

Graphical Display of Histopathology Data from Toxicology Studies: An Industry Survey

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Abstract

Histopathology data comprise a critical component of toxicology studies and are typically presented as organ-specific incidence counts, tabulated in study reports. Various software applications are available to convert histopathology data into graphical displays for visual presentation. Intra-industry surveys were conducted within the FDA PhUSE Nonclinical Working Group and at the 2015 European Society for Toxicologic Pathology annual meeting regarding the use and limitations of graphical displays of histopathology data. Survey results, along with representative graphics of histopathology data, are presented in this poster. The working group discussed visual cues, use-cases and the value of cross-domain visualizations (e.g. histopathology versus organ weight data).

Conclusions

- Graphical displays appear advantageous as a communication tool to both pathologists and non-pathologists
- Graphical exploration of data can support hypothesis-generation which could include cross-domain interactive visualizations and/or aggregating large datasets from multiple studies to observe/display patterns and trends
- Graphics can support more efficient communication between teams

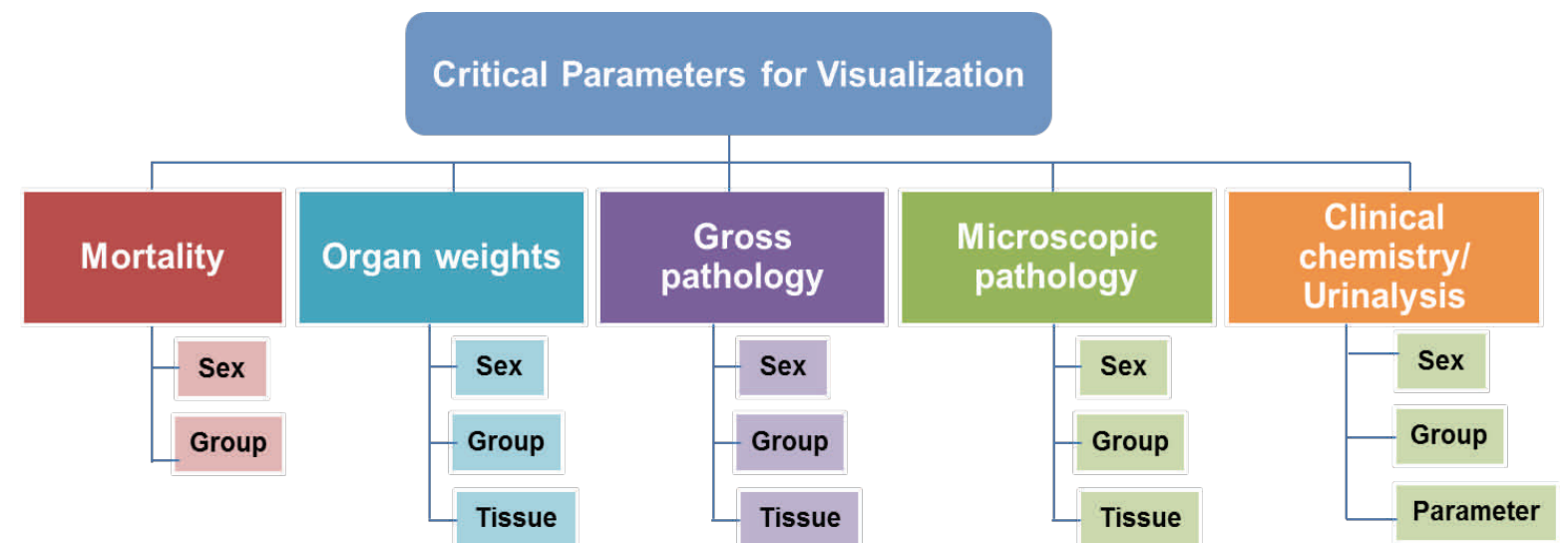
Future Directions

- What would cross-domain graphical displays (e.g. histopathology versus organ weights) look like?
 - Could cross-domain analysis of histopathology data with exploratory biomarkers be used for hypothesis generation and/or analyses?
 - How could historical control histopathology data be aggregated and graphed for analysis and presentation?
 - How do we guard against potential data misrepresentation? Are rules required to ensure that graphical displays do not encourage over-simplification which could lead to false conclusions?
- To maintain the momentum of this project, progress will be dependent on the creation of a library of use-case examples**

Survey questions and collated responses from the FDA PhUSE Nonclinical Working Group

A1: What scientific questions or specific analyses appear most appropriate for graphical displays of pathology data (gross observations, histopathology findings, pathology scoring systems)?

Analyses considered appropriate for graphical displays are shown in the flow chart below:



- Critical objective is to determine the purpose of graphical displays:
 - for data analysis/interpretation
 - for data presentation
- Graphical displays should be helpful to compare/aggregate data across multiple studies and/or multiple compounds. Historical control/background lesion data could be collected and displayed from multiple studies
- Graphical displays will be more helpful if gross & histopathology data can be correlated to clinical laboratory/organ weight data

A2: In what instances (use cases) would graphical/visual display of pathology data provide significant value?

- To understand treatment or dose related effects
- To correlate between different findings in other domains
- To recognize patterns across studies
- To support biomarker qualification studies
- To aggregate data from multiple studies
- To understand trends based on historical control groups
- To communicate pathology findings to project teams
- To understand the overall effects of a drug/compound at multiple systems level

B1: What software tools are individuals currently using for graphically displaying/ analyzing histopathology data? Are these tools commercially available or in-house custom designs?

Software tools currently being used for graphical display of pathology data:

- | | |
|---|--------------------------------|
| <ul style="list-style-type: none">PathData (PDS/Excel)Pristima (Xyblon)Provantis (Instem)SEND Explorer (INDS)ToxVision (PointCross) | Dedicated applications |
| <ul style="list-style-type: none">ExcelImage MinerMatlabMiniTabRSASSigma-PlotSpotfireTableau | Generic applications |
| <ul style="list-style-type: none">Translational Safety Platform (Novartis) | In-house (custom) applications |

B2: Are these tools being used for analyses within a single study or across multiple studies?

- Both single (primarily) and multiple studies

B3: What are the strengths and weaknesses of the current tools? What functionalities are currently missing or unaddressed which would be beneficial?

- Strengths**
- Graphical displays allow incorporation of datasets from other domains
 - Standard data tables provide incidence, severity and lesion description

- Weaknesses**
- Software is not user friendly
 - User interface and functionality challenges
 - Lack of familiarity with software tools

C1: What visual displays, cues or guides would provide the greatest benefit for analysis and communication of treatment-related changes?

- Color coding/grey scale for severity scores
- Heat maps
- Histograms
- Boxes of variable size based on incidence of lesions
- Linking data from various domains
- New ways to display incidence and severity data

C2: What limitations or caveats exist for displaying and analyzing histopathology data using visual/graphical displays versus standard data tables and written statements? (Examples include variance in lesion terminology and the qualitative nature in assigning severity scores, differences across labs and studies, etc.)

- Impact of background lesions and/or changes in control group on interpretation of changes seen in drug-treated groups
- Statistical analysis of histopathology data is problematic
- Variances in terminology for lesions across studies
- Differences in ranges and definitions for severity scores across studies
- Qualitative and subjective nature for describing/evaluating/scoring pathology data
- Ability to present detailed descriptive data in visual display

C3: What cross-domain analyses (e.g. histopathology, clinical lab data, organ weights, TK/exposure data) lend themselves to graphical display?

- Numerical data are important
- Macroscopic to microscopic correlations
- Important to use tools in focused fashion, versus general searches/fishing expeditions
- Cross-domain analysis on case-by-case basis to investigate specific questions
- Cross-domain analysis listed above plus linking to -omics data, cardiovascular assessments, clinical signs, imaging data

Poster Presenters

Alan Brown (Novartis)
&
Phil Drew (PDS Consultants)

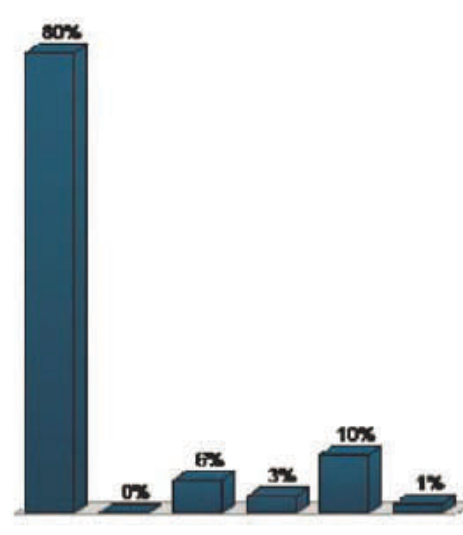
Contributing Organizations



Survey results from 2015 European Society for Toxicologic Pathology meeting

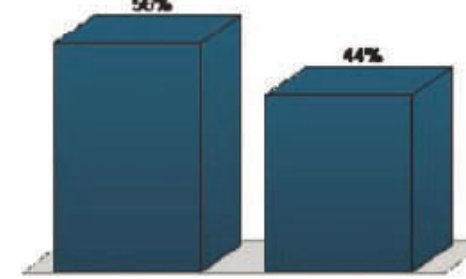
1. What is your current occupation? (Demographic Assignment)

Responses		
	Percent	Count
Pathologist	79.71%	55
Clinical Pathologist	0%	0
Scientist	5.8%	4
Researcher	2.9%	2
Management	10.14%	7
Other	1.45%	1
Totals	100%	69



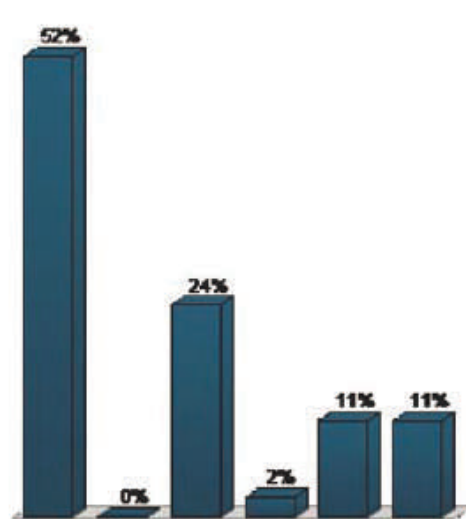
4. Have you used graphical displays of histopathological data for either analysis or communication? (Multiple Choice)

Responses		
	Percent	Count
Yes	56.45%	35
No	43.55%	27
Totals	100%	62



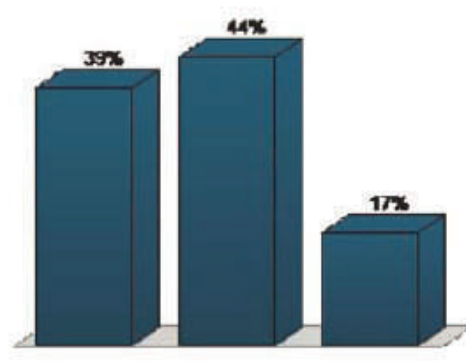
5. If you have answered "yes" - which type of visualization did you use? (Multiple Choice)

Responses		
	Percent	Count
Bar chart	52.17%	24
Pie chart	0%	0
Histogram	23.91%	11
Line chart	2.17%	1
Heat map	10.87%	5
Other	10.87%	5
Totals	100%	46



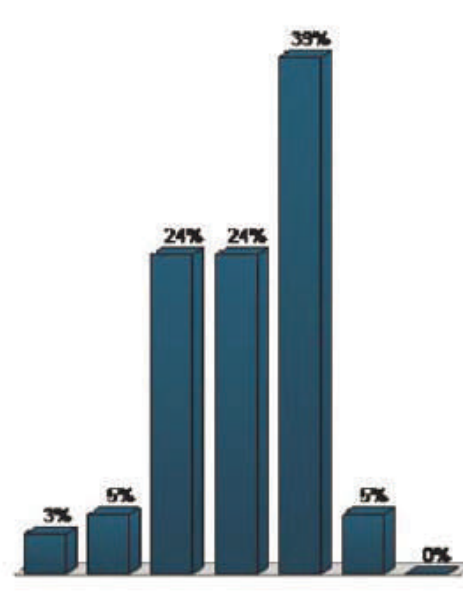
6. What cross-domain analyses with histopathology data do you think are the most valuable? (Multiple Choice)

Responses		
	Percent	Count
Organ weights	39.02%	16
Clinical pathology	43.9%	18
Toxicokinetics	17.07%	7
Totals	100%	41



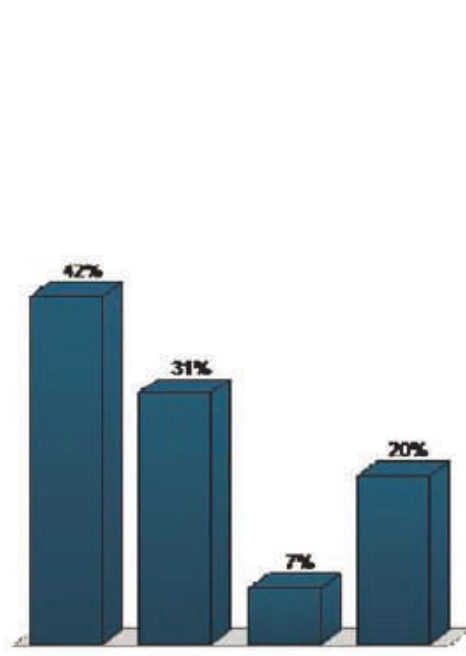
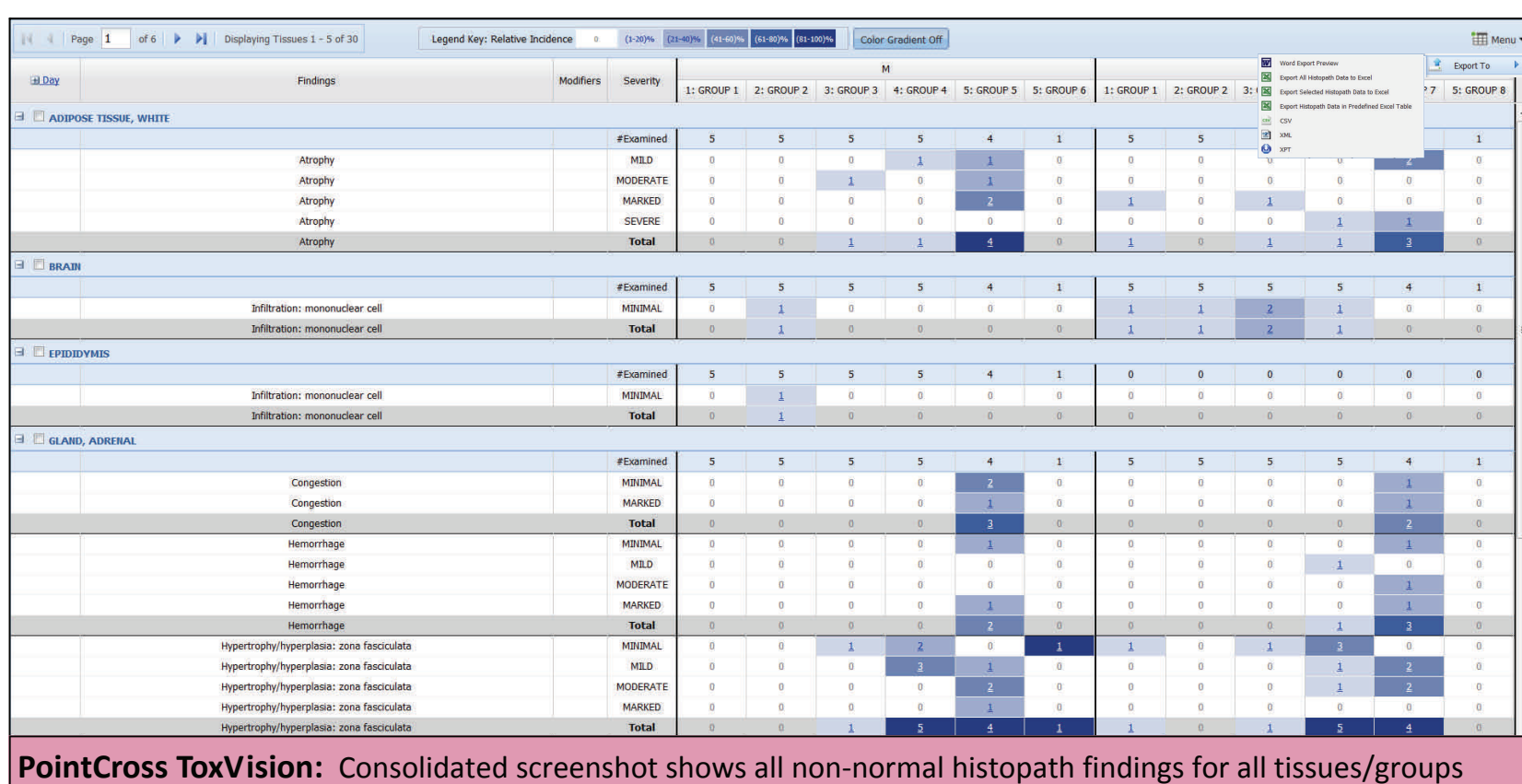
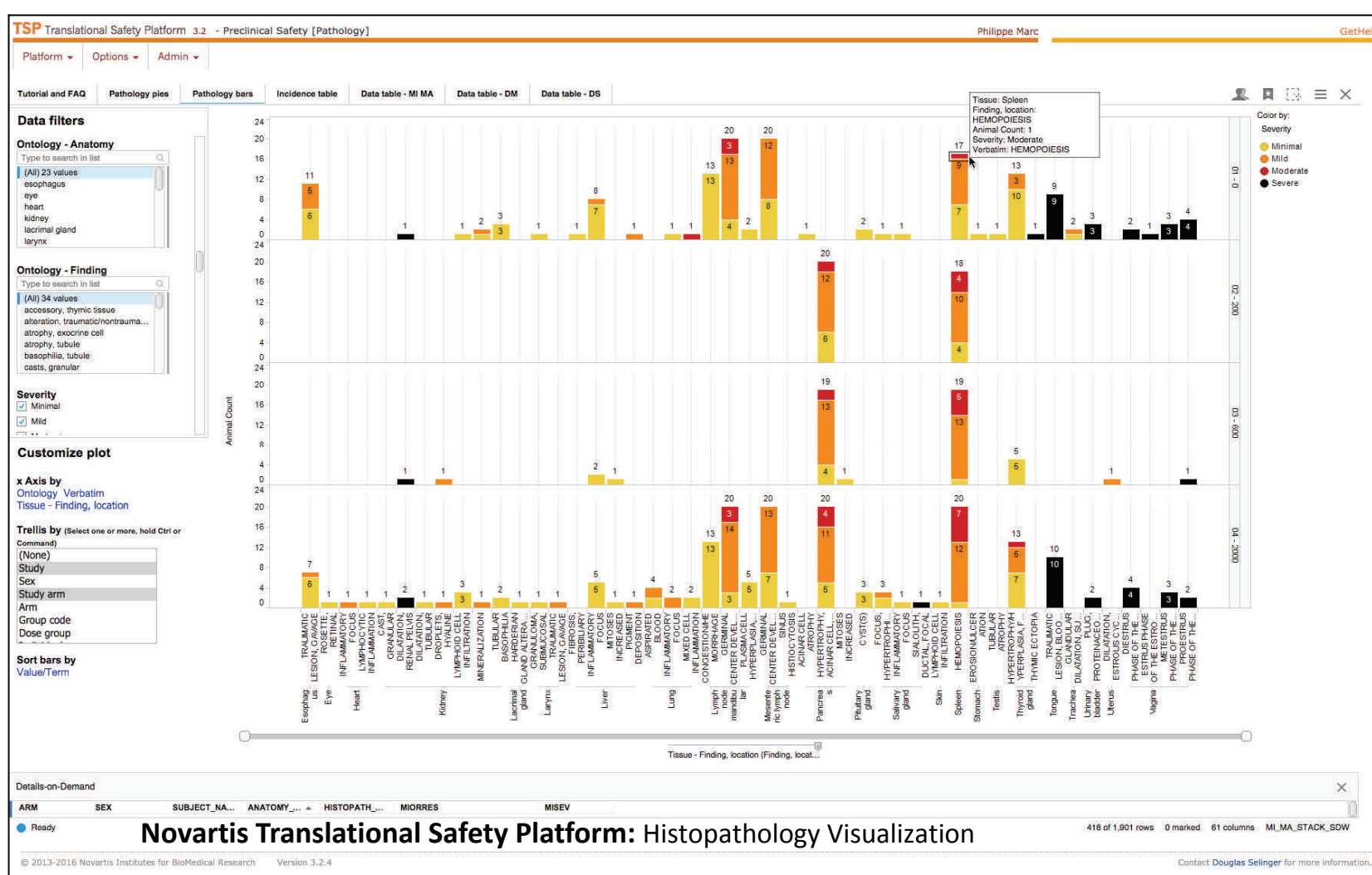
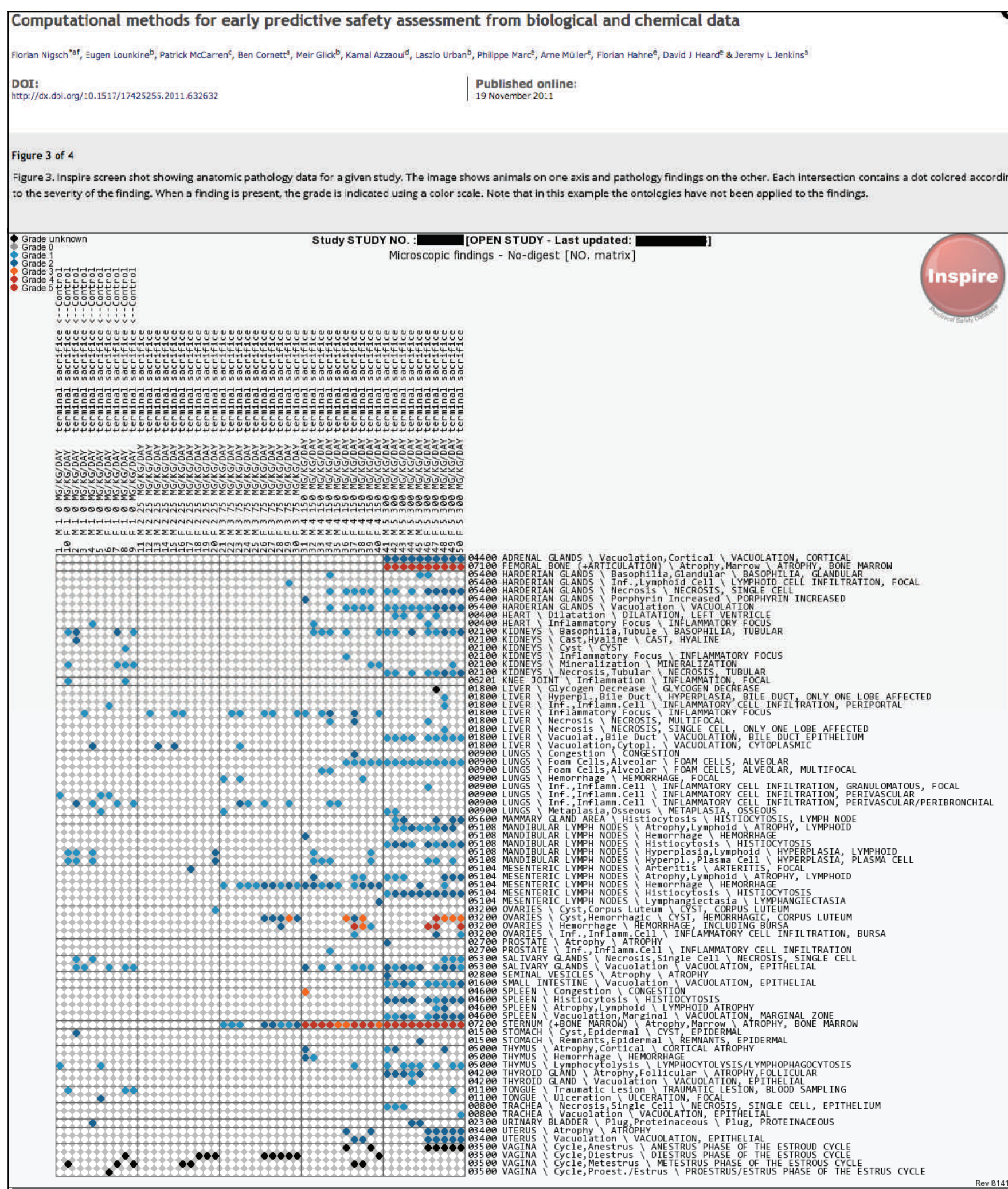
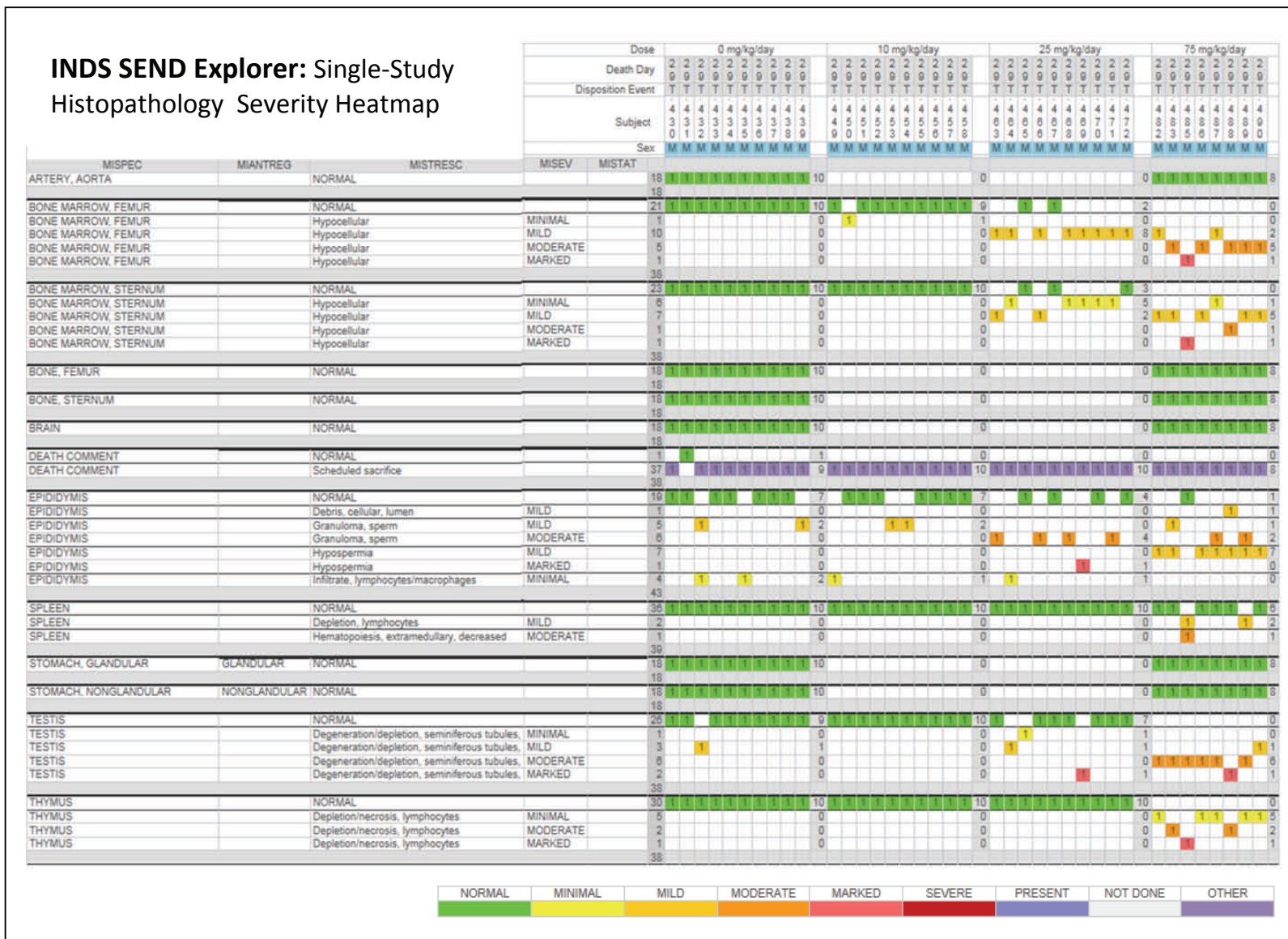
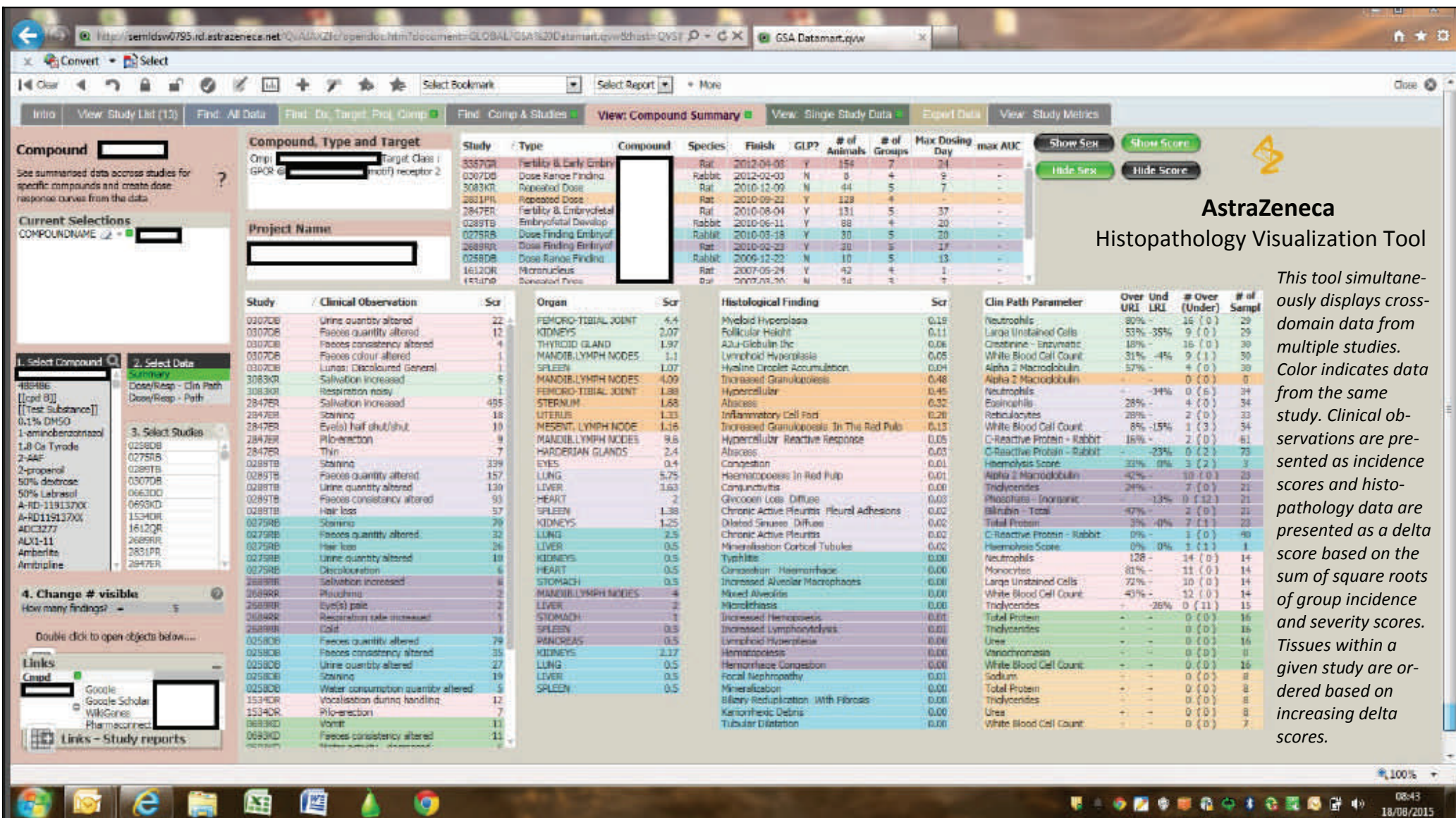
3. Based on your experience - do you think that data communication is usually straightforward? (Multiple Choice)

Responses		
	Percent	Count
Very true	3.03%	2
True	4.55%	3
Somewhat true	24.24%	16
Somewhat not true	24.24%	16
Not true	39.39%	26
Not true at all	4.55%	3
Don't know	0%	0
Totals	100%	66



7. In what instance would the graphical display of histopathology data provide the greatest value? (Multiple Choice)

Responses		
	Percent	Count
communicate findings to non-pathologists	42.37%	25
identify trends or patterns across studies	30.51%	18
investigate changes across data domains	6.78%	4
understand dose-related effects	20.34%	12
Totals	100%	59



INDS SEND Explorer: Multi-Study Histopathology Treemap

