent"
    - "…plateaued"
    - "…downward trend"

Hence, a call for…
Harmonization of Clinical Immunogenicity Reporting by
The Therapeutic Protein Immunogenicity Focus Group (TPIFG) of the American Association Pharmaceutical Scientists (AAPS)

***Our Goal*:**
Produce a whitepaper proposing standardized terminology and a harmonized approach to biologic drug immunogenicity data interpretation and presentation. Recommending key aspects of product immunogenicity that can enable appropriate decision-making by sponsors, health authorities, physicians, and inform patients.

Draft manuscript in progress (anticipated publication in 2013):

• Standardized terminology and definitions – clinically meaningful characteristics of immunogenicity and standardized descriptions of those characteristics

• Recommended sampling schema that can enable acquisition of necessary information on key aspects of immunogenicity.

• Suggest approaches to describe clinical relevance of immunogenicity and determine clinical cutoffs (thresholds).

Harmonization of Clinical Immunogenicity Reporting

An Initiative of the Therapeutic Protein Immunogenicity Focus Group (TPIFG) of the American Association Pharmaceutical Scientists (AAPS)

The Whitepaper Team:

- Gopi Shankar, Ph.D. (*Janssen R&D / Johnson & Johnson*)
- Arno Kromminga, Ph.D. (*European Immunogenicity Platform*)
- Steven Arkin, MD (*Pfizer*)
- Meena Subramanyam, Ph.D. (*Biogen–Idec*)
- Laurent Cocea, MD, Ph.D. (*Health Canada, CERB/Clinical Evaluation Division*)
- Daniela Verthelyi, MD, Ph.D. (*FDA, CDER/Office of Therapeutic Proteins*)
- Susan Kirshner, Ph.D. (*FDA, CDER/Office of Therapeutic Proteins*)
- Mark Borigini, MD (*FDA, CBER/Office of Cellular and Gene Therapies*)
- Sarah Yim (*FDA, Division of Pulmonary, Allergy and Rheumatology Products*)
- Vishwanath Devanarayan (AbbVie)

Previously at the 3rd EIP symposium (2011)…

- Presentation titled "*A Call For Harmonizing Approaches To Clinical Immunogenicity Data Analyses And Presentations*"
- What was available:
  - Regulatory agency (FDA, EMA) guidance documents and some publications by their representatives
  - Several AAPS Whitepapers
- Gap analysis:
  - Inconsistent use of terms (definitions)
  - Inconsistent analysis/ presentation of results
  - Information not particularly useful to healthcare professionals
- An AAPS Survey on Immunogenicity *for Physicians only:* interim results

Previously at the 4th EIP symposium (2012)…

- Presentation titled "*Harmonization of Clinical Immunogenicity Reporting*"
- An AAPS Survey on Immunogenicity *for Physicians only:* final results
- *Work in progress* of the AAPS-TPIFG "*Uniform Reporting of Immunogenicity*" Whitepaper Team
  - *Draft* Sampling Recommendations
  - Some *Draft* Terms and Definitions
  - *Draft* ADA kinetics illustration and descriptive statistics

Feb 27, 2013: EIP Social Event at the *Englischer Garten SeeHaus* Restaurant

Melody#3 from Monty Python:

Always look on the bright side of life…

(I think we made Eric Idle proud last night!)

ADA could be a HAHA, HACA or not ?
La la la la la la la la
We don't know what it means, but that's what we got
La la la la la la la la

And thus cried the gleefully cacophonous E
choir, begging for clarity in the semantics
HACA and HAHA…

HACA and HAHA clarification…

HACA (**Human anti-chimeric antibody**)**:** *Human antibodies against non-human epitopes present in a chimeric mAb drug molecule.* Those epitopes can be xenotypic or result from the fusion of two human epitopes (a junctional neoepitope), but are not naturally expressed in the human population. Taken literally, this term can be interpreted to mean that the ADA can potentially cross-react with other chimeric antibodies, raising concern over the administration of other chimeric mAb drugs to ADA positive subjects. When cross-reactivity with other chimeric antibodies is not confirmed, it is recommended to avoid the term HACA to refer to ADAs against chimeric mAb drugs.

HAHA (Human anti-human antibody): *Human antibodies against human epitopes present in a humanized or fully human mAb drug molecule.* Taken literally, this term can be interpreted to mean that the ADA can potentially cross-react with other human sequence based antibodies, raising concern over the administration of other human mAb drugs to ADA positive subjects. When cross-reactivity with other human sequence based antibodies is not confirmed, it is recommended to avoid the term HAHA to refer to ADAs against humanized or human mAb drugs.

Terms & Definitions - *draft*

- **Simple terminology requiring clarification**:
  - ADA, Binding ADA, Neutralizing ADA, Non-neutralizing ADA, HAMA, HACA, HAHA.
- **Terms used to describe ADA status of a sample:**
  - **ADA Positive Sample, ADA Negative Sample**
  - **ADA Inconclusive Sample:** when ADA is not detected in a sample but drug is present in the same sample at a level that can produce interference in the ADA detection method, then the negative ADA result cannot be incontrovertibly confirmed and the sample classification for ADA status should be considered inconclusive.
  - **Unevaluable Sample:** when a sample could not be tested for ADA due sample loss, mishandling, or errors in sample collection, processing, storage, etc.
- **Terms used to describe ADA status of a subject:**
  - ADA Positive, ADA Negative, ADA Inconclusive, Unevaluable
- **Terms relationship of ADA to drug exposure in a study:**
  - Baseline (Pre-existing) ADA, treatment-boosted ADA, treatment-induced ADA

Terms & Definitions - *draft*

- **Terms used to describe the characteristics of treatment-induced ADA immune response in a sample set:**

  - ADA prevalence: the proportion of a population with baseline ADA. This term should not be confused with the term "ADA incidence". Additionally, the terms "rate of baseline ADA" or "rate of pre-existing antibodies" should not be used, because "rate" usually implies a measured unit over time, whereas "prevalence" relates the measured unit to the total population of units.

  - ADA incidence: the proportion of the study population found to have seroconverted or boosted their pre-existing ADA during the study period. It is the sum of both **treatment-induced** and **treatment-boosted ADA positive subjects** as a proportion of the evaluable subject population. This should not be confused with the term "ADA prevalence". Additionally, the term "rate of ADA" should not be used to mean ADA incidence, because "rate" usually implies a measured unit over time, whereas "incidence" relates the measured unit to the total population of units.

Terms & Definitions - *draft*

- **Terms used to describe the kinetics of treatment-induced ADA immune response in a sample set:**

  Duration: Transient ADA, Persistent ADA

  Onset of ADA: refers to the time period between the initial administration of the biologic drug and the first instance of treatment-induced ADA.

Reporting of Results - *draft*

(*Tabular format may be easiest…*)

- **ADA Prevalence, titer and boosting:**
  - Baseline ADA positive subjects as a percentage of the total number of subjects whose baseline samples were tested for ADA.
  - Titer range (median, IQR) of the baseline ADA positive samples
  - Percentage of baseline ADA positive subjects with significant increases in ADA titer after biologic drug administration

- **ADA incidence and titer:**
  - Overall ADA incidence: combined results of treatment-boosted ADA positive subjects and treatment-induced ADA positive subjects. Compute as a percentage of the total number of evaluable subjects, excluding baseline positive subjects without any samples available after drug administration.
  - Treatment-induced ADA incidence computed as a percentage of the total number of evaluable subjects that were ADA negative at baseline. Also report peak positive titer and range (median, IQR) for this group of subjects.
  - Treatment-boosted ADA computed as a percentage of the total number of evaluable subjects that were ADA positive at baseline. Also compute the fold-increase in titer (ratio of peak post-administration titer to baseline titer) and range of titer increases (median, IQR).

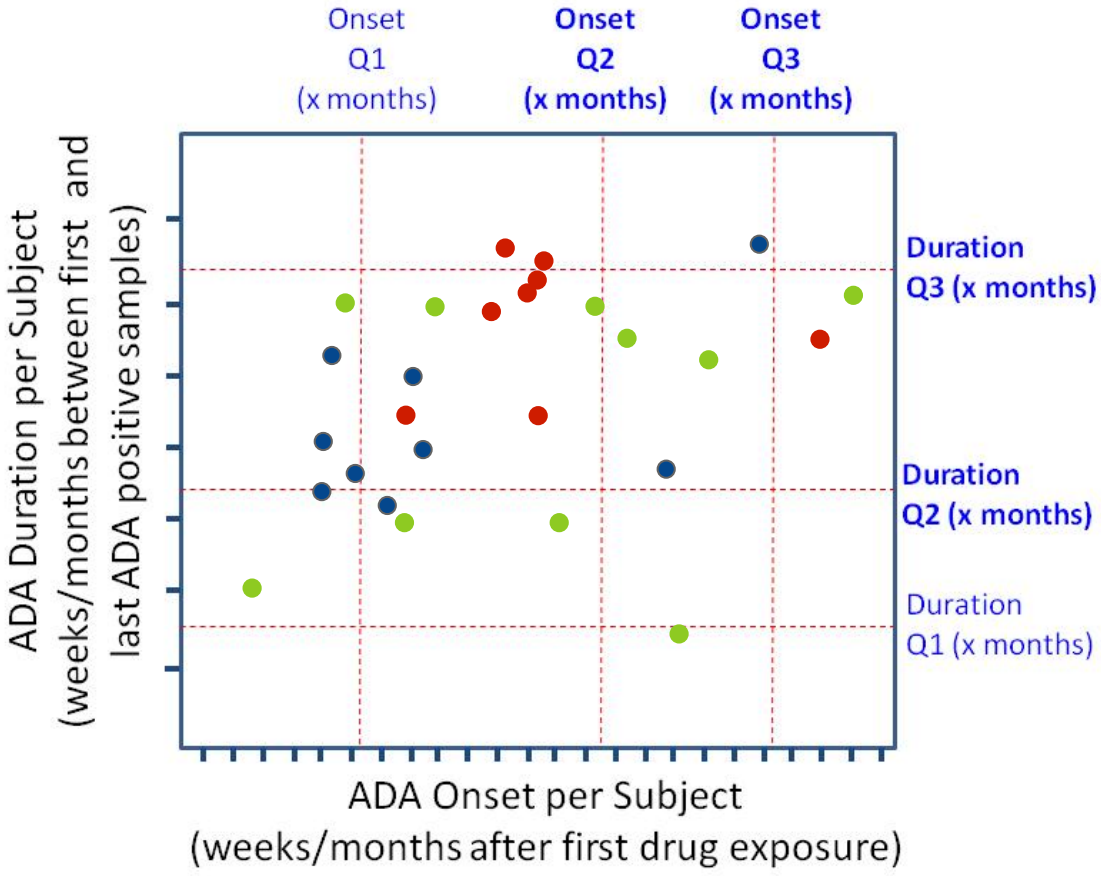
Reporting of Results - *draft*

- **Neutralizing ADA (Nab):** when applicable, report the prevalence, boosting and incidence as described above. If all ADA are neutralizing in all subjects a separate analysis is obviously redundant.
- **Kinetics of ADA:** the timing of ADA development and its duration can be useful information for a clinician to monitor treatment progress. To the drug developer, knowledge of ADA kinetics can help optimize the sampling schedule in subsequent studies of the same biological drug. And, in instances of ADA monitoring post-marketing as part of pharmacovigilance plans, the surveillance schedule and the design of risk management and mitigation strategy can be optimized by understanding ADA kinetics.

Illustration of ADA Kinetics - *draft*

- A simple graph/plot **by posology** can provide an intuitive view of the kinetics of ADA, such as:

- **Dose level 1, Q2W**
- **Dose level 2, Q2W**
- **Dose level 1, Q4W**



Descriptive statistics for ADA Kinetics - *draft*

- This approach obviates definitions for ADA immune response kinetics – the onset (early/ late) or duration (transient/persistent).
- Applicable only to Treatment-Induced ADA.
- Enables the design of risk management and mitigation strategy because it informs your surveillance schedule.
- *Caveat*: feasible only when sample size is statistically significant. Frequently complex studies with multiple arms and satellite studies may not allow for statistical assessments of immunogenicity.
- For ADA Onset: present the median value (Q2, the "Median time to antibody formation") and the inter-quartile range (Q1 and Q3)
  - Eg: "When half of the subjects seroconverted" OR "when 75% (majority) of the subjects seroconverted"
- For ADA Duration: present the median value (Q2, the "Median time of antibody duration") and the inter-quartile range (Q1 and Q3)
  - Eg: "The ADAs lasted x months in half of the subjects" OR "The ADAs lasted x months in 75% of the subjects"

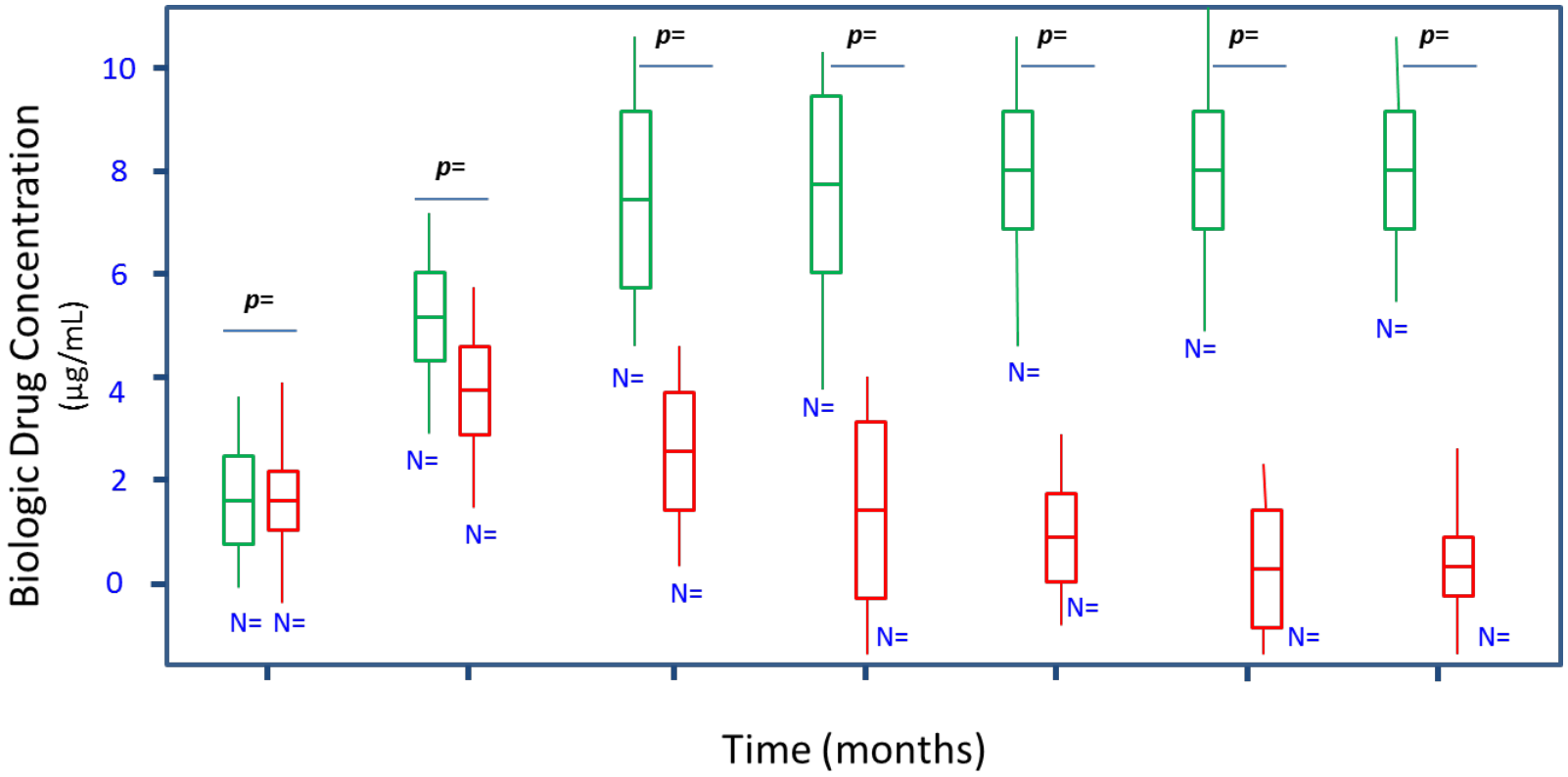
Relationships with clinical endpoints- *draft*

- Reporting the clinical relevance of immunogenicity requires an integrated analysis of PK (serum conc, clearance rate), PD (when applicable), Efficacy, and AEs) in relation to the intended posology (tested in pivotal trials).

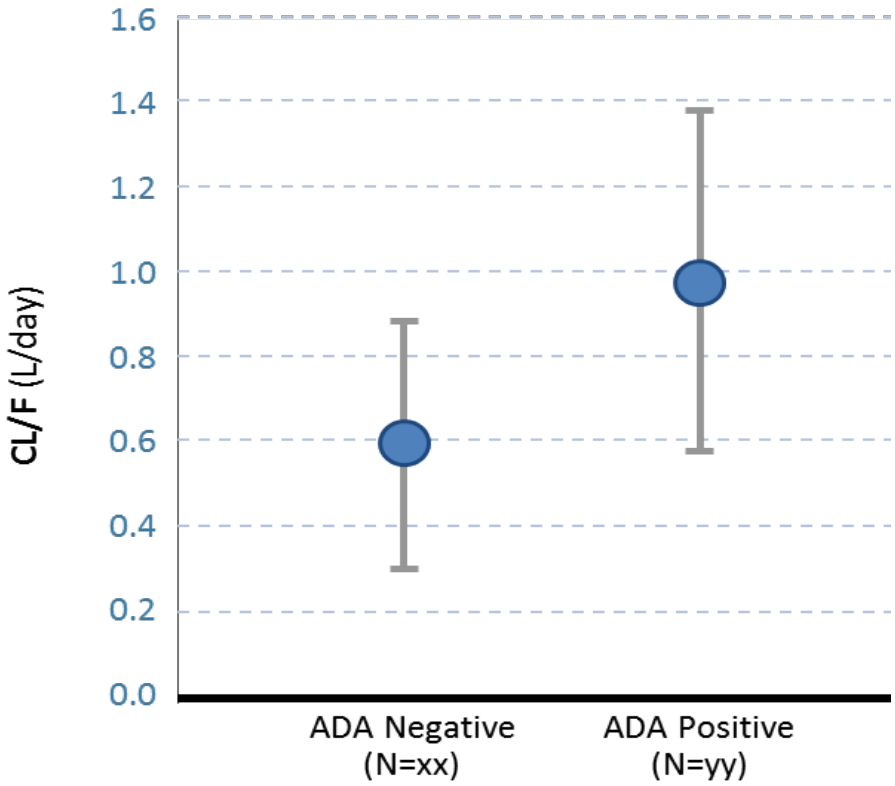
- For determining a clinicaly relevant "cutoff", ROC or Classification and Regression Tree (CART/"Partition") analyses of the raw data against PK/PD, changes in disease parameters (efficacy), and levels of AE, may be able to identify clinical thresholds (*Caveat – sample size*).

Influence of ADA on PK (trough serum concentrations)

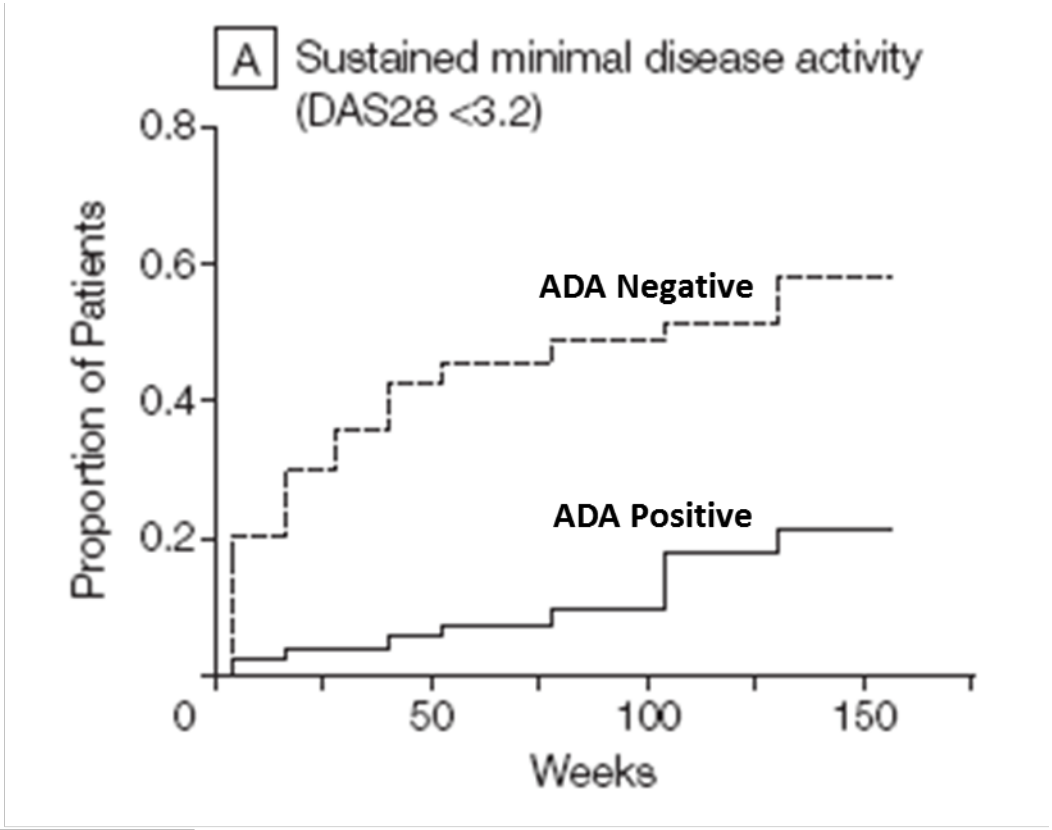
Red = ADA Positive subjects
Green = ADA Negative subjects



Influence of ADA on PK (clearance rate)



Influence of ADA on Clinical Efficacy



ADA Negative	196	151	135	118
ADA Positive	76	59	43	29

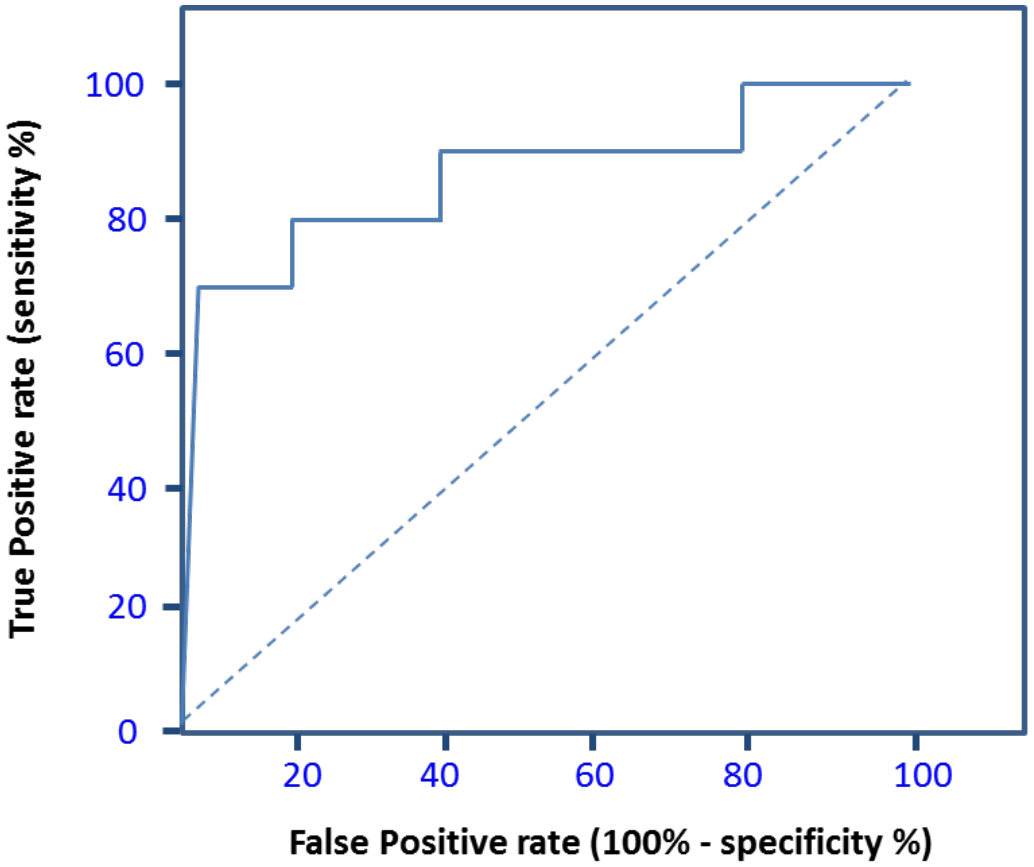
From: Barthelds et al 2011 JAMA, 305(14):1460-1468

Clinically Relevant Cutoff/Threshold: ROC Model

For evaluating the association with binary clinical endpoints, Receiver Operating Characteristic (ROC) curves can be used.

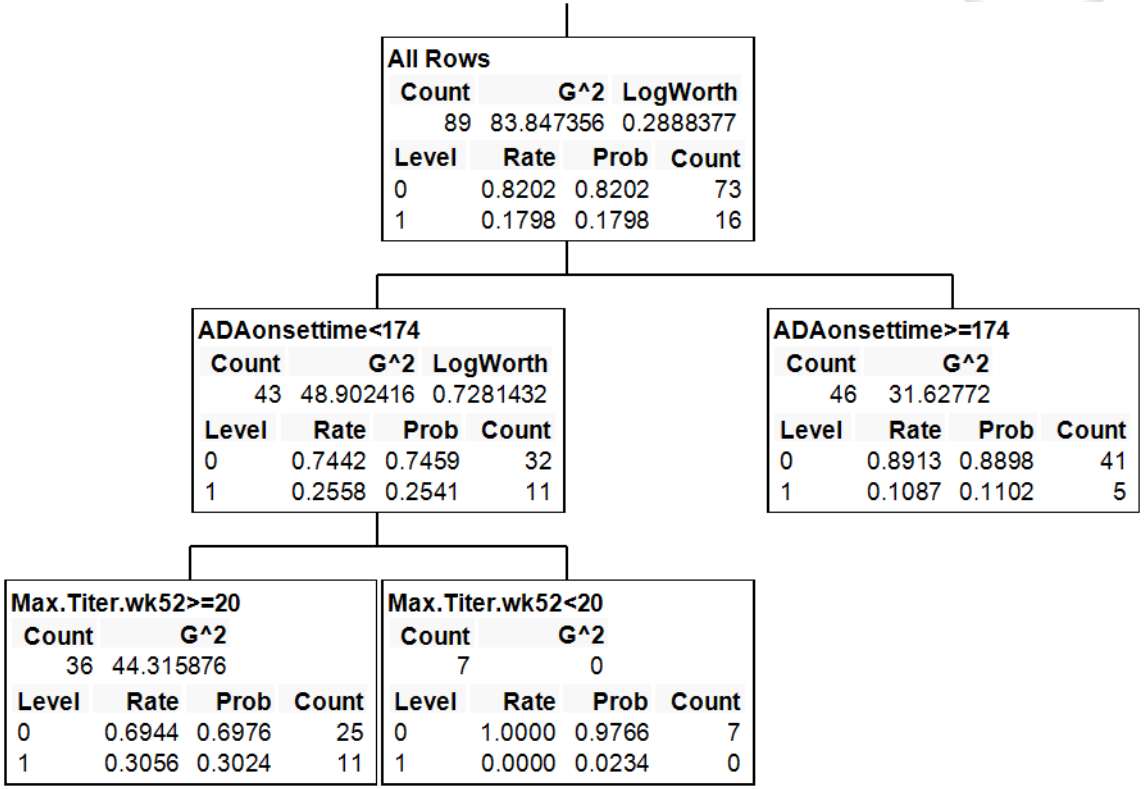
Eg, ADA Titer vs. Loss of response

Generally possible for the association of only one predictor variable at a time.



Clinically Relevant Cutoff/Threshold: CART (Partition/Decision Tree) Model

For evaluating the association with several clinical endpoints (multivariate), CART analysis can be used.



Note:
P value = 10 $^{-(\text{LogWorth})}$

So, for P<0.05, LogWorth must be >1.3
& for P<0.01, LogWorth must be >2

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Thank You.

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