Immune Tolerance Network




ITN TrialShare: From Concept to Deployment

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What is Immune Tolerance?

- Where the immune system ignores or fails to react to a protein, cell or tissue in our body
  - During development the immune system learns to tell the difference between things that should be ignored vs. invaders that should be attacked to protect the body
- Challenges when system gets this wrong

  Autoimmune diseases
  - Allergy & Asthma
  - Organ transplantation

Immune Tolerance Network(ITN) Mission

- Advance the clinical application of immune tolerance therapies
  - Perform high quality clinical trials of emerging therapeutics
  - Integrate with mechanism-based research assays
- Innovation and collaboration
  - Rigorous and reproducible research
  - Adherence to standardized platforms and processes
  - Use best available statistical methodology and data management practices
  - Dissemination of data and results to research community

Reproducibility of results in published literature

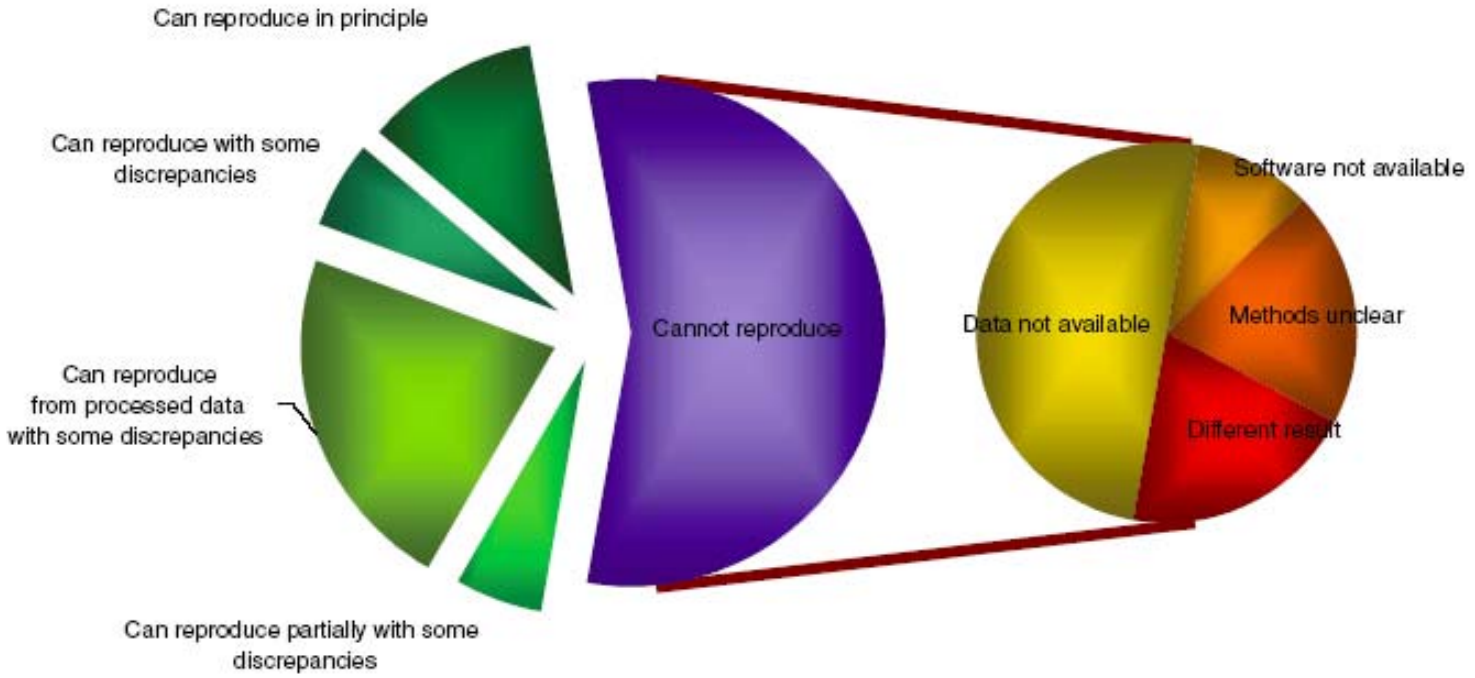


Figure 1 Summary of the efforts to replicate the published analyses.

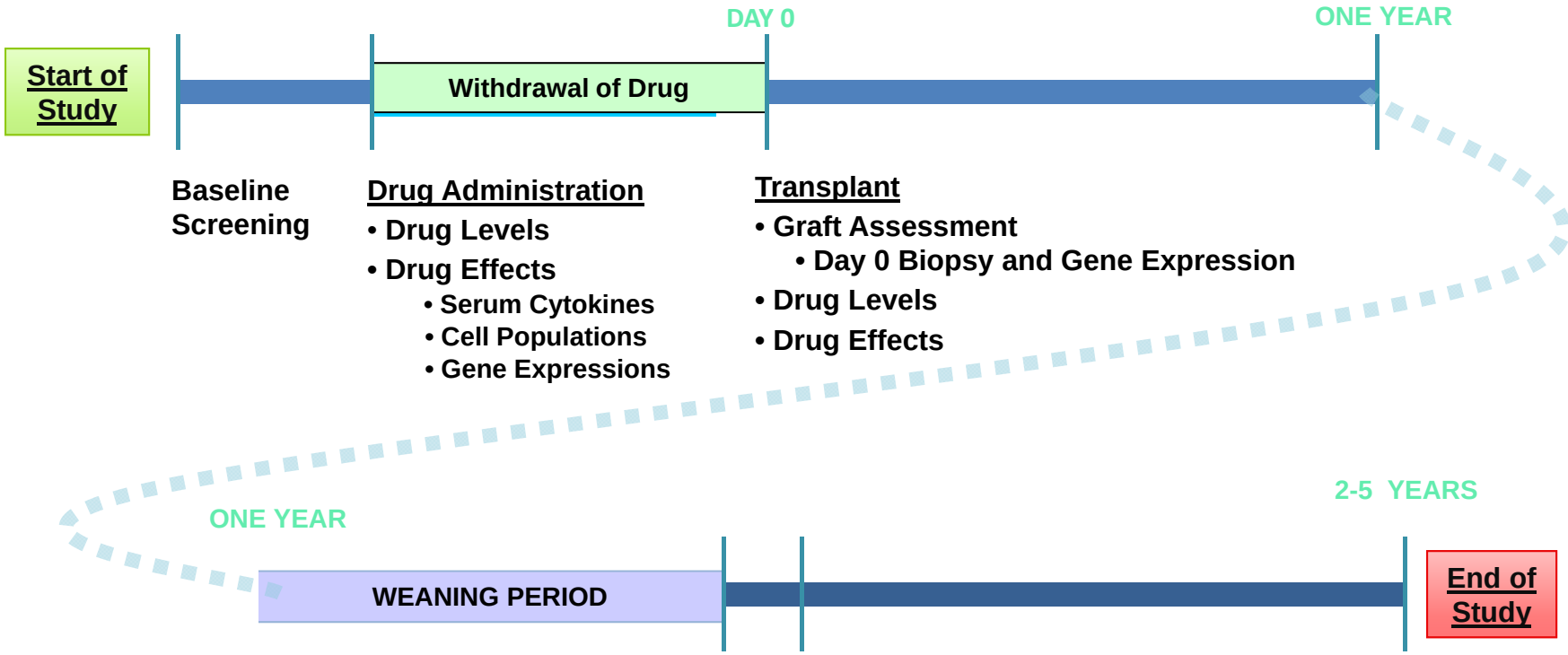
Ionnidis, P. et al. *Repeatability of published microarray gene expression analyses. Nat Gen , 41:2, Feb 2009*

Reproducible Research

- Computation is central to the scientific enterprise
  - Impossible to verify most results that computational scientists present in meetings and in papers
  - Relaxed attitudes in communicating computational details and validation of results is causing a large and growing credibility gap
  - The ability to verify previous results allows future scientists to build upon prior work
  - Sharing of raw data or processed result data is not adequate without annotated statistical code base

"Editorial Expression of Concern,", Science, Vol 327. no. 5962, p. 144, Jan 8, 2010.
D. Donoho et al., "Reproducible Research in Computational Harmonic Analysis," Computing in Science and Engineering, Jan/Feb 2009(vol. 11 no. 1), pp. 8-18

Integrating Research Assay Data with Clinical Outcomes



ISDrug Withdrawal
- Immune Response
- Cell Populations – Flow Cytometry
- T Cell Function - Drug Effects
- Rejection- Gene Expression

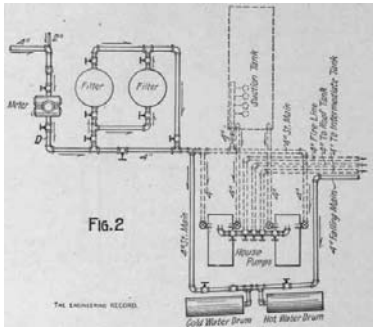
Immediate Post Withdrawal
- Organ Rejection - Gene Expression
- Cell Populations - Flow
- T Cell Function

Follow Up: 2-5 years
- Tolerance Marker ID
- Gene Expression
- Regulatory Cells - Flow Cytometry
- Th1/Th2 Shift
- Serum Profiles
- Other Assays

Flexible framework for rapid portal deployment

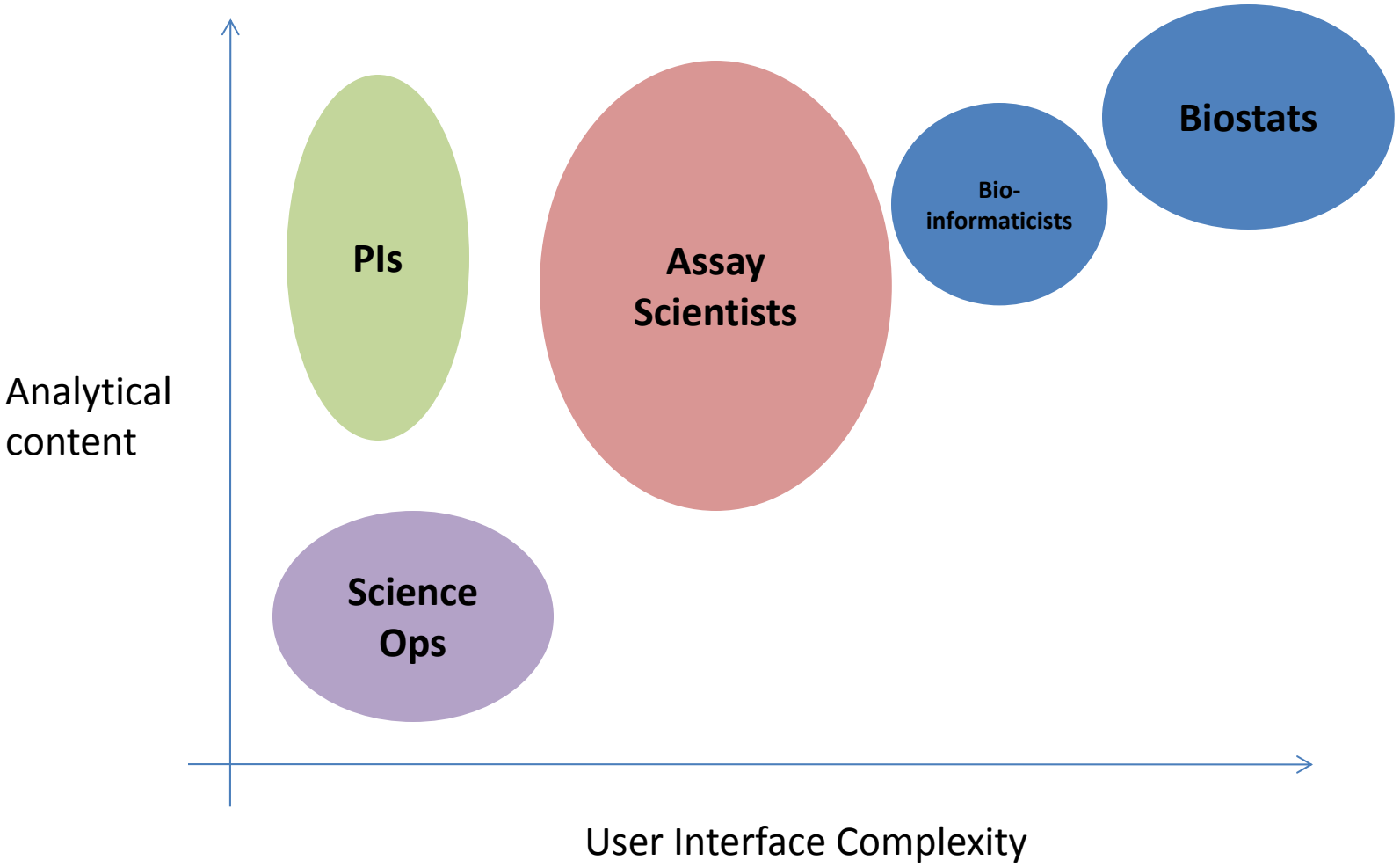
Rapidly adapt design as needed

Application framework that allows different data 'work environments' as needed



Data pipeline

System should address broad spectrum of users

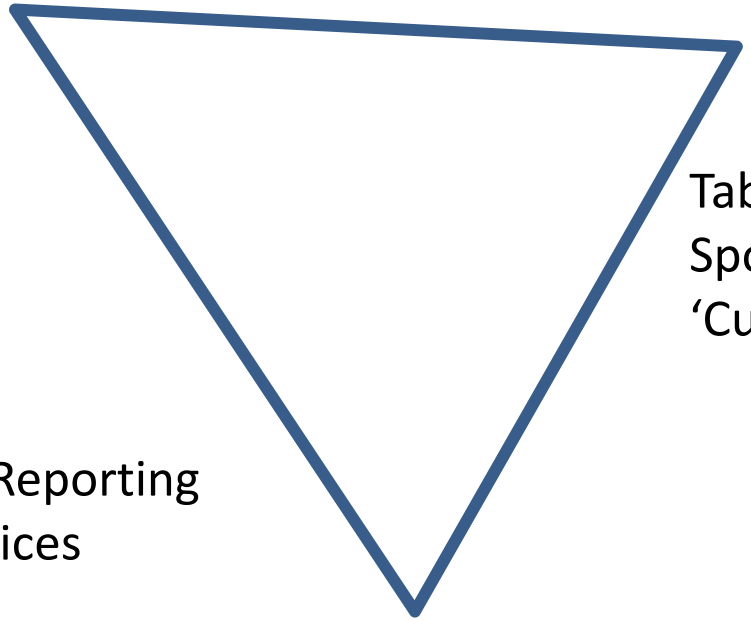


ITN TrialShare goals and objectives

- Data Management / Application Framework
  - Standardized syntax and naming convention across sample sets
  - Data loading is consistent, streamlined, semi-automated
  - Extensible application framework for adding assays, analytical workflows, and tools as needed
- Scientific / Analytical
  - Rapid access to clinical, assay and specimen data that can be readily merged as needed
    - ***Researchers need not rely on asking ITN staff for data***
  - Collaboration system for review of findings with other researchers
    - ***Users provide feedback or request follow-up: Make sample, assay and/or analytical support requests***
  - Simple tools and visualizations for interpretation of data within or across studies
    - ***Researchers potentially use system for hypothesis generation, study tracking, or other types of assessments***

Tools initially considered

Framework needed to tie components together. Most tools lacked context and flexibility



Business Intelligence (BI)

Crystal Reports

Simpler interface, fewer options, but easier for novices to use immediately.

MS Reporting Services

Interactive Visualization

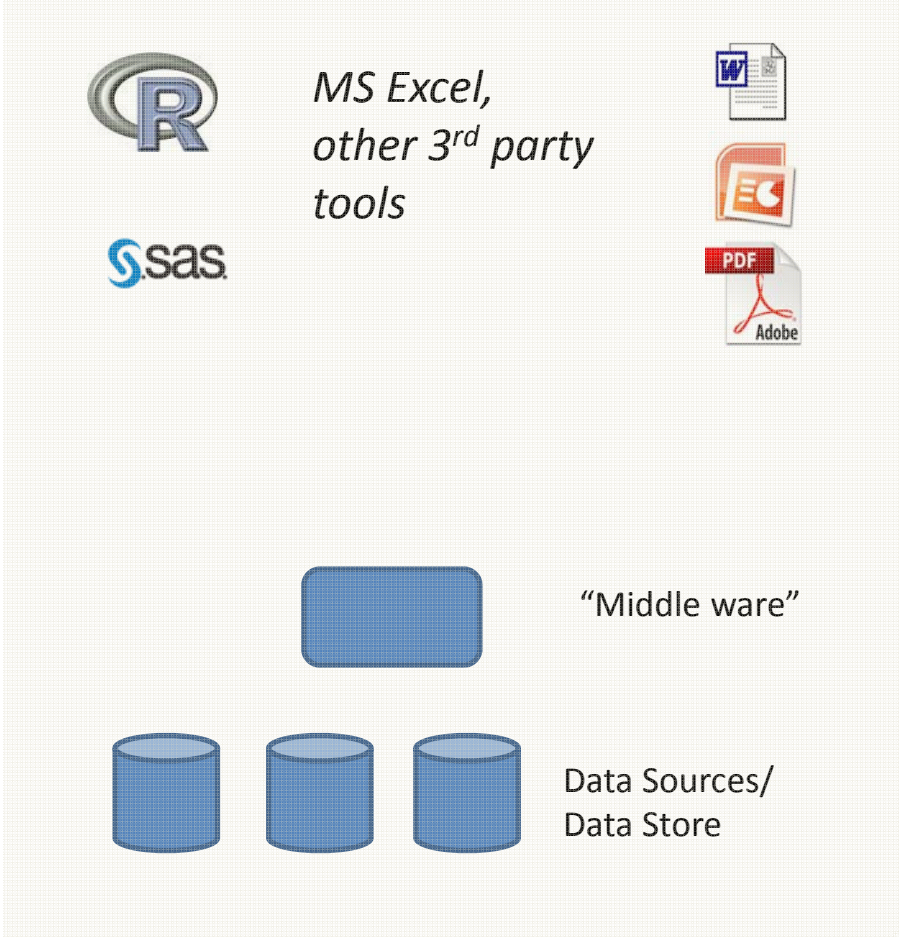
Tableau
Spotfire
'Custom'

Requires technical expertise, and authoring of "work book" viewer.

Difficult for novices to immediately.

MS Excel

LabKey Integrated Solution



- **Standard, reporting tool functionality embedded within a portal framework**
- **Framework for operational workflows, Analysis, Reporting & Visualization**

Publication ready analyses and report presentations (power-point)

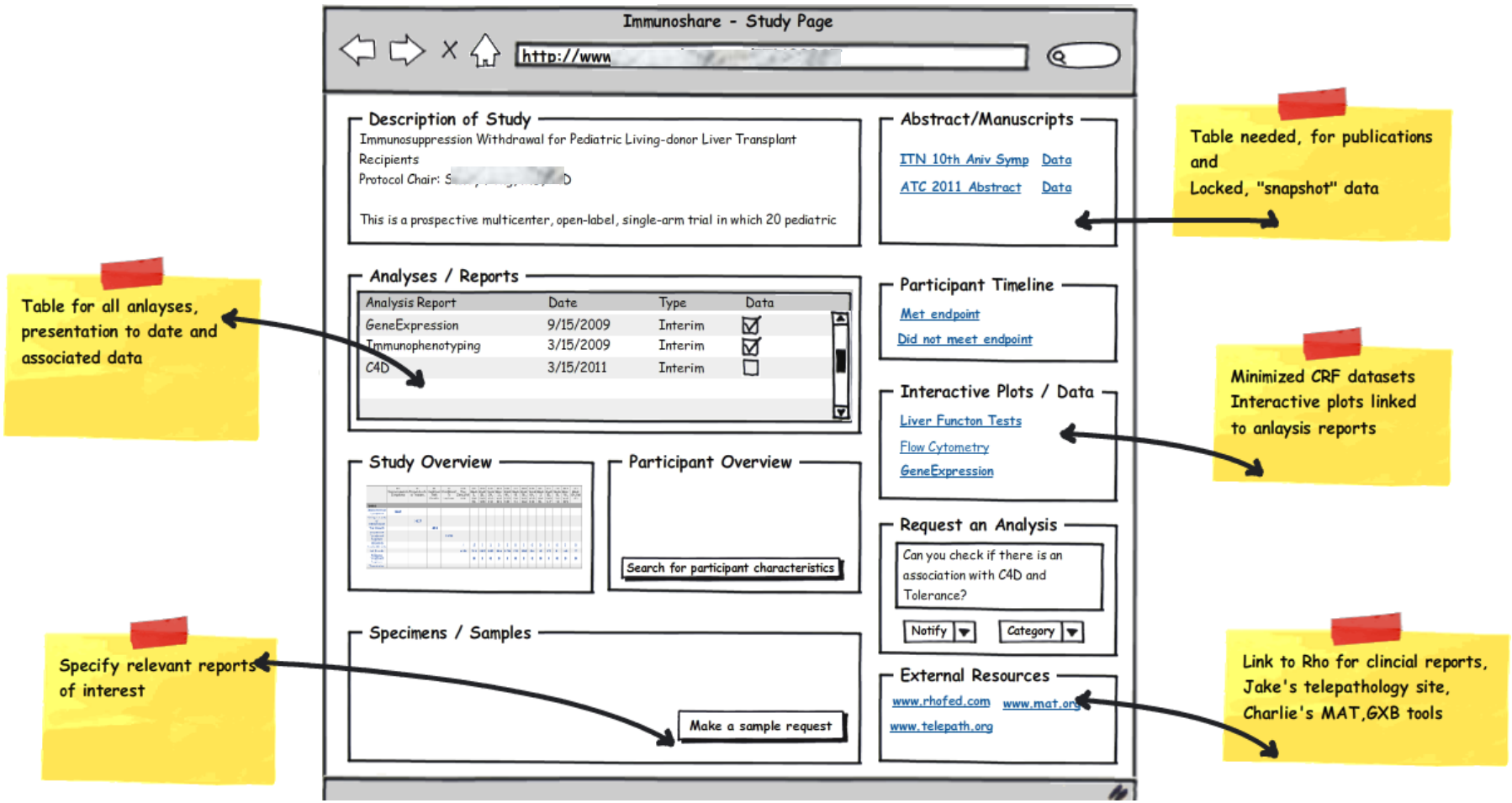
Complex assay layout, experimental design and analysis strategies

Integration across specimen repository and data sets

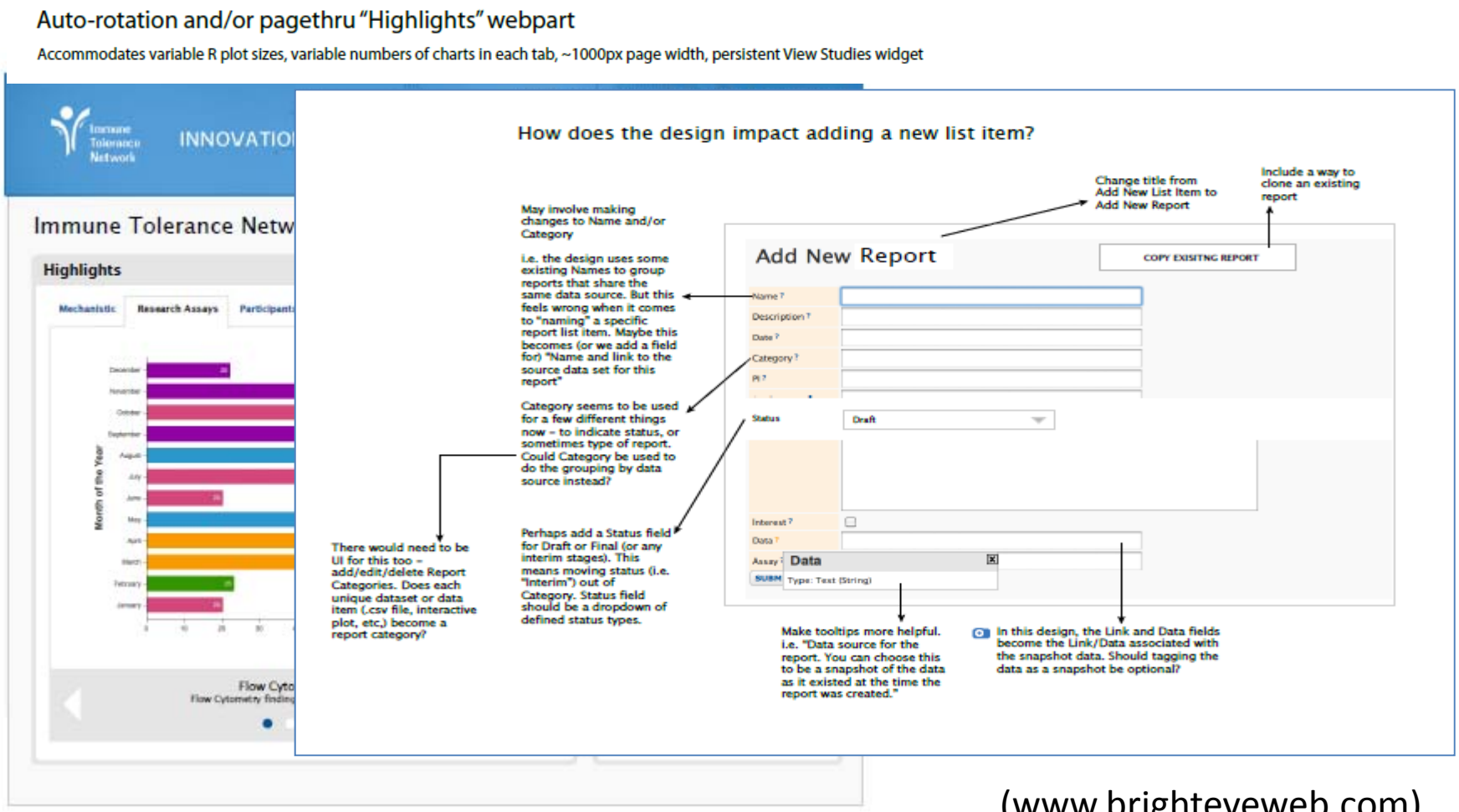
Data Management, Analysis, & Dissemination

Capture	Reconcile	Analyze	Interpret	Report, Collaborate
Internal/Operational			Portal Framework	
• Data extraction routines • Standardize data elements	• Reconcile sample identifiers • Account for missing samples	• Merge datasets • Perform QA, assess batch effects, normalize data • Develop statistical models, • Generate manuscript ready figures	• Generate hypotheses • Draft reports, manuscripts, presentations • Design follow up experiments	• Facilitate scientific discovery through collaboration • Support analysis and hypothesis generation by external groups • Solicit proposals for follow-up experiments

Layout & workflow requirements

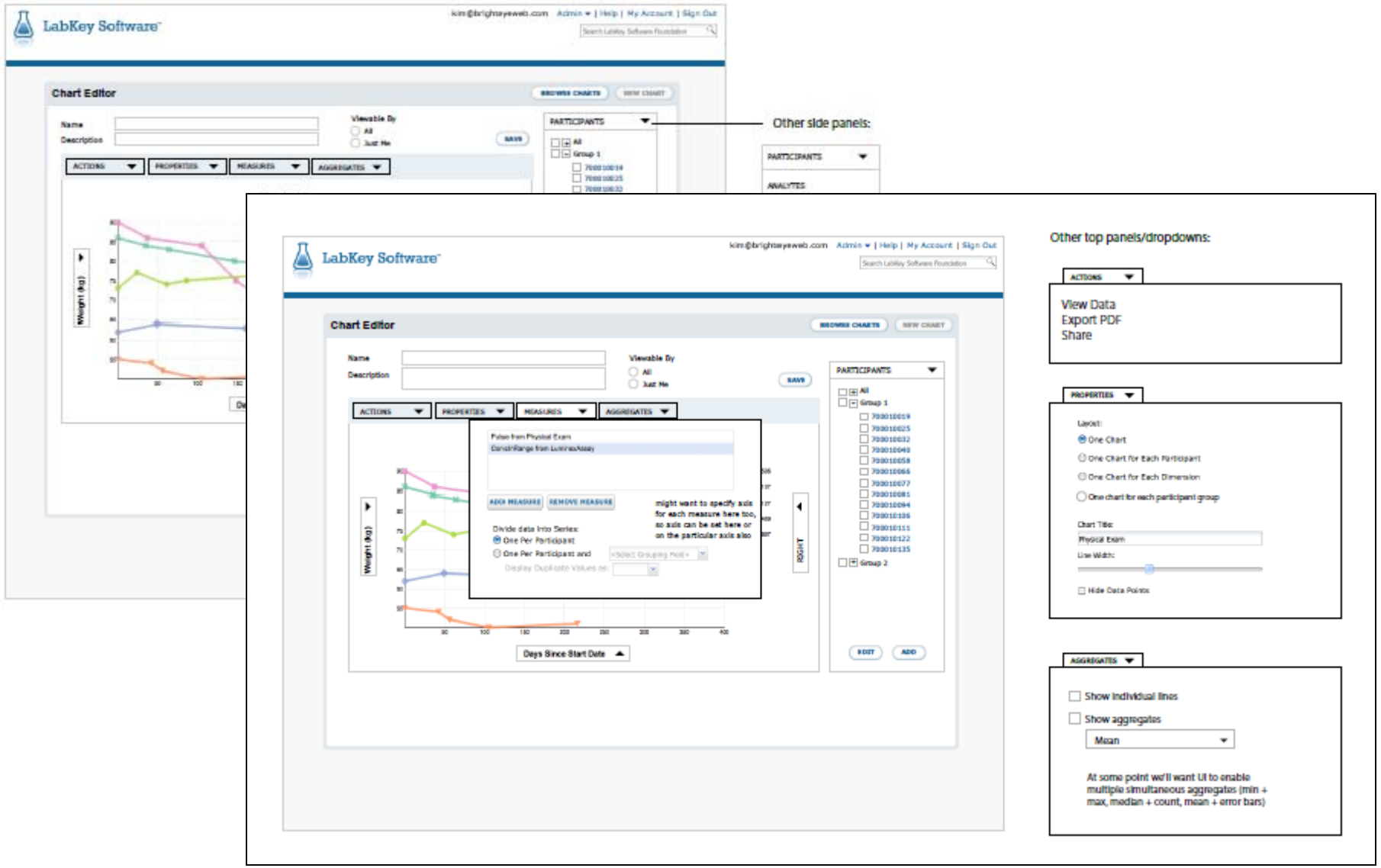


Storyboard design mock-ups: Report management

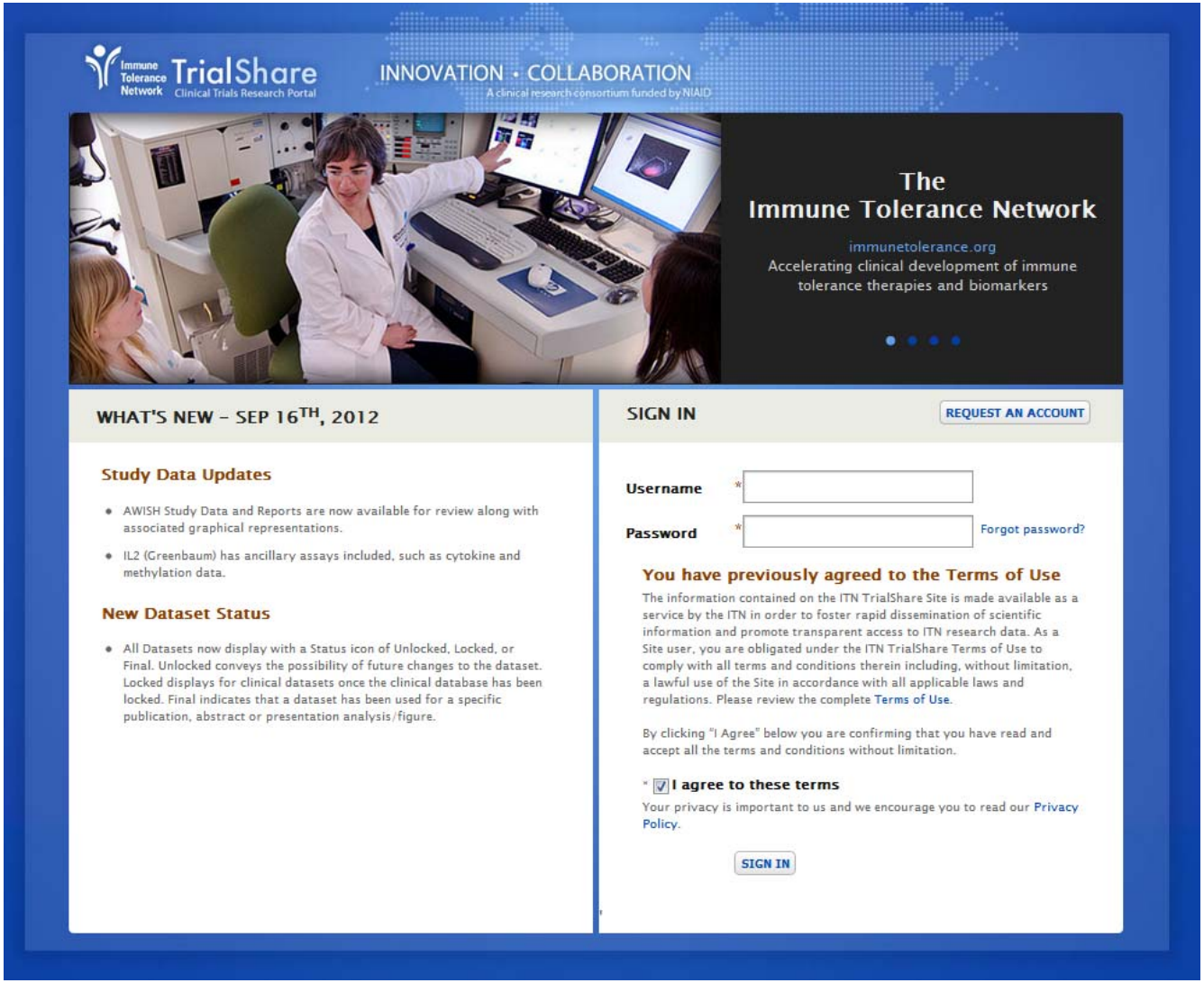


(www.brighteyeweb.com)

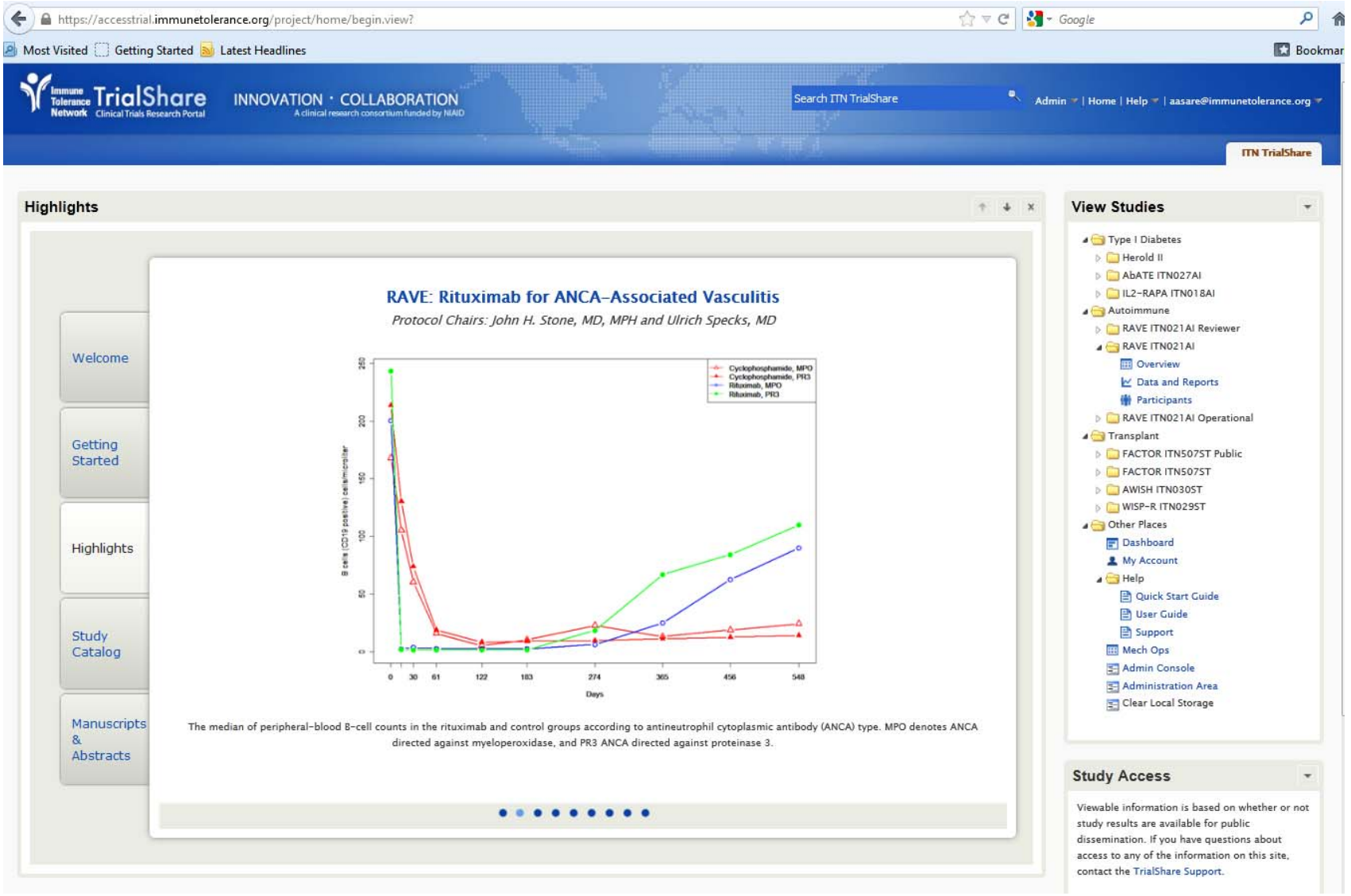
Visualization storyboards



System brought online within a year of development



Dashboard


https://accesstrial.immunetolerance.org/project/home/begin.view?
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A clinical research consortium funded by NIAID
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Highlights
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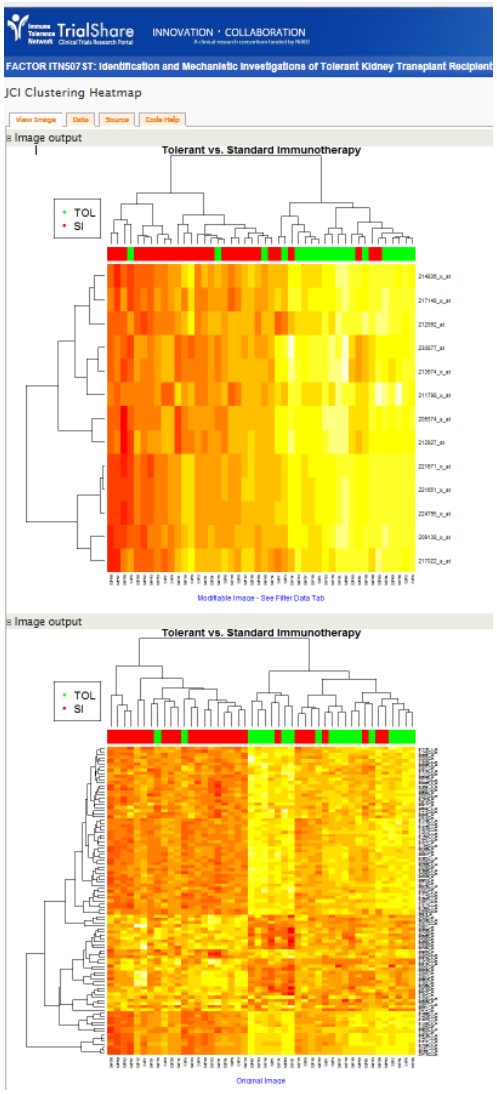
Highlights
Study Catalog
Manuscripts & Abstracts
RAVE: Rituximab for ANCA–Associated Vasculitis
Protocol Chairs: John H. Stone, MD, MPH and Ulrich Specks, MD
Cyclophosphamide, MPO
Cyclophosphamide, PR3
Rituximab, MPO
Rituximab, PR3
B cells (CD19 positive) cells/microliter
Days
0
30
61
122
183
274
365
456
548
The median of peripheral-blood B-cell counts in the rituximab and control groups according to antineutrophil cytoplasmic antibody (ANCA) type. MPO denotes ANCA directed against myeloperoxidase, and PR3 ANCA directed against proteinase 3.
View Studies
Type I Diabetes
Herold II
AbATE ITN027AI
IL2-RAPA ITN018AI
Autoimmune
RAVE ITN021AI Reviewer
RAVE ITN021AI
Overview
Data and Reports
Participants
RAVE ITN021AI Operational
Transplant
FACTOR ITN507ST Public
FACTOR ITN507ST
AWISH ITN030ST
WISP-R ITN029ST
Other Places
Dashboard
My Account
Help
Quick Start Guide
User Guide
Support
Mech Ops
Admin Console
Administration Area
Clear Local Storage
Study Access
Viewable information is based on whether or not study results are available for public dissemination. If you have questions about access to any of the information on this site, contact the TrialShare Support.

Manuscript Figures using R-console



FACTOR ITN507ST: Identification and Mechanistic Investigations of Tolerant Kidney Transplant Recipients

Overview | Data & Reports | Participants | Manage

JCI Clustering Heatmap

View Image | Data | Source Code | Code Help

Download input data ?

Probe	Symbol	Description	Uni Gene	OMIM	Pathway	Raw P	Fdr P	Log2ratio	Ratio	FC
200811_at	CIRBP	cold inducible RNA binding protein	Hs.634522	602649	---	0.0024	0.19733501	0.321199343	1.249368744	1.249368744
200972_at	TSPAN3	tetraspanin 3	Hs.5062	---	---	0.0022	0.189720599	0.628052513	1.545477352	1.545477352
200973_s_at	TSPAN3	tetraspanin 3	Hs.5062	---	---	0.0016	0.164996779	0.557432298	1.471647653	1.471647653
202154_x_at	TUBB3	tubulin, beta 3	Hs.511743	602661	Circadian_Exercise // GenMAPP /// Circadian_Exercise // GenMAPP	0.0003	0.102969119	-0.686292857	0.621448672	-1.609143353
202548_s_at	ARHGEF7	Rho guanine nucleotide exchange factor (GEF) 7	Hs.508738	605477	---	0.001	0.134685505	0.329969562	1.256986855	1.256986855
202724_s_at	FOXO1	forkhead box O1	Hs.370666	136533 /// 268220	---	0.0023	0.1933591	0.430610448	1.347803753	1.347803753
203221_at	TLE1	transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)	Hs.197320	600189	---	0.0023	0.1933591	0.682530102	1.604951945	1.604951945
203717_at	DPP4	dipeptidyl-peptidase 4 (CD26, adenosine deaminase complexing protein 2)	Hs.368912	102720	---	0.0013	0.151214086	0.636200135	1.55423013	1.55423013
203865_s_at	ADARB1	adenosine deaminase, RNA-specific, B1 (RED1 homolog rat)	Hs.474018	601218	---	0.0003	0.102969119	0.749622179	1.681352451	1.681352451
204141_at	TUBB2A	tubulin, beta 2A	Hs.654543	---	---	<.0001	0.023520644	-2.877084207	0.136116682	-7.346638094
205513_at	TCN1	transcobalamin I (vitamin B12 binding protein, R	Hs.2012	189905	---	0.0019	0.174604019	-1.142359062	0.453018207	-2.2074168
205557_at	BPI									
205671_s_at	HLA-DOB									

FACTOR ITN507ST: Identification and Mechanistic Investigations of Tolerant Kidney Transplant Recipients

Overview | Data & Reports | Participants | Manage

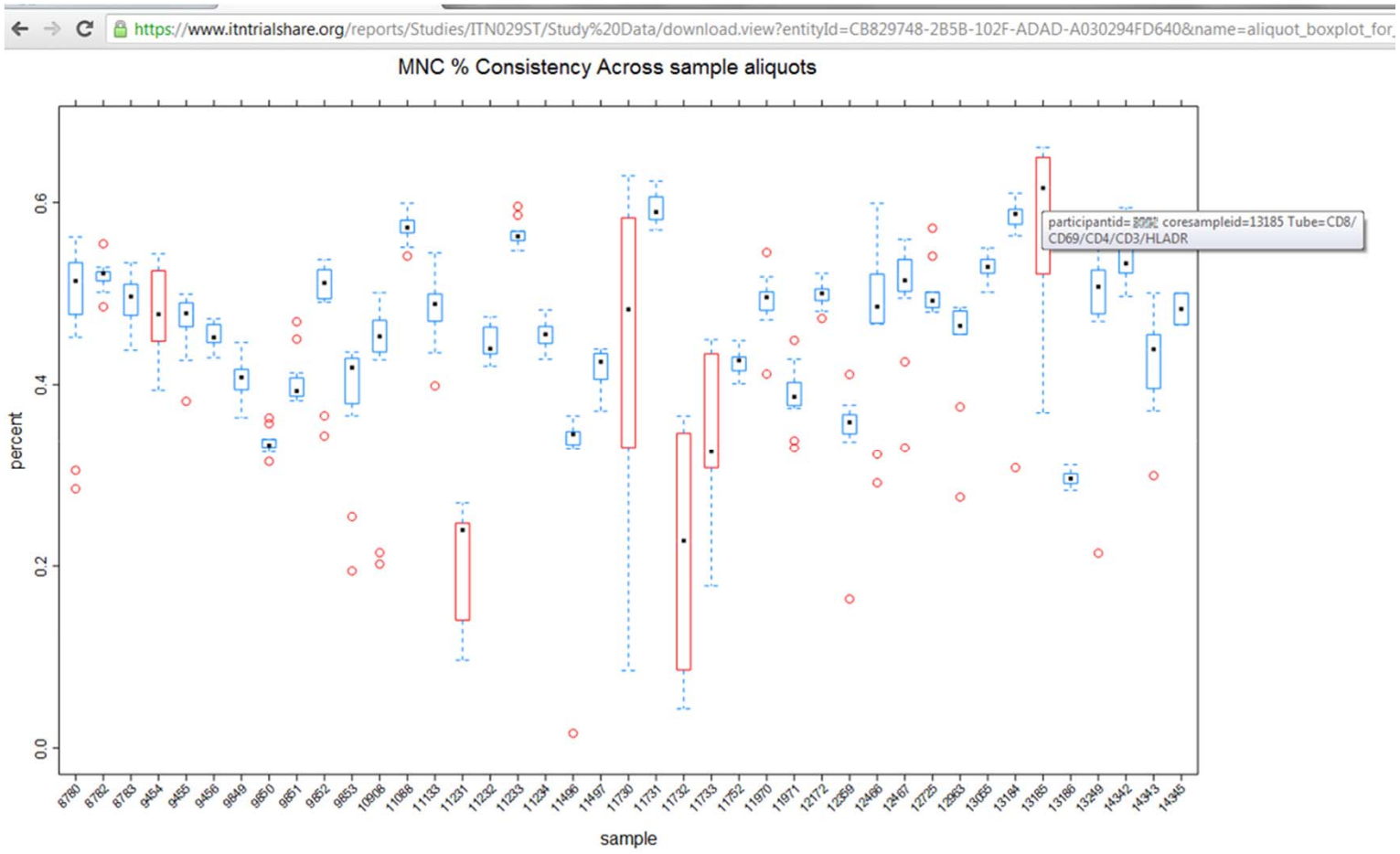
JCI Clustering Heatmap

View Image | Data | Source | Code Help

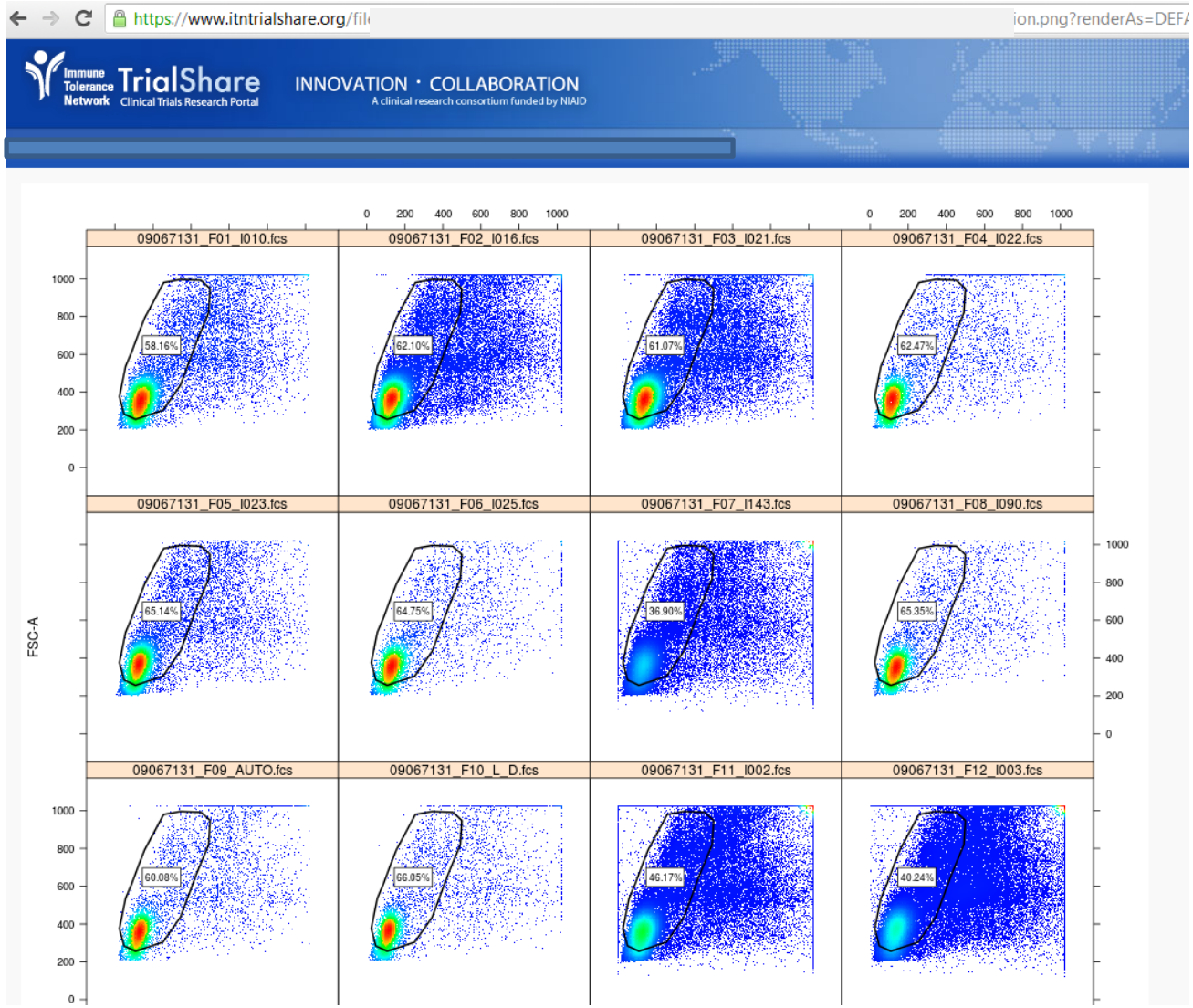
```
### read in top gene table (SI vs. TOL)
##############################################
toptable<-labkey.data;
#dim(toptable);
#toptable;
topgenes<-as.character(toptable$probe);
#topgenes;
library(Rlabkey)
toptabq<-labkey.selectRows(labkey.url.base,labkey.url.path,schemaName="lists",queryName ="Genelist", colNameOpt="rname")
topgenq<-as.character(toptabq$probe);

##############################################
### load filtered expression data and pData
##############################################
load("D:/Program Files/Labkey Server/files/Studies/ITN507ST/Study
Data/@files/assaydata/Newell_20081202_V0_badEx_nodup_DMHC_RMA_expression_filtered_grpCor.Rdata");
load("D:/Program Files/Labkey Server/files/Studies/ITN507ST/Study
Data/@files/assaydata/Newell_20081202_V0_badEx_nodup_DMHC_grpCor_phenoData.Rdata");

#expression2.filtered.grpCor[1:5,];
#dim(expression2.filtered.grpCor);

#pd;
#dim(pd)
```

- [x] Toggle editor
- [x] Make this view available to all users
  - [ ] Show source tab to all users
- [x] Make this view available in child folders ?
- [ ] Run this view in the background as a pipeline job

Specialized statistical pipeline work

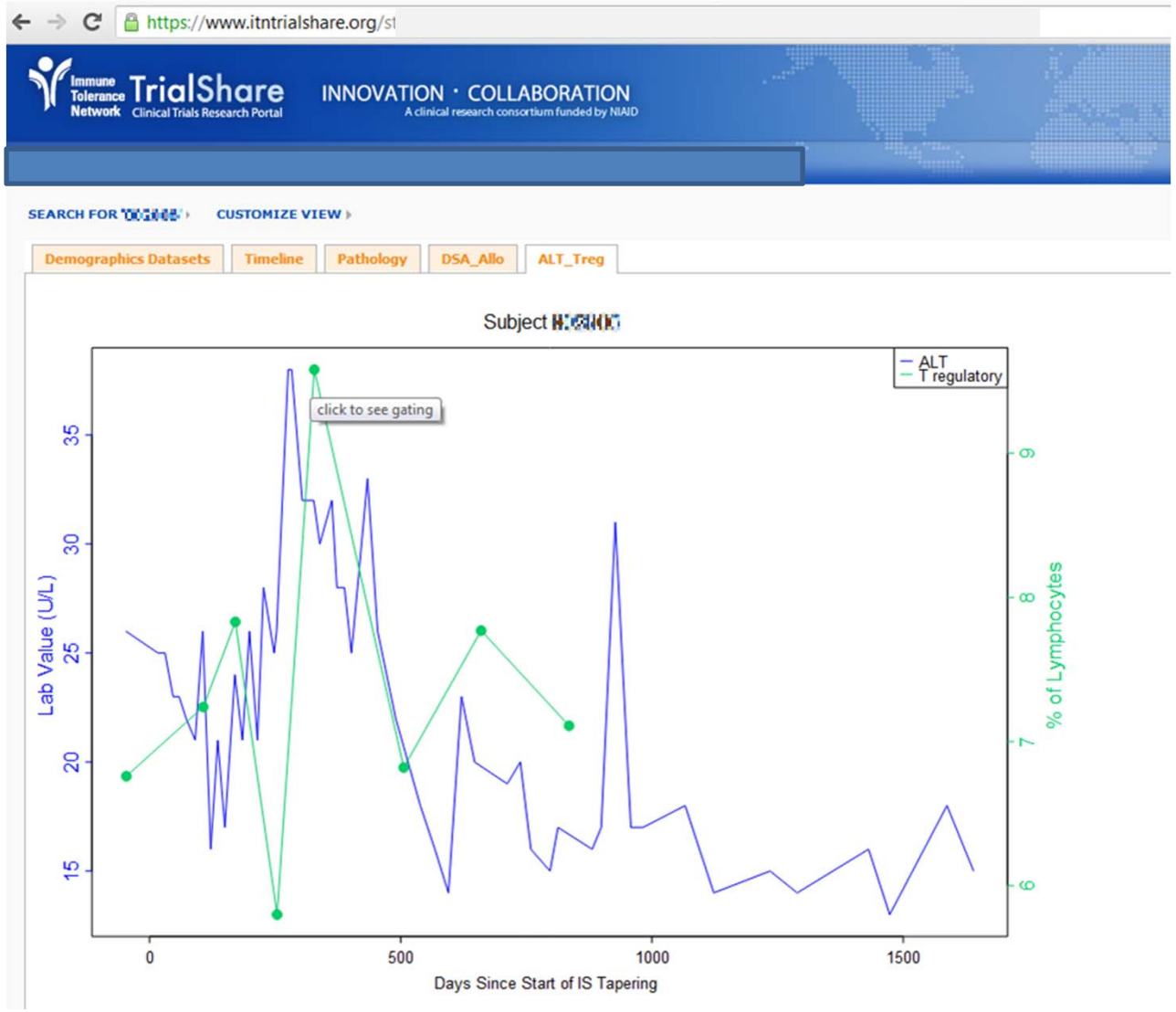


Review of underlying flow gating

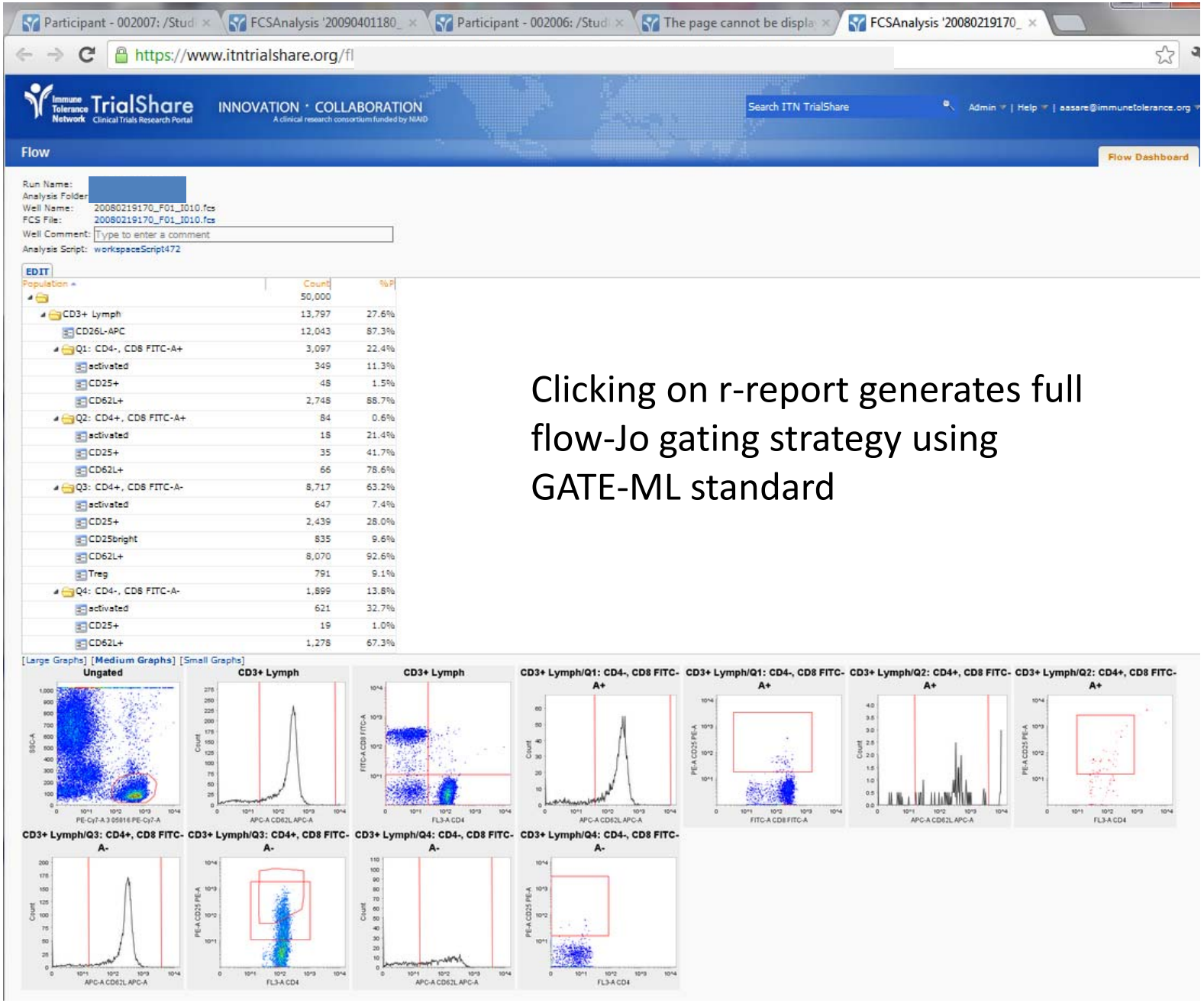


Domain experts with no expertise in R can review plots rapidly

Link plots to “flow assay module”



Click on results



Clicking on r-report generates full flow-Jo gating strategy using GATE-ML standard

LabKey functionality sponsored by ITN

- Report management
  - Data report browser layout, design
- Participant sub-setting
  - Participant groups, categorization in drop-downs
- Visualization
  - Enhancements to Time-charts
  - Box-plots
  - Scatter plot overlays
- Flow Cytometry module
  - GATING-ML standard for FlowJo data parsing
- “Publishing” studies
  - Enhancement to snapshot tool, de-identification for public dissemination

ITN data & software development work

- All upstream data management, cleaning, transformations
- Automated loading
- Dashboard log-in messaging, configuration
- Specimen workflow UI enhancements
- Automated public-account registration
- R-plot configuration design and workflows

Next steps

- Public Launch October 2012
- Continue refining workflows
  - Use focus groups and surveys to assess investigator pressure points and areas for further enhancement
- Work with LabKey to add additional functionality within the core system
- Expand out into customized applications and modules

Conclusions

- LabKey allows rapid application development and prototyping for TrialShare
- Minimized creating core components from scratch
  - "Modules", web-parts or frames could be inserted and laid out for workflows as needed
- Potentially a standard framework for other clinical trial consortia to consider in dissemination of research assay data

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JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

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Food
Allergy
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