

Planning for informatics in your grant applications

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Center for Research Informatics

Applications - Systems - Bioinformatics - Data warehousing - Clinical trials

At the end of this talk, you will...

- Know what parts of a grant need informatics consideration
- Understand how important it is to seek help early
- Feel comfortable reaching out to CRI and asking for help

CRI vs. ??

- CBIS
- Research Computing Center (RCC)
- Computation Institute (CI)
- ITS
- CDIS
- Biostatistics core
- Center for Health Delivery Sciences and Innovation

The idealized process...

- Have an idea
- Get preliminary data
- Write a proposal
- Get funding
- Do work
- Repeat



What often happens...

- Have an idea or an extension of current work
- Apply for grant using old preliminary data
- Get award for new work
- Figure out how to actually do (and pay for) the work



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Scenario #1 - The sequencer

- Researcher gets a pilot grant to study colon cancer patients using ChIP-Seq
- Pilot grant only for cost of sequencing
- No provisions made for **analysis** and **interpretation**



Scenario #2 - The multi-center trial

- Researcher gets U grant for testing a new survey tool at 30 cooperative sites
- Grant has no provisions for any research informatics **support**



Scenario #3 - The Big Data™ user

- Researcher gets funding to sequence 1000 whole genomes
- Gets funding for sequencing but then needs 20TB of storage space
- No grant provisions for **storage** or **backup**



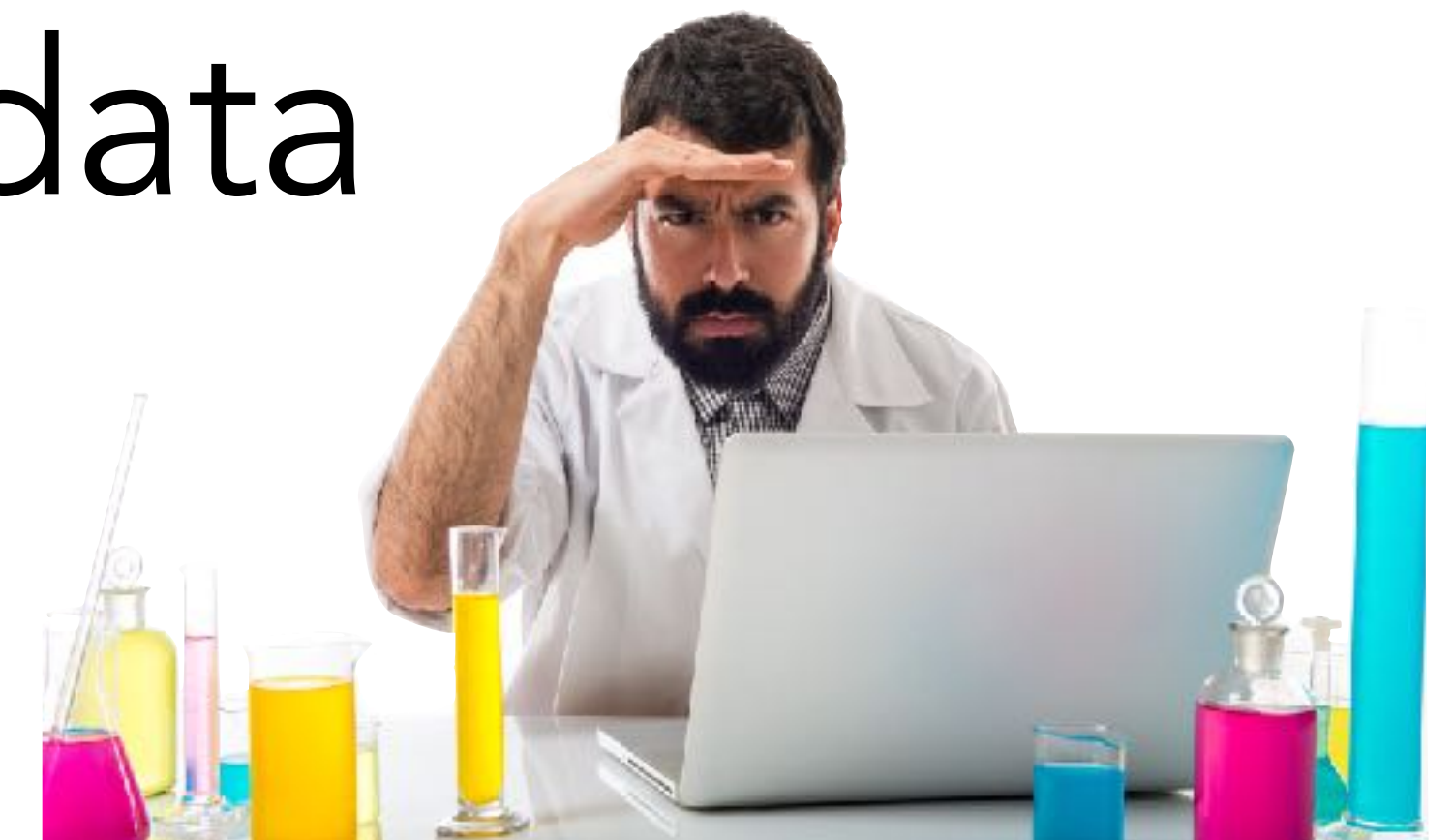
Scenario #4 - The simulator

- Researcher gets funding to design, perform, and test molecular simulations on millions of drug-target combinations
- Requires millions of hours of **HPC** usage
- No funding for HPC



Scenario #5 - The analyzer

- Funding secured for pulling a large comprehensive data set from the data warehouse to perform disease modeling
- Data is pulled and given to research team but there is no one to **analyze** the data



There are many opportunities to consider informatics resources



The best time is when you're just thinking about a project or writing about it.

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The screenshot shows the homepage of the Center for Research Informatics. At the top, there is a dark navigation bar with links: "Get an Account", "Contact Us", "FAQ", "Technical Help", and "CRI Careers". Below this, the "CENTER FOR RESEARCH INFORMATICS" logo is on the left, and a secondary navigation bar contains "Services", "Research", "Education & Training", and "About", followed by a search icon. The main banner features a blurred image of a laptop and a tablet, with the text "STRENGTHEN YOUR FALL GRANT APPLICATIONS" in large, bold letters. Below this, a smaller line of text says "Join us August 1 for a free session on including informatics resources at all stages of grant preparation." and a button labeled "LEARN MORE & REGISTER". Below the banner, a section titled "GET STARTED NOW" contains three columns of services, each with an icon and a list of resources.

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Common to all proposals

- IRB writing / consideration
- Contracts, data use agreements
- Data storage, movement, backup
- Data security
- Letters of support
- Facilities and resources documentation
- Data governance and stewardship
- Data sharing / software dissemination



IRB

- Do you need and IRB? An exemption?
- CRI has extensive experience in writing IRB protocols and shepherding them through the process
- Many of the issues have already been encountered for other proposals
- Engage the CRI **early** in the process

Contracts and data use agreements

- Sharing data outside the BSD requires an agreement
- Contracts may be needed for IP, data use, etc.
- The Data Use and Innovation Group meets monthly to address these issues **proactively** (CRI, OCR, IRB, legal, security, privacy)



Data storage, movement, backup

- CRI has extensive storage and backup capabilities
- Every investigator gets 2TB storage and backup for “free” as a lab share
- More extensive data usage needs to have a budget



A word about storage

These aren't good places
to store your data.
Why?



A word about storage

These aren't good places
to store your data.
Why?

- Not HIPAA compliant
- Insecure
- No redundant backup
- Little chance of recovery if loss

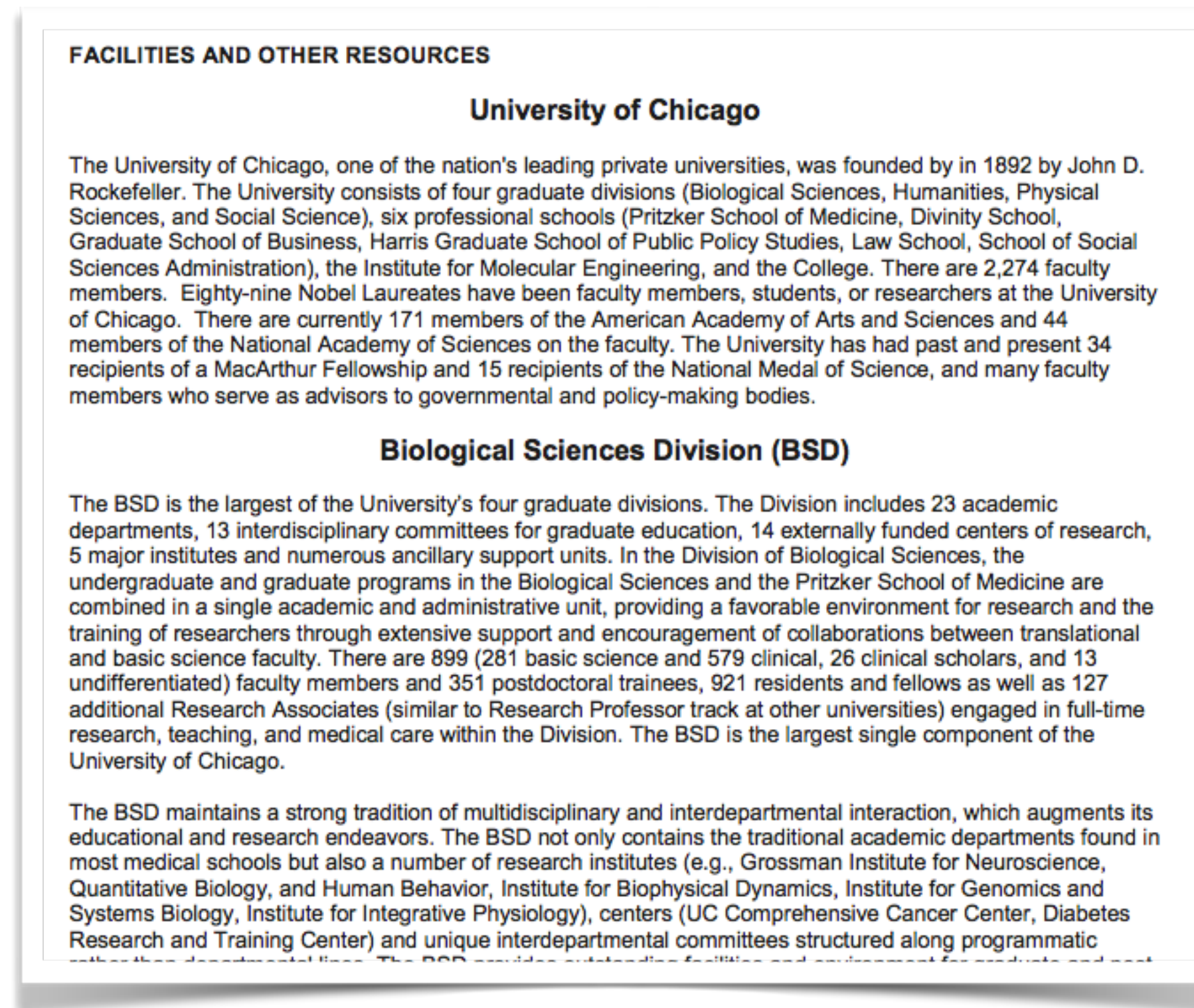


Letters of support

- General letter from CRI
- Specific support for project from CRI leadership
- Contact the CRI director service line director for any LoS issues
- Do this early. A draft is always appreciated.



Facilities and resources pages



CRI has boilerplate language for grants



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Common

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Bioinformatics

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CRDW

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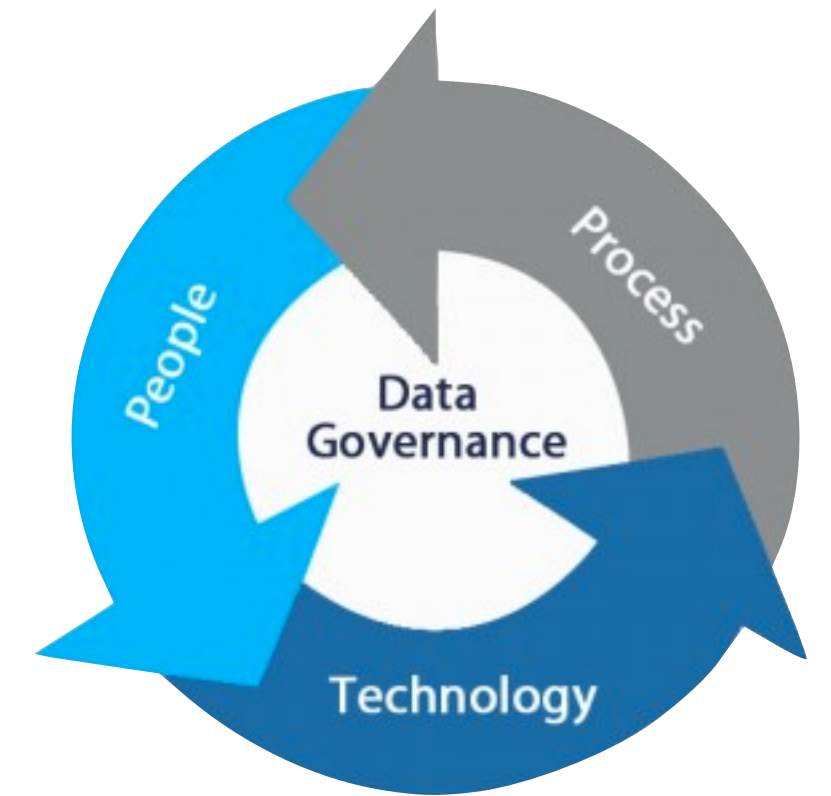
Applications

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Systems

Data governance and stewardship

- Grant readers are looking for documentation of data governance procedures
- CRI can help document these procedures for your proposal



Examples of data governance considerations

- Why controls access to data?
- How is security documented?
- Will people have encrypted laptops?
- Is the storage HIPAA compliant?
- Are data being backed up regularly?
- How is data being moved securely between researchers?



Examples of data governance considerations

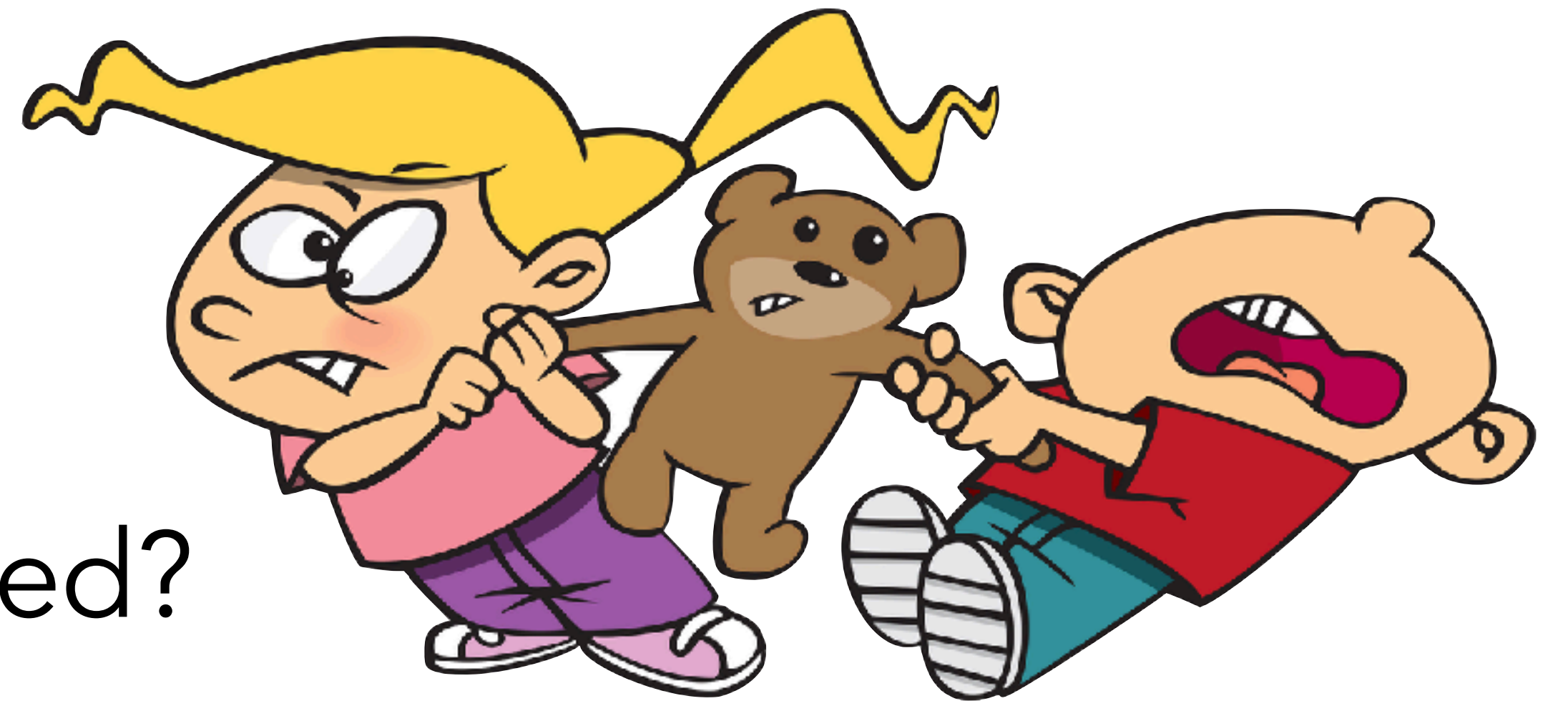
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Failure to address these questions can doom a proposal.

Data sharing plan

- Data sharing
 - Discussion of how data will be deposited in common repositories and shared
- Software dissemination
 - How will software be shared?
 - What kind of license will be used?
- CRI will help with this



Security considerations

- The Information Security Office in the BSD can help you with securing your data
- <http://security.bsd.uchicago.edu/>
- All proposals must adhere to policies and procedures (University and hospital)



Bioinformatics considerations



Bioinformatics - Methods and study design

- What kind of analysis?
RNA-Seq? ChIP-seq? WGS? WES?
- What depth of coverage?
- Power calculations: How many samples?
Technical replicates? Biological replicates?

Bioinformatics - Budget planning for data generation

- How many chips? What cost to run?
- How about sample collection and preparation?
- CRI can help broker this process



Bioinformatics - Grant writing

- CRI can help with all phases of grant writing
 - Background
 - Preliminary data
 - Methods
 - Research plan



Bioinformatics - Data storage, movement, backup

- How much storage is needed?
- How will data be transferred between investigators?
- Are data being redundantly backed up?
- CRI can help ensure that all phases are secure



Bioinformatics - Analysis and interpretation
















Bioinformatics - Analysis and interpretation

- Best to involve a bioinformatician from the start
- Partnership is key for a successful collaboration
- Project time is charged on an hourly basis or through dedicated time on grants
- Co-authorship is expected, where appropriate










Publications

2015

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Bioinformatics - Data integration

- Consider both phenotype and genotype data
- How will the clinical data be collected?
- Who is integrating these data into the analysis?
- CRI can get the clinical data and integrate it with the genomics information - this may require engaging the CRDW



Bioinformatics - Manuscript preparation and submission

combining data from these batches difficult. We removed two outliers and the batch of 8 samples with the largest variation. We then applied *ComBat* algorithm to adjust the batch effects among the rest of 46 arrays. For Germany data set, no obvious outliers were observed. The same batch effect correction procedure was performed.

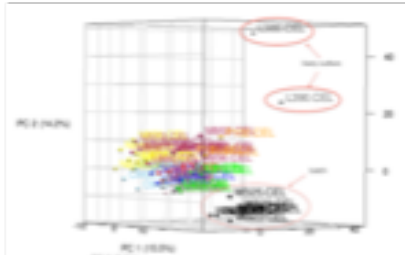


Fig. 2. Illustration of the outliers and batch effects in the COG gene expression data

Differential gene expression analysis identified 33 genes that expressed differently between two survival statuses in the COG data set

We applied moderated t-test implemented in the *Limma* package to the expression data of 10,824 preprocessed genes in the COG data set. The total of 33 genes were identified as differentially expressed between alive and dead sample group (FDR < 0.2 and |fold change| > 1.3) (Table S1). It is noted that the threshold for DE genes are less stringent compared to commonly used cutoff (FDR < 0.05 and |fold change| > 1.5–2). The subsequent functional enrichment analysis reveals that GO terms such as integrin binding (GO:0005178), cell migration (GO:0016477), cell adhesion (GO:0007155), regulation of cell proliferation (GO:0042127), blood vessel development (GO:0001568), response to wounding (GO:0009611), etc. were significantly enriched in the DE genes (Table S2).

Candidate gene expression signatures from DEGs have better prognostic performance in the COG data set than that of the random gene sets

For random signatures of 5, 10, and 20 DE genes, a signature testing procedure described in section 2 was applied. Fig. 3 shows that the random 5-gene candidate signatures from DE genes have average higher AUCs compared to the random gene sets in the COG data set. Similar results have also been observed in size 10 and 20 gene sets. This suggests that the candidate prognostic gene signatures could be derived from the DE genes between the different clinical outcomes.

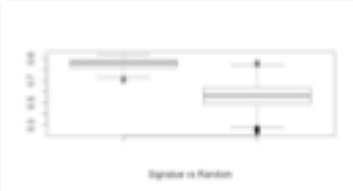


Fig. 3. Boxplot of AUCs between 5-gene candidate signatures and random gene sets

We also selected 5, 10 and 20 DE genes according to their VIM ranks and conducted the signature testing. The AUCs are compatible with the random signature sets. Candidate signatures based on VIM ranks can be used to reduce the number of random sampling of the signatures.

Putative gene signatures identified using random forests classification in the COG data set

By applying the procedure described in Section 2 and illustrated in Fig. 1, we trained and tested 100 candidate signatures from 33 DE genes for each size 5, 10 and 20 gene set. Table 1 shows the selected signatures with higher AUC among 300 signatures.

Table 1. Selected candidate gene signatures for the prediction of the survival status in the COG data set

Signature	AUC	Accuracy	Sensitivity	Specificity
CTSL,IGF1R,CDH15,SLC29A1	0.925	0.929	1.000	0.900
CTSC,ANPEP,ITGA9,DCBLD1	0.913	0.857	1.000	0.800
SLC29A1,CDL1,SPAN15,DDIT3,MR2	0.925	0.857	1.000	0.800
DCBLD1,GSTM2,LYN,RAFD1F5	0.925	0.857	0.750	0.900
ANPEP,CDH15,LOC100132167,NR1H3,PLEK	1.000	1.000	1.000	1.000
CTSC,DCBLD1,IGF1R,ITGA9,CTSL	1.000	0.929	1.000	0.900
ITGA9,CTSL,LOC100132167,ITGA9,CTSL	0.950	0.929	1.000	0.900
CTSC,ITGA9,CTSL,ITGA9,CTSL	1.000	1.000	1.000	1.000
CTSC,ITGA9,CTSL,ITGA9,CTSL	0.975	0.857	0.750	0.900

Validation on the Germany data set showed poor performance of the putative gene signatures from the COG data set

An ideal prognostic gene signature derived from the COG data set is expected to predict the survival status of Germany data set with high accuracy given the expression data from two data sets show similar distribution. However, we did not observe high prediction accuracy, sensitivity or specificity on the validation data set using the best RF classification models from the COG data set (data not shown).

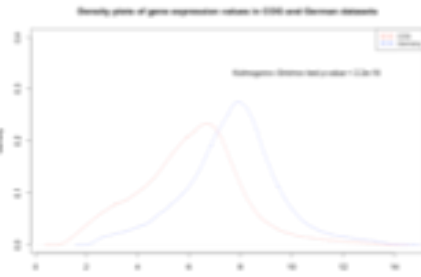


Fig. 4. Density plots of gene expression data in the COG and Germany datasets. The possible reasons could be (1) the expression data of the validation set is significantly different from the COG data; or (2) the RF

models from the training data set might be over-fitted. Our analysis confirmed that the expression densities in the COG and Germany data set are significantly different (Kolmogorov-Smirnov test P-value < 2.2E-16, Fig. 4).

Differential gene expression analysis identified 24 genes that expressed differently between two survival statuses in the COG data set from the combined data set

To minimize the effect caused by the distribution difference, we pre-processed the CEL files of 46 COG patients and 39 German patients together and separate the two data sets after batch effect correction. By applying moderated t-test from *Limma* package to the expression data of 10,824 preprocessed genes in the COG data set from the combined data, we identified 24 differentially expressed genes between alive and dead patient groups (FDR < 0.2 and |fold change| > 1.3, Table S3). The subsequent functional enrichment analysis reveals that GO terms such as integrin binding (GO:0005178), cell migration (GO:0016477), cell adhesion (GO:0007155), response to wounding (GO:0009611), etc. were significantly enriched in the DE genes (Table S4).

Candidate gene signatures derived from the combined preprocessed COG data set still performed poorly on the validation data

Following similar procedure discussed previously, we randomly selected 100 DE genes for each of the sizes 5, 10 and 20 as the candidate signatures. For each candidate signature, we built up a RF classifier using their expression data to predict the survival status of the patients in the Germany data set. In general, the RF classifiers performed worse on the validation data than on the testing sets during model cross-validation. Specifically, the sensitivity of the prediction for the majority of the candidate signatures is less than 0.2, which means most of the dead patients were predicted as alive by the corresponding candidate signatures.

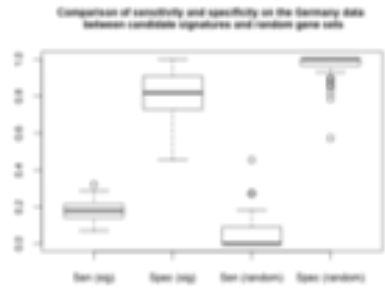


Fig. 5. Boxplot of sensitivity and specificity in the prediction of the survival status on the Germany data set using 5-gene candidate signatures and random gene sets. Left two are sensitivity and specificity of the candidate signatures and right two are sensitivity and specificity of the random sets.

To compare the performance of the signatures from DE genes with the random gene sets of the same size, 100 randomly selected gene sets for each of sizes 5, 10 and 20 were trained on the COG data set and validated on the Germany data set. As can be seen in Fig. 5, even though the sensitivities of the signatures from DE genes are low, they are still significantly higher than those of the random sets

(for 5-gene sets, t-test p-value < 2E-16; for 10-gene sets, t-test p-value < 2E-16).

Consensus clustering failed to reveal association between the gene expression of the COG and Germany data set and their corresponding survival status

Fig. 6 shows the clusters obtained from consensus clustering analysis for the COG and Germany data set after the combined preprocessing. As can be seen in Fig. 7 and Table S5, the survival status and cluster memberships are not concordant with each other. It implies that the gene expression patterns in both data sets are not able to classify the samples by the survival status.

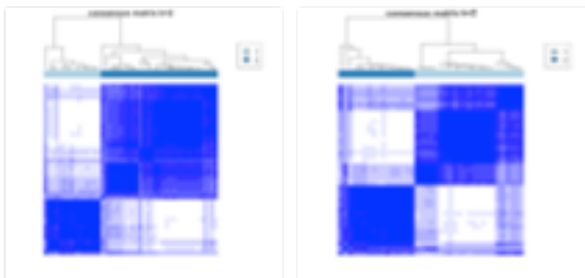


Fig. 6. Consensus clustering using gene expression data from the COG data set (left) and the Germany data set (right).

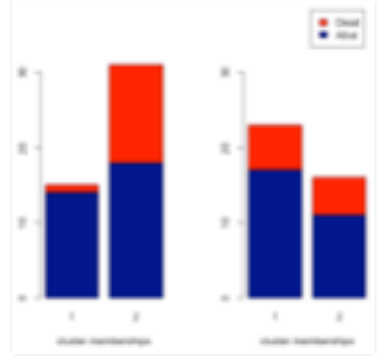


Fig. 7. Stacked barplots for the distribution of survival status between consensus clusters. Left: COG data set; right: Germany data set.

No common genes among the most differentially expressed genes between the COG and Germany data sets

We applied moderated t-test in *Limma* package to the expression data of the Germany data set and ranked genes based on their FDR values. We then compared the most differentially expressed genes corresponding to the survival status in the COG and Germany data set and found no common genes for the given DE gene cutoff (FDR < 0.2 and |fold change| > 1.3; DE analysis based on the separately preprocessed expression data for each data set, Table 2 and S6).

Table 2. Number of the common differentially expressed genes between the COG and Germany data sets

Ranked genes	# Common genes
top 5	0



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Epic
sunquest

The Uchicago Clinical Research Data Warehouse



850,000
patients

Epic
sunquest

The Uchicago Clinical Research Data Warehouse



850,000
patients



9.6 million
encounters

Epic
squest

The Uchicago Clinical Research Data Warehouse



48 million
procedures



850,000
patients

9.6 million
encounters

Epic
sunquest

The Uchicago Clinical Research Data Warehouse



48 million
procedures



8.8 million
medications

850,000
patients

9.6 million
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Epic
sunquest

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48 million
procedures



8.8 million
medications

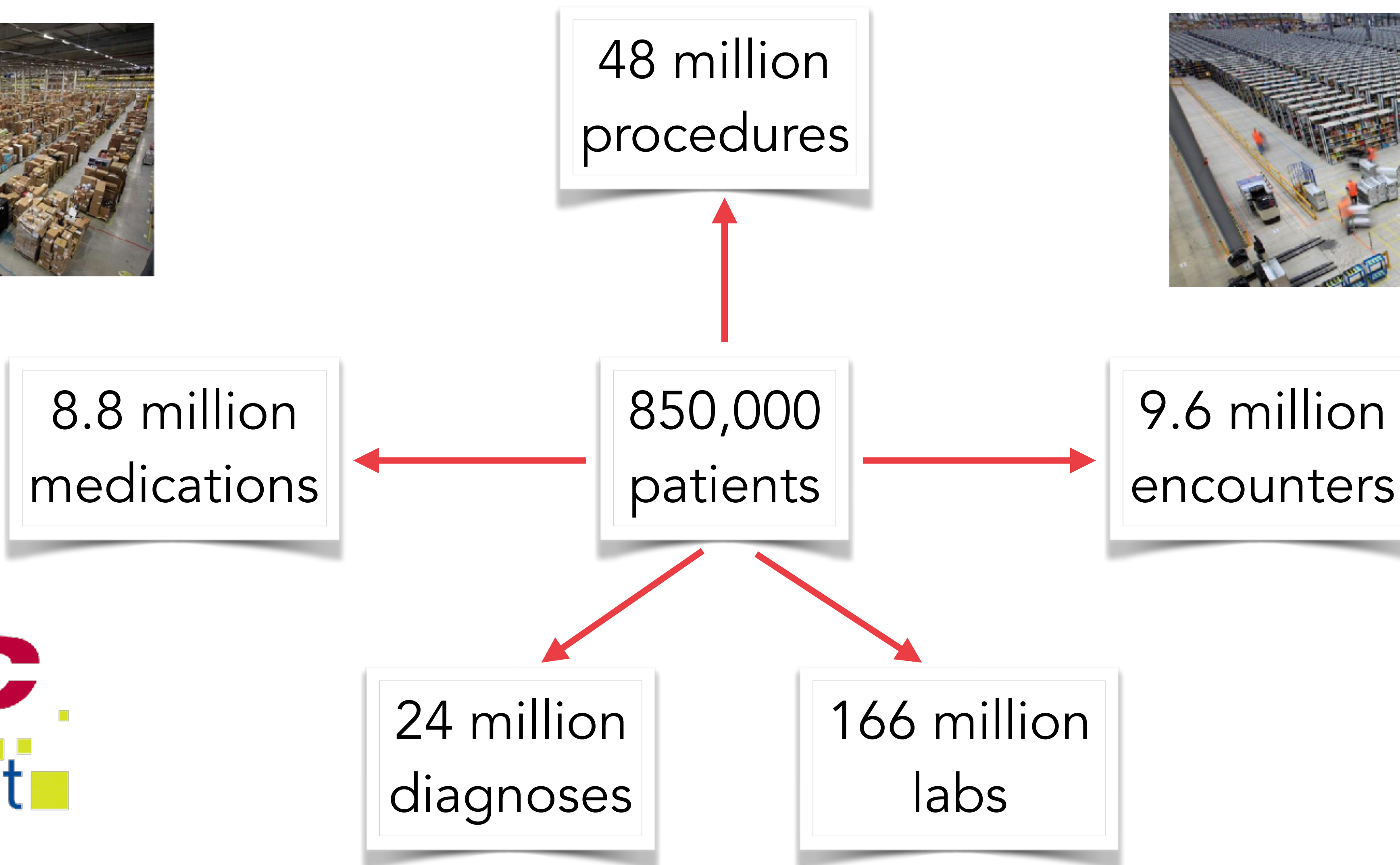
850,000
patients

9.6 million
encounters

24 million
diagnoses

Epic
sunquest

The Uchicago Clinical Research Data Warehouse



Clinical Research Data Warehouse



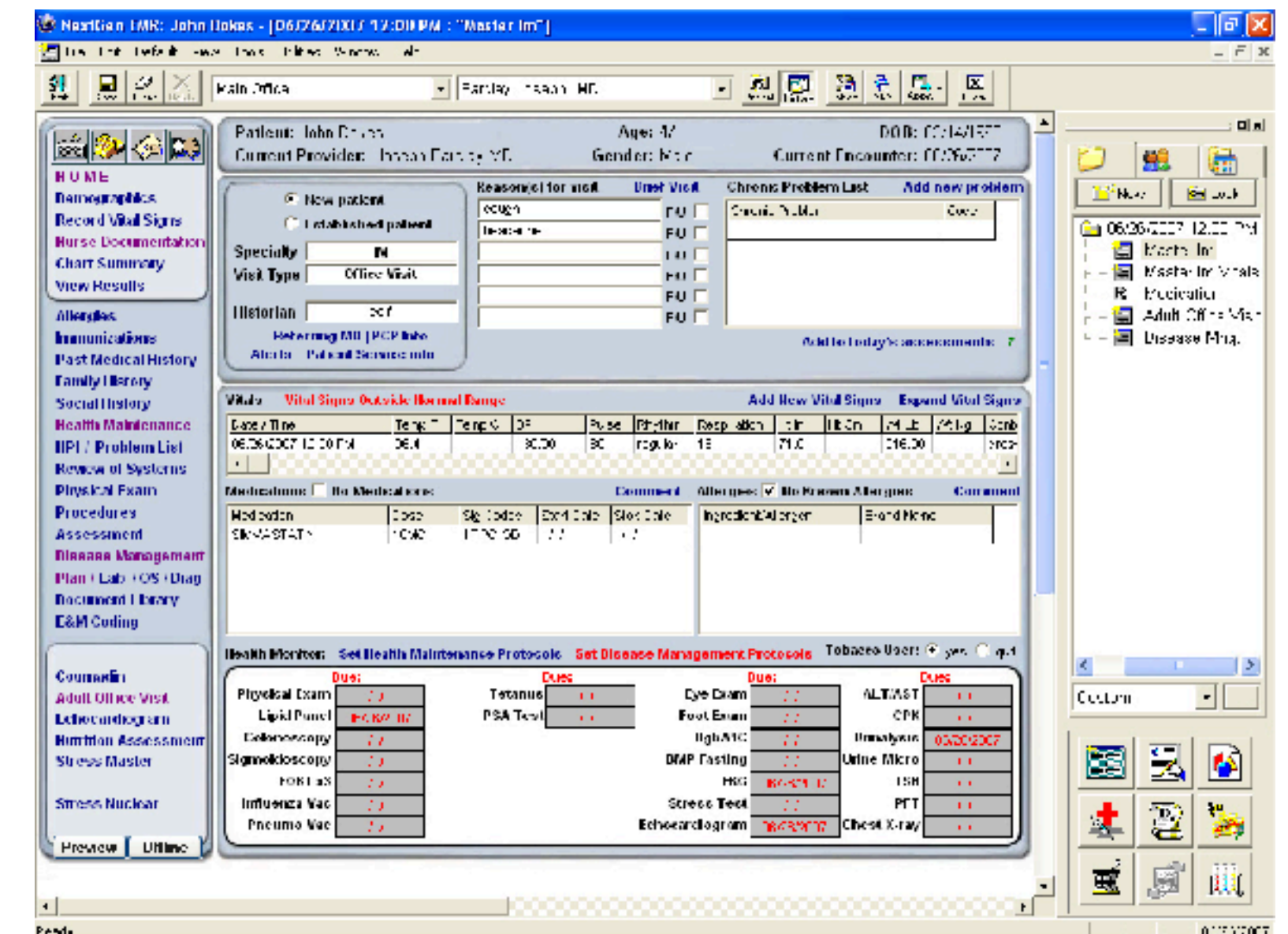
CRDW - Preliminary data / Cohort identification

- It can be hard to identify cohorts
- CRI has specialists to help
- Reviewers like to see preliminary identification of cohorts - "Can they really get the data"
- Sometimes new data has to be sourced

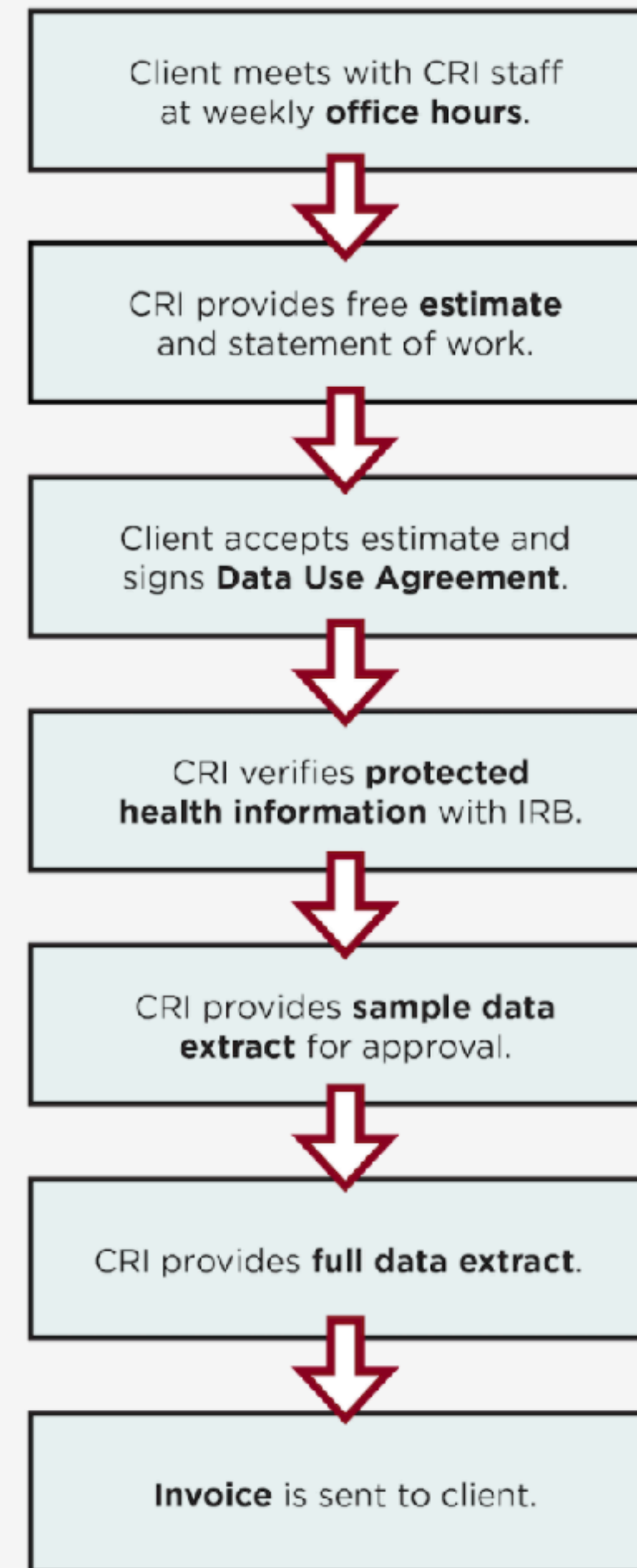


CRDW - Data element identification

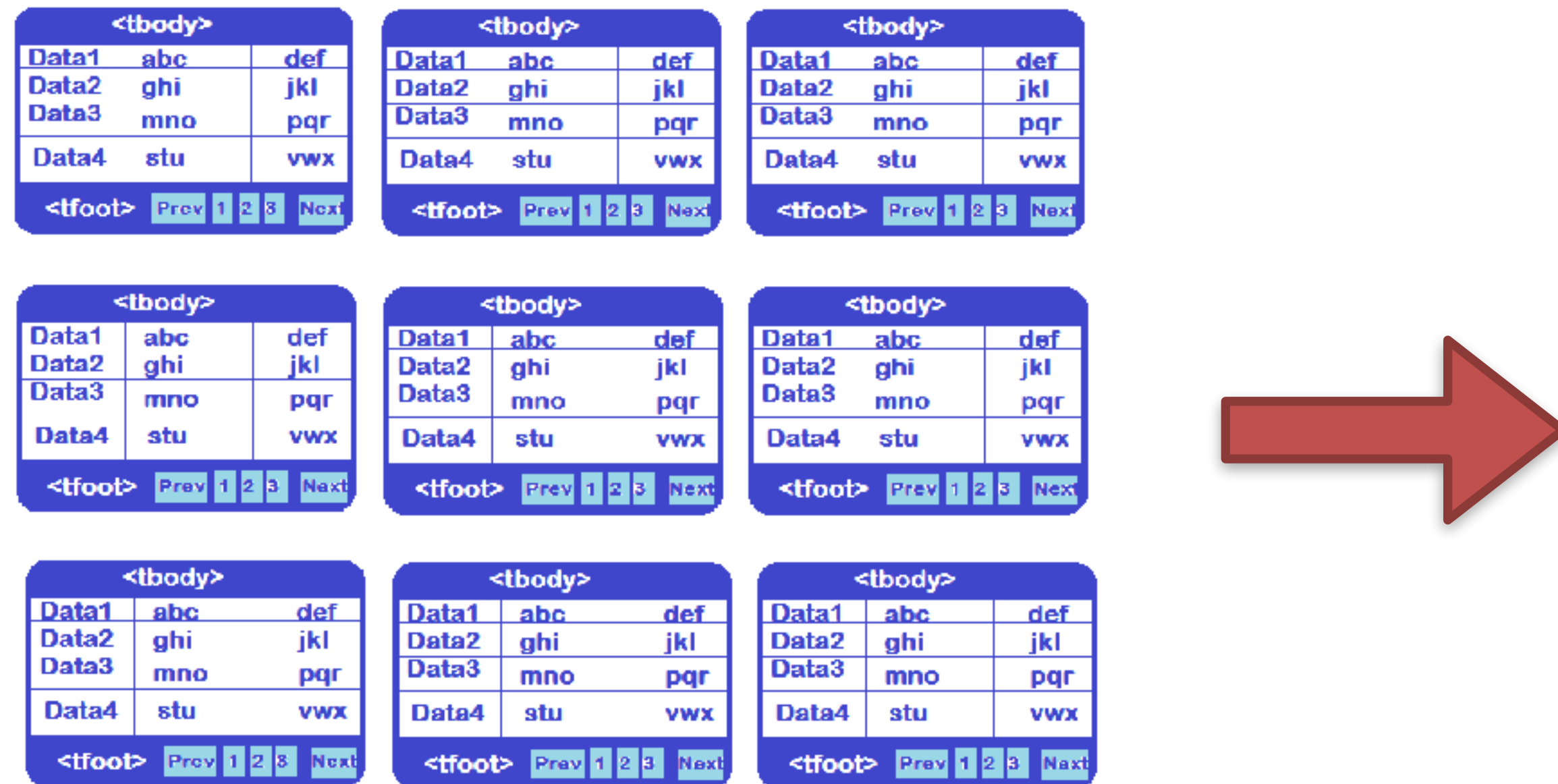
- Identifying elements to pull from the CRDW is an iterative process
- Requires input from the CRDW and the investigator
- Delineation of data elements in the grant is essential



Data request process



CRDW - Data aggregation and normalization



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Data2	ghi	jkl
Data3	mno	pqr
Data4	stu	vwx
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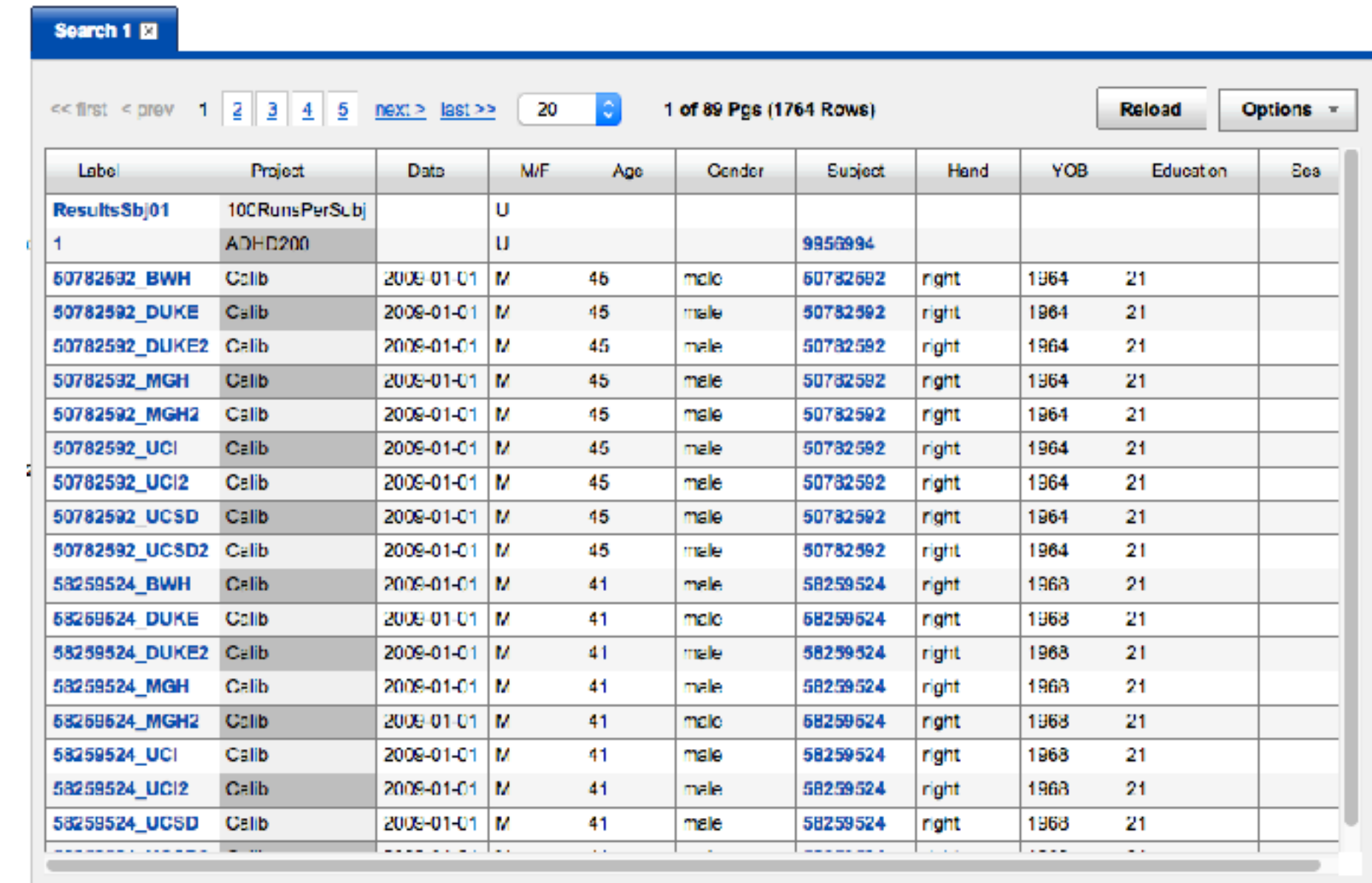
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1	ADHD200		U			9959994				
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50782592_DUKE	Calib	2009-01-01	M	45	male	50782592	right	1964	21	
50782592_DUKE2	Calib	2009-01-01	M	45	male	50782592	right	1964	21	
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50782592_UC12	Calib	2009-01-01	M	45	male	50782592	right	1964	21	
50782592_UCSD	Calib	2009-01-01	M	45	male	50782592	right	1964	21	
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58259524_UC12	Calib	2009-01-01	M	41	male	58259524	right	1968	21	
58259524_UCSD	Calib	2009-01-01	M	41	male	58259524	right	1968	21	

Taking the complex, multidimensional data from the CRDW and creating a usable data set for subsequent analysis requires special skills and should be included in the budget for data acquisition

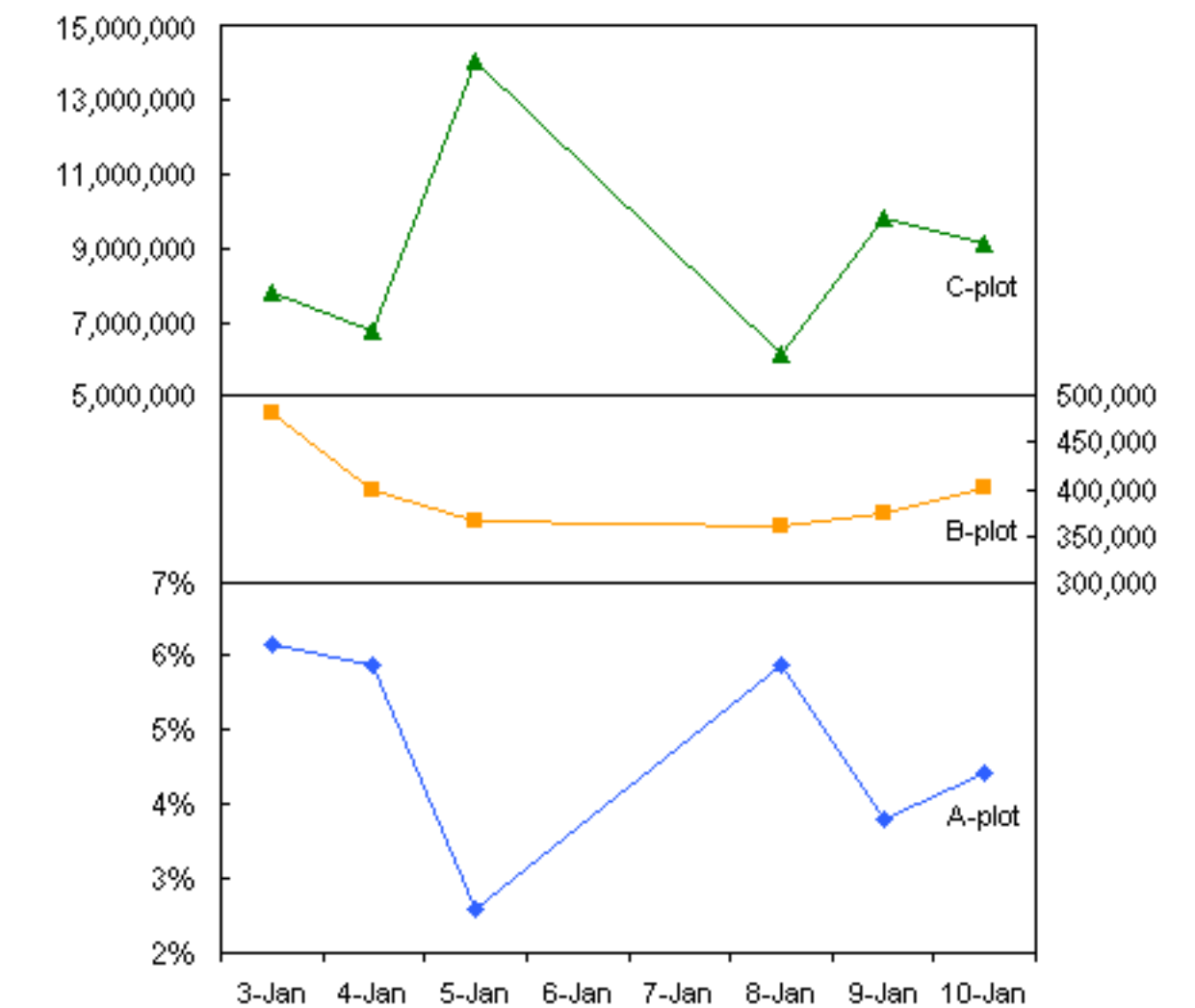
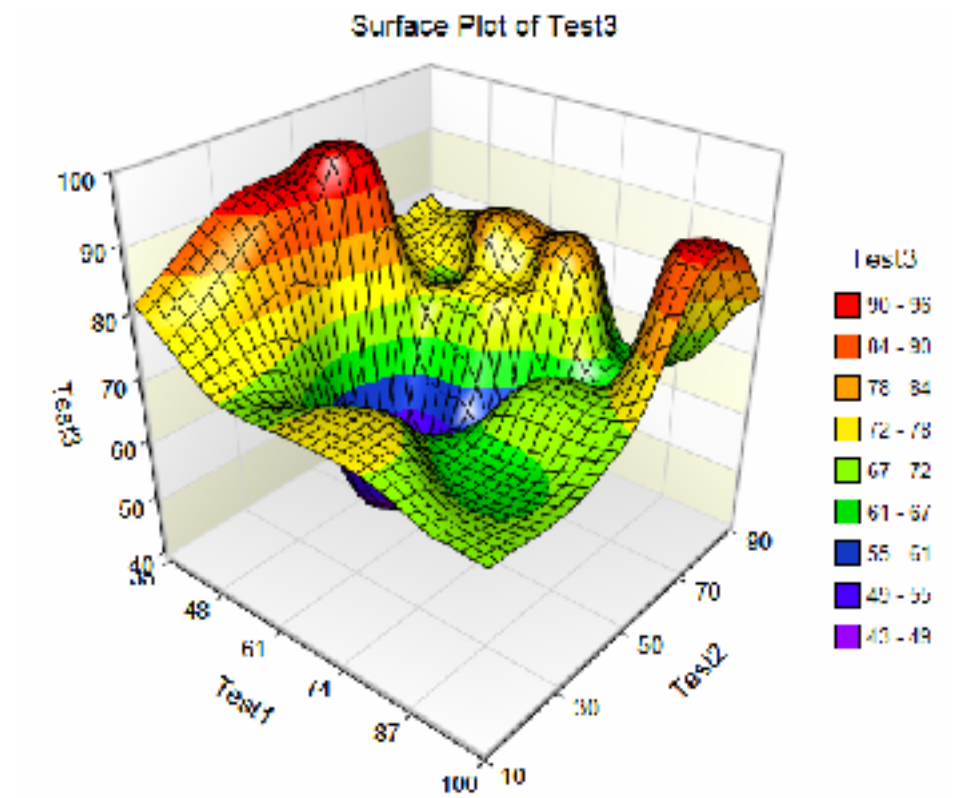
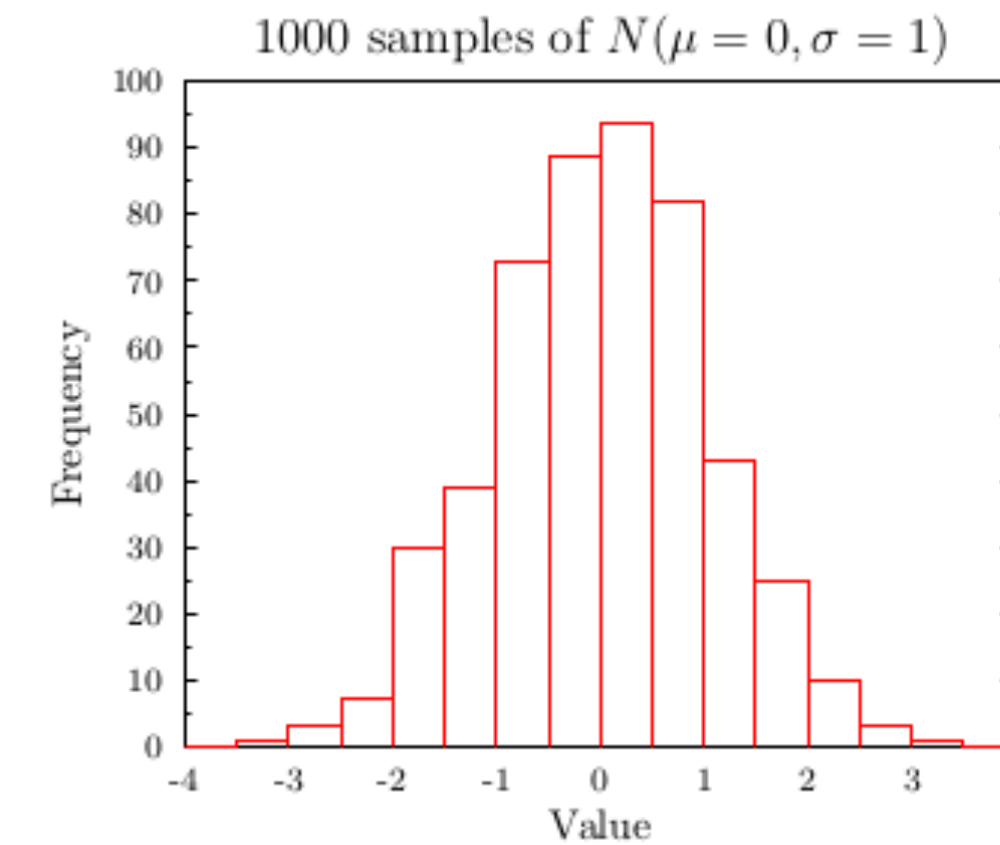
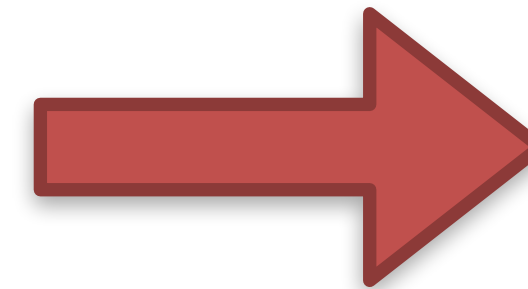


CRDW - Data analysis and interpretation

Search 1

<< first < prev 1 2 3 4 5 next > last >> 20 1 of 89 Pgs (1764 Rows) Reload Options

Label	Project	Date	M/F	Age	Gender	Subject	Hand	YOB	Education	Sex
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1	ADHD200		U			9956994				
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58259524_UCSD	Calib	2008-01-01	M	41	male	58259524	right	1968	21	



Data analysis can be costly and time-consuming.
Consider adding an analyst to your budget vs. chargeback

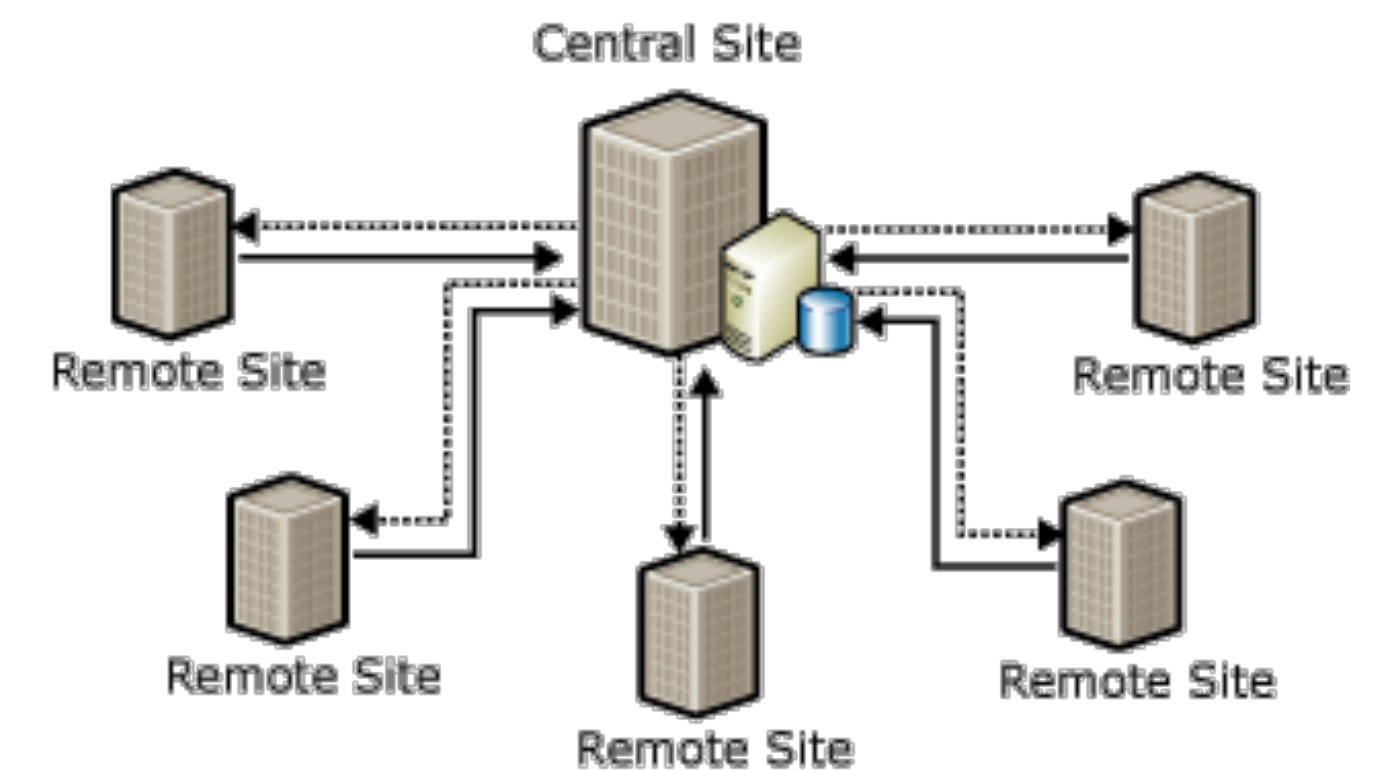


Application Development

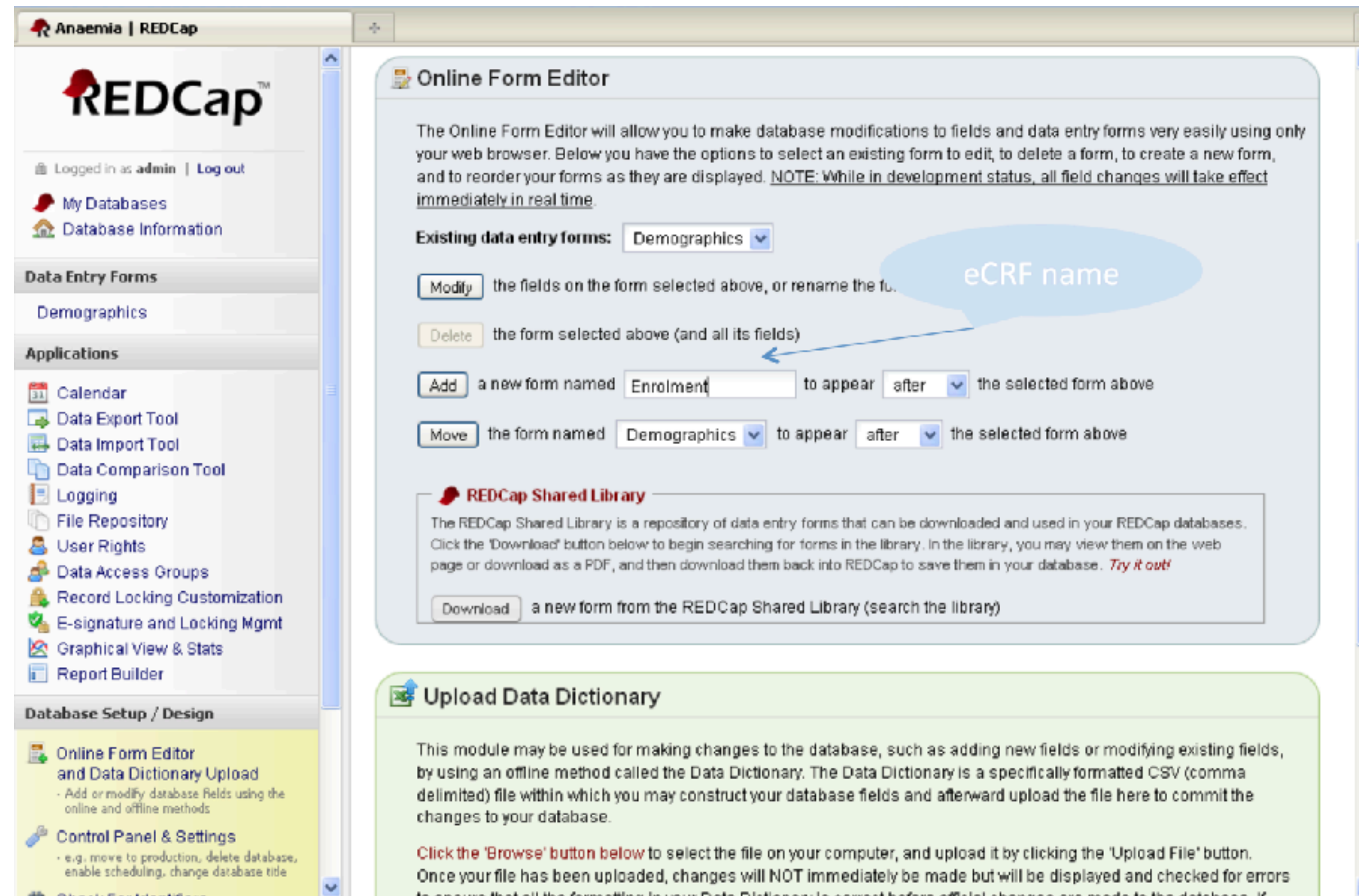


Multi-site data collection, transfer, and storage

- If multiple sites enrolling, there are special considerations for IRB, contracts, data use agreements, and application development
- These must be tackled long before your proposal is submitted



REDCap



HIPAA-compliant data collection and storage



REDCap

- It's easy to get a REDCap account - and it's free
- Non-BSD collaborators will need BSD accounts - and this can take time (start early)
- Most form generation can be performed by the investigators
- CRI helps with complex forms and other needs
- We can help with boilerplate grant language for REDCap

Custom application development / programming

- Do you need a website?
- How about a customized platform for data collection?
- Online tools?
- The CRI can build anything you need, but there must be budget for programmer costs
- We can help estimate the budget and write up the relevant parts of the proposal

March of Dimes Prematurity Research Center

March of Dimes
Participating Site



Site Coordinator

External Sites

Web-based subject
enrollment, tissue
collection, and sample
tracking system



March of Dimes
Coordinating Center



Res. Coord.



Lab Scientists



Bioinformaticians

University of Chicago

Genomics Core

Secure Storage - CRI

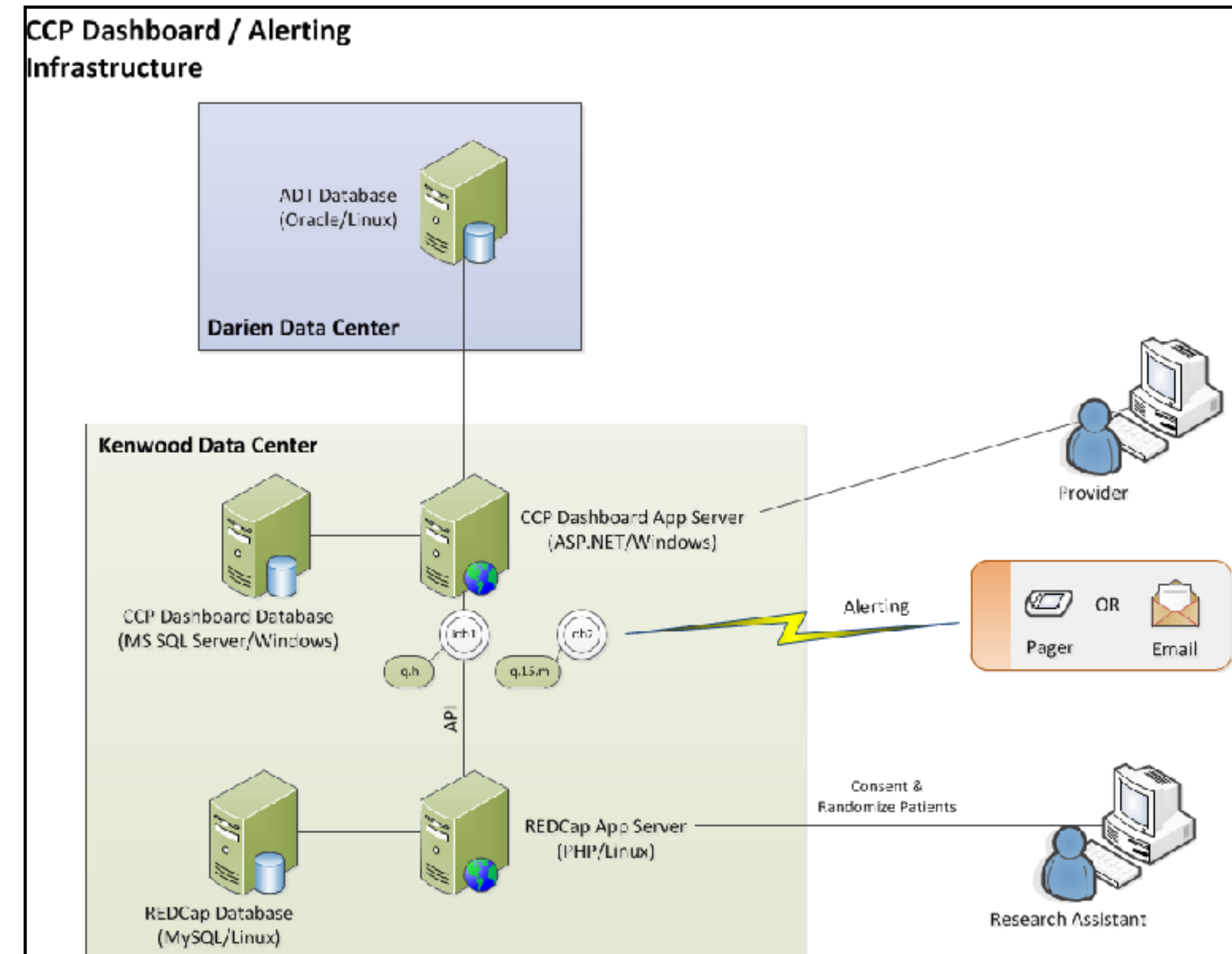
1200 Patients GPS

- Web application developed for UChicago pharmacogenomics study
- Interfaces with PubMed and CRI survey engines
- Produces a patient-specific eligibility list on a per clinic level
- Patient enrollment directly in application



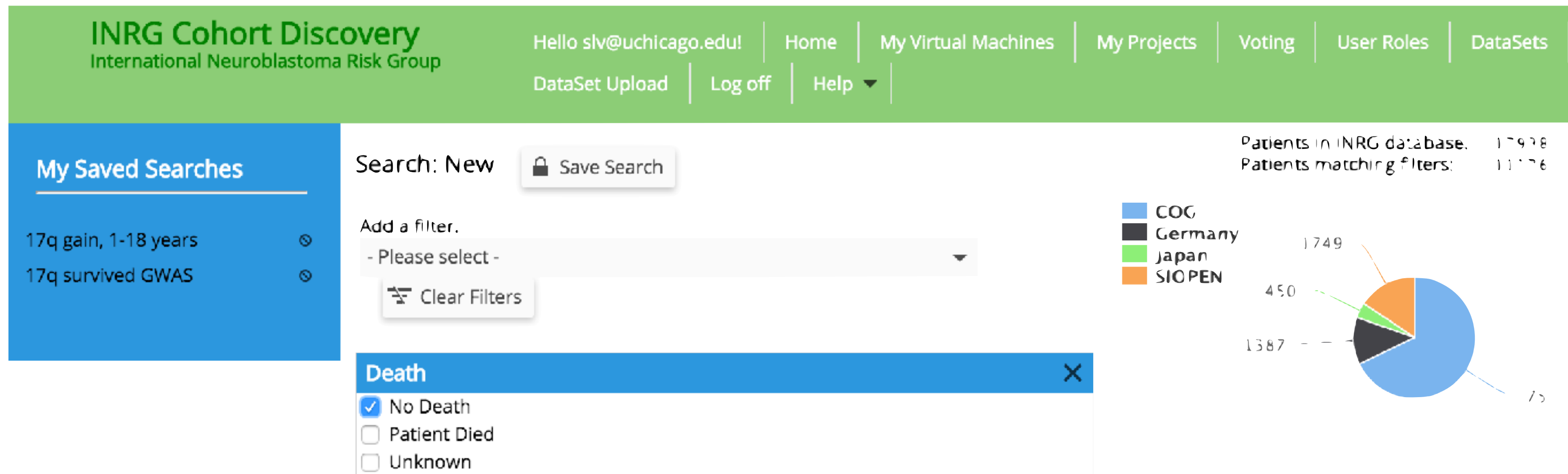
Comprehensive Care Program

- CRI developed applications to support enrollment and management of patients to this multi-arm CMMS-sponsored UChicago study
- Web application-enabled aggregation of data from multiple sources (REDCap, Epic Clarity, Centricity Billing, ADT)
- Alerting infrastructure built to notify providers of patient events



International Neuroblastoma Risk Group Database

- Web portal for cohort discovery
- International data governance
- Strict auditing of data revisions

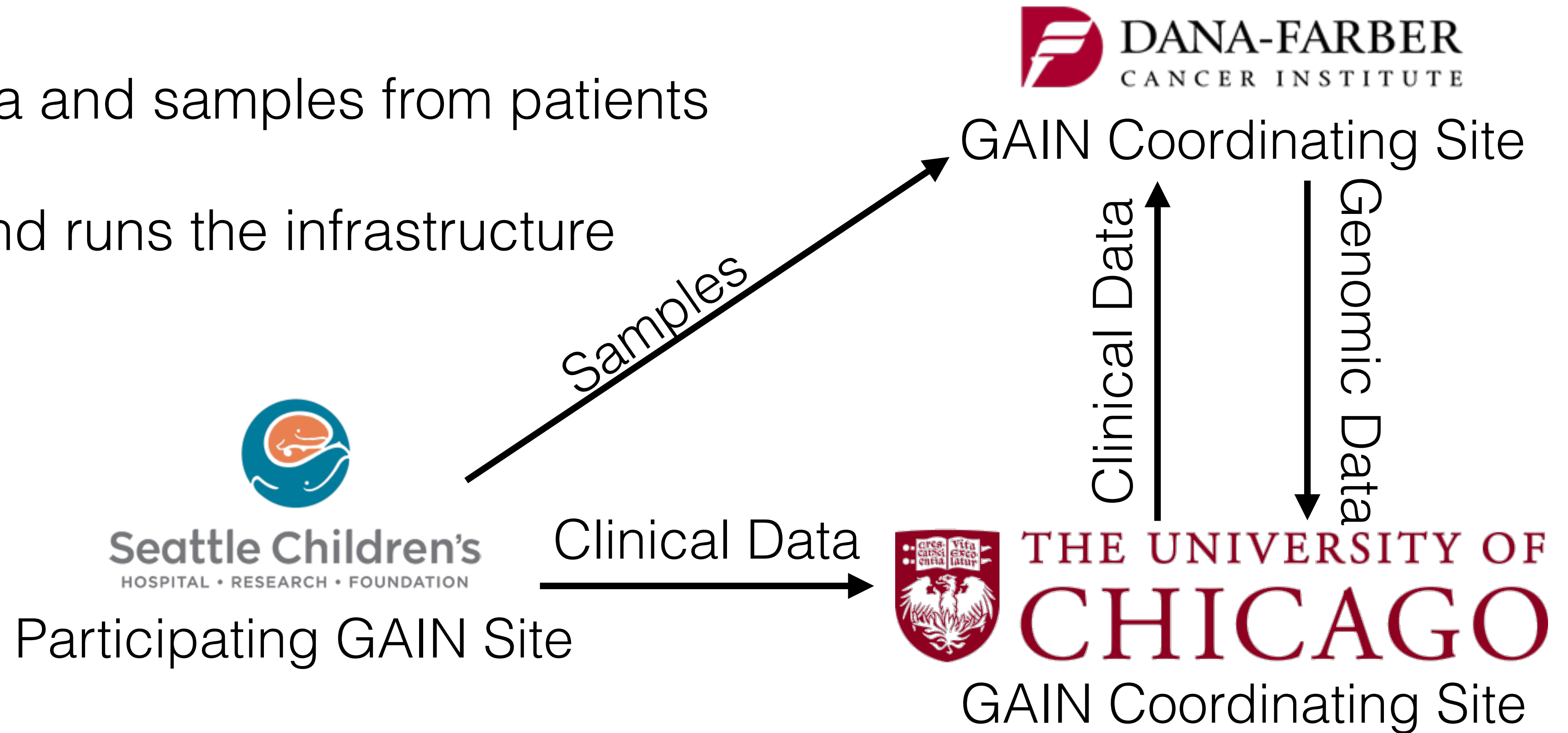


Pediatric GAIN Project

- Multi-center (20+) pediatric cancer trial
- Collect data and samples from patients
- CRI built and runs the infrastructure

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- Multi-center (20+) pediatric cancer trial
- Collect data and samples from patients
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Systems and infrastructure

Systems - Offsite access

- Do researchers outside of UChicago need access to your data?
- Collaborator accounts take time to obtain - and the CRI can help




Systems - Growing / flexible storage needs

- Some projects do not require much storage in the beginning, but needs grow
- Consider the entire project, not just the first year when crafting the budget for systems



Systems - HPC

- There are many options for HPC. CRI has one of the biggest and fastest clusters on campus
- CRI also has dedicated support for helping you prepare your grant and complete your research



	TARBELL	New Cluster GARDNER
Standard Compute Nodes	38	88
Mid-Tier Compute Nodes	0	28
Large Memory Nodes	2	4
GPU Nodes	0	5
Xeon Phi Nodes	0	1
Theoretical Performance	44.2 TFLOPs	112.8 TFLOPs
Measured Performance	21.2 TFLOPs	97 TFLOPs
Total Memory	12 TB	31.6 TB
Scratch Storage	110 TB	350 TB
Interconnect Bandwidth	40 GB/s	56 GB/s

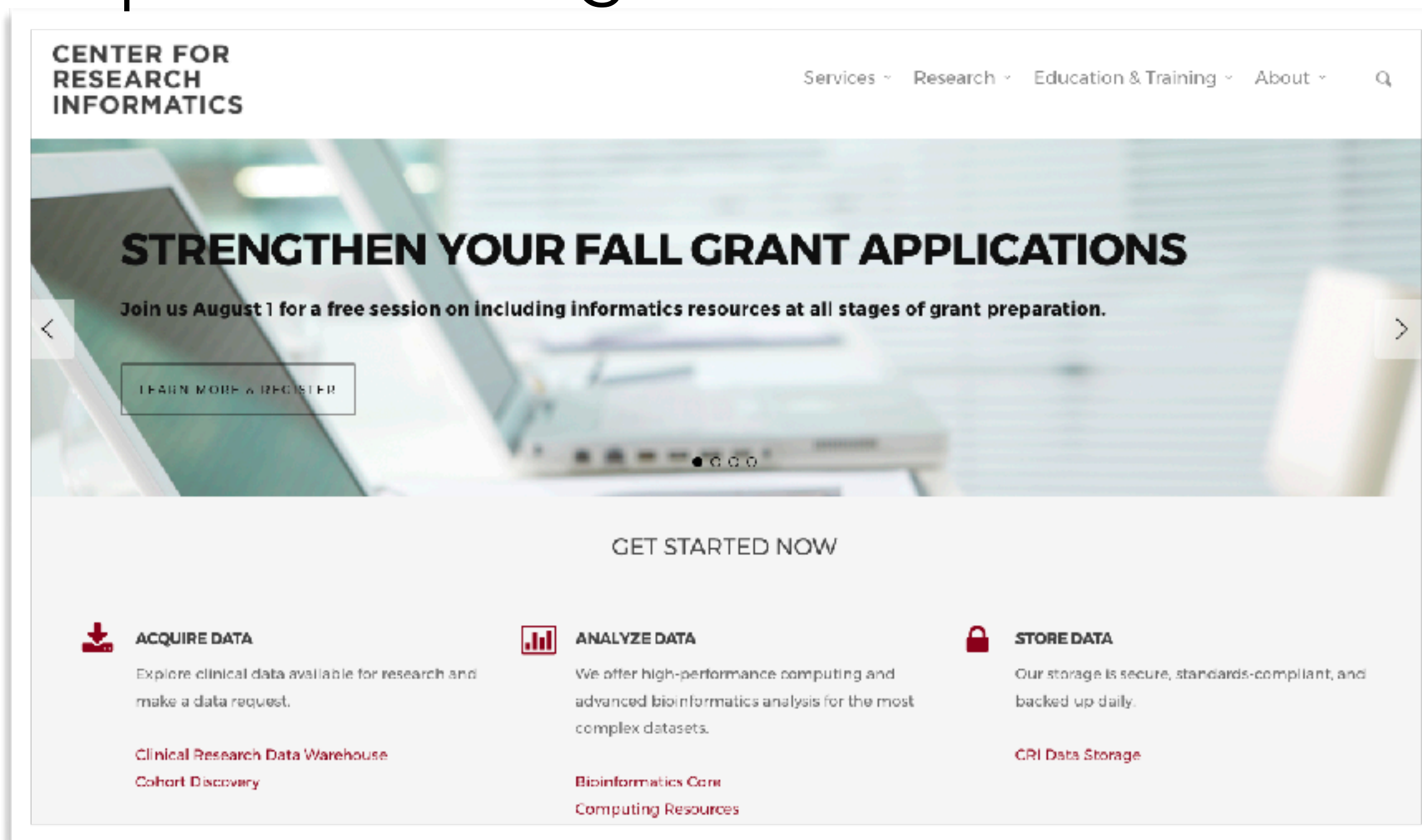
Systems - Virtual machines / servers

- Setting up and maintaining VMs is expensive
- CRI will help you develop your budget
- This is commonly left out of grant applications/budgets



Ways to get help

<http://cri.uchicago.edu>



Sam Volchenbom
Director



Michael Baltasi
Deputy Director



Brian Furner
Applications



Thorbjorn Axelsson
Systems



Jorge Andrade
Bioinformatics



Tim Holper
Data Warehouse



Julissa Acevedo
REDCap



Julie Johnson
Data Warehouse



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Applications - Systems - Bioinformatics - Data Warehousing

Questions?



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