Federated Data Sharing, Natural Language Processing and Deep Phenotyping to Advance Precision Medicine

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"Identifying specific clinical phenotypes from EHR data require use algorithms incorporating demographic data, diagnostic and procedure codes, lab values, medications, and natural language processing (NLP) of text documents."

"Such 'deep phenotyping', as it is known, gathers details about disease manifestations in a more individual and finer-grained way, and uses sophisticated algorithms to integrate the resulting wealth of data with other...information.



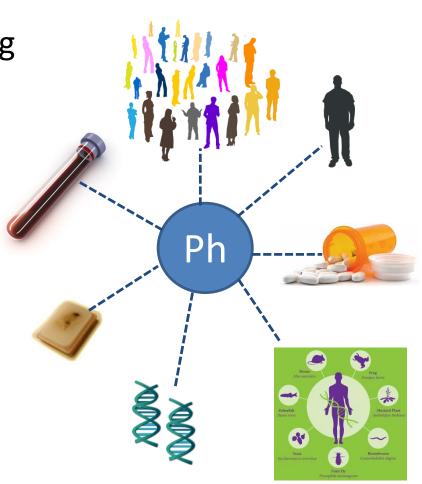
Nature, November 5 2015



"Data sharing can break down barriers between institutions, including those in the public and private sectors, to enable maximum knowledge gained and patients helped."

Phenotyping Use Cases

- Cohort discovery supporting translational science
- Targeted Therapeutics and Personalized Medicine
- Biomarker Discovery and Validation
- Pharmacogenomics
- Pharmacovigilence
- Disease Surveillance
- Drug repurposing



What's different now?

- Speed and depth in which we can interrogate the human genome, cancer genome, microbiome
- Widespread adoption of EMRs, availability of data with positives and negatives
- Increasingly challenging technical and regulatory environment
- Advancing science of Ontology and NLP, model organisms, more widespread use
- Ability to aggregate data across organizations makes it possible to identify and study rare phenotypes
- 'Direct to consumer' phenotyping (e.g. 23andMe)

Cancer Phenotyping

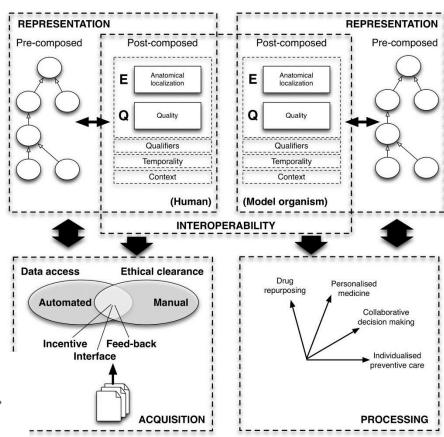
- Less about defining a specific cohort with the disease (except for familial risk)
- More about identifying specific subpopulations with different behaviors that can drive forward molecular classification, systems biology, inform treatment decisions
- Annotation of cancer specimens (retrospective and prospective) will be a critical factor in success



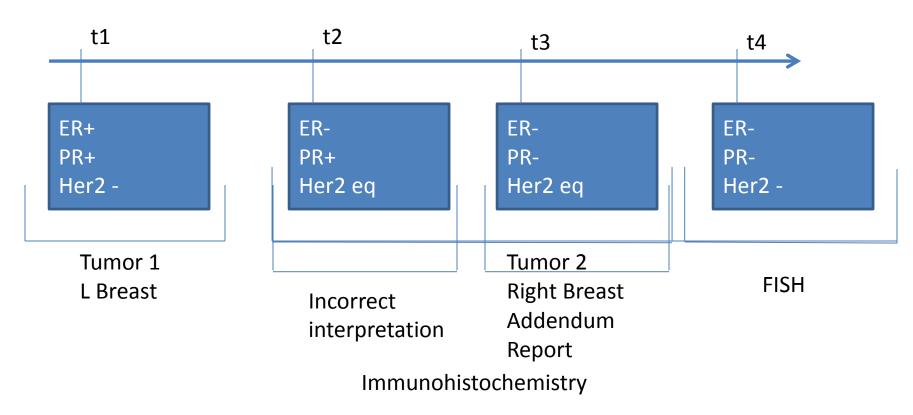
The digital revolution in phenotyping

Anika Oellrich*, Nigel Collier*, Tudor Groza*, Dietrich Rebholz-Schuhmann*, Nigam Shah*, Olivier Bodenreider, Mary Regina Boland, Ivo Georgiev, Hongfang Liu, Kevin Livingston, Augustin Luna, Ann-Marie Mallon, Prashanti Manda, Peter N. Robinson, Gabriella Rustici, Michelle Simon,

Liqin Wang, Rainer Winnenburg and Michel Dumontier Corresponding author. Anika Oellrich, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, CB10 1SD, United Kingdom. E-mail: anika.oellrich@kcl.ac.uk * These authors contributed equally to this work. Anika Oellrich et al. Brief Bioinform 2015



The Acquisition Problem: What is the ER, PR, Her2 status of this patient?



Biomarker Phenotyping Rules: Her2/Neu Values

- Her2/Neu phenotype preferentially obtained from Pathology Report
- Lab interpretation (e.g. "positive") should be extracted in preference over raw scores (e.g. "2+")
- In the absence of explicit interpretation statement:
 - IHC 3+ or greater is positive
 - IHC 0 or 1+ is negative
 - IHC 2+ is equivocal
- FISH/CISH interpretation of
 - "amplified" = positive
 - "not amplified" = negative
- Value from FISH or CISH takes precedence over IHC except when IHC is done <u>after</u> an equivocal FISH test

Importance of NLP/IE

- Despite progress, most important clinical data for phenotyping still mainly free text (especially pathology and radiology)
- One of many seminal lessons from eMERGE is that NLP is important to accurate EMR-based phenotyping
- Challenges abound: temporality, summarization, coreference resolution, cross-document, taskspecific
- Going from mentions (and/or EHR result) to phenotypes for a wide range of purposes will require advances in the science of phenotyping

DeepPhe Project

http://cancer.healthnlp.org

- Collaboration between DBMI and BCH
- Goal is to develop next generation <u>cancer deep</u> <u>phenotyping</u> methods
- Addresses information extraction but also representation and visualization
- Support high throughput approach process and annotate all data at multiple levels (from mention to phenotype) and across time
- Combine IE with structured data (cancer registry)
- Develop phenotyping rules/reasoners/classifiers
- Driven by translational research scientific goals

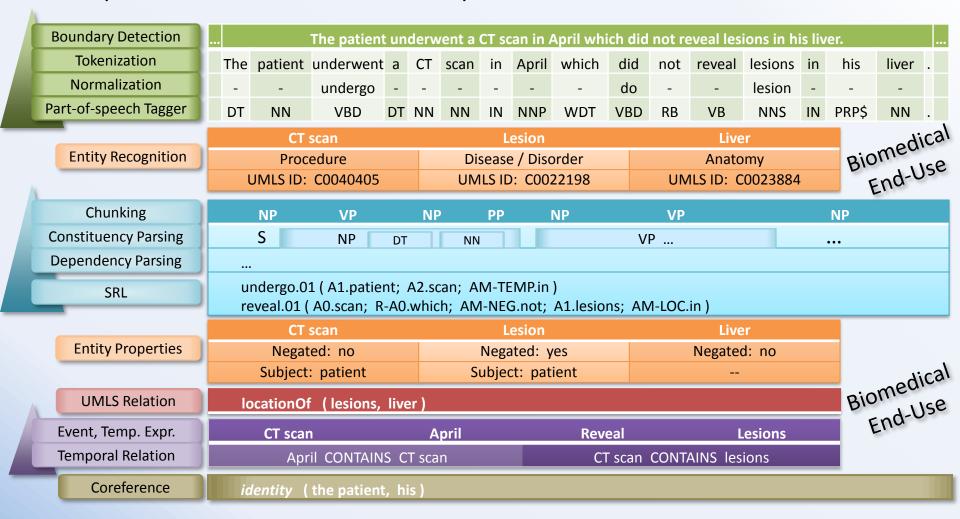
Example phenotypic features

- Histopathologic type
- TNM Stage
- Comorbidities
- Medications
- Biomarkers
- Clinical mutation testing (e.g. BRAF)
- Local recurrence
- Distant recurrence

Apache cTAKES: Sample Pipeline



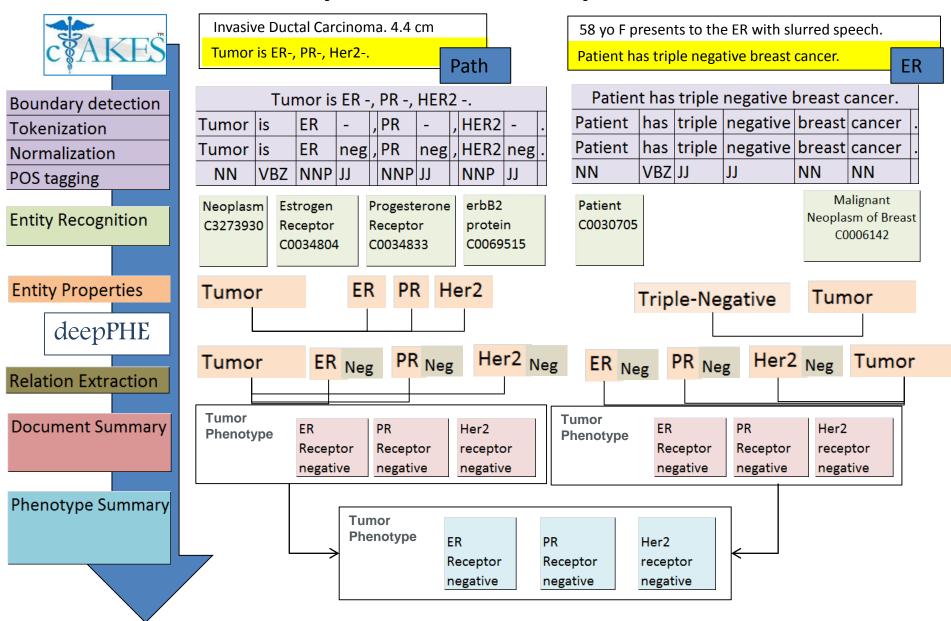
The patient underwent a CT scan in April which did not reveal lesions in his liver.

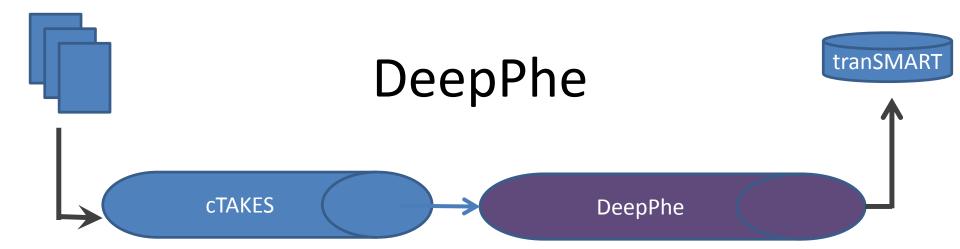




cTAKES Component or Function	Score	Score Type
Sentence boundary [2]	0.949	Accuracy
Context sensitive tokenizer [2]	0.949	Accuracy
Part-of-speech tagging [2] [10]	0.936 – 0.943	Accuracy
Shallow parser [2]	0.952 ; 0.924	Accuracy; F1
Entity recognition [2]	0.715 / 0.824	F1 ¹
Concept mapping (SNOMED CT and RxNORM) [2]	0.957 / 0.580	Accuracy ¹
Negation NegEx [11] [2]	0.943 / 0.939	Accuracy ¹
Uncertainty, modified NegEx [11] [2]	0.859 / 0.839	Accuracy ¹
Constituency parsing [12]	0.810	F1
Dependency parsing [10]	0.854 / 0.833	F1 ²
Semantic role labeling [10]	0.881 / 0.799	F1 ³
Coreference resolution, within-document [12]	0.352 ; 0.690 ; 0.486 ; 0.596	MUC; B^3; CEAF; BLANC
Relation discovery [13]	0.740-0.908 / 0.905-0.929	F1 ⁴
Events (publication in preparation)	0.850	F1
Temporal expression identification [14]	0.750	F1
Temporal relations: event to note creation time [15]	0.834	F1
Temporal relations: on i2b2 challenge data [15]	0.695	F1

DeepPhe NLP Pipeline





Detailed NLP annotation (information extraction)

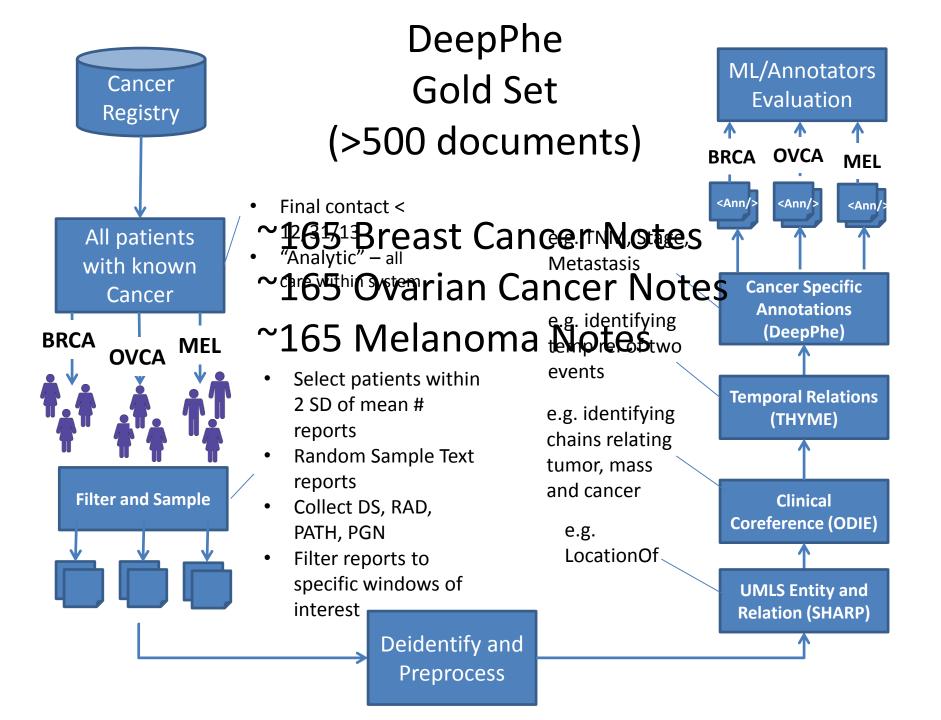
- Concepts (e.g. Dis/Disord, AL, procedure, findings, medication statements)
- Negation
- Coreference chains
- Temporal expressions and relations
- Relation extraction (e.g. attribute-value pairs)

Document Summarization

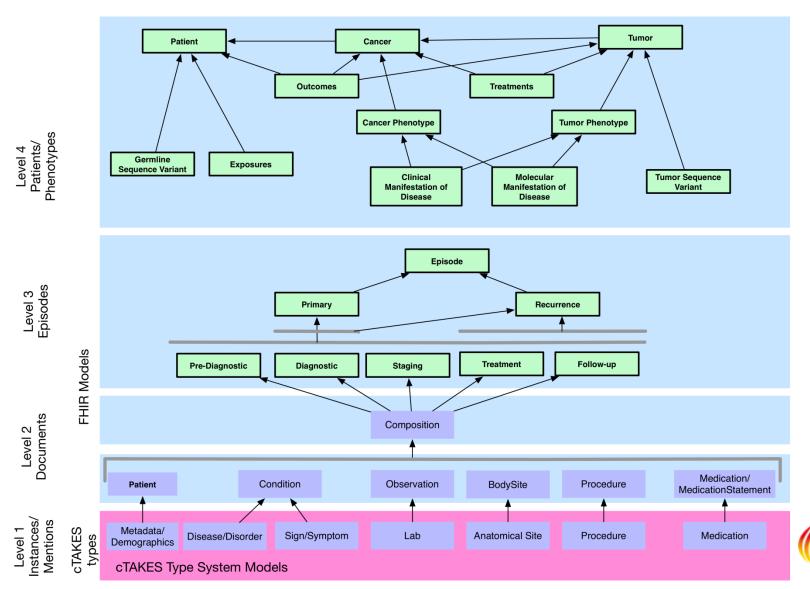
- Classification from multiple mentions
- Relationship of mentions to higher level entities (e.g. tumor)

Phenotype Summarization

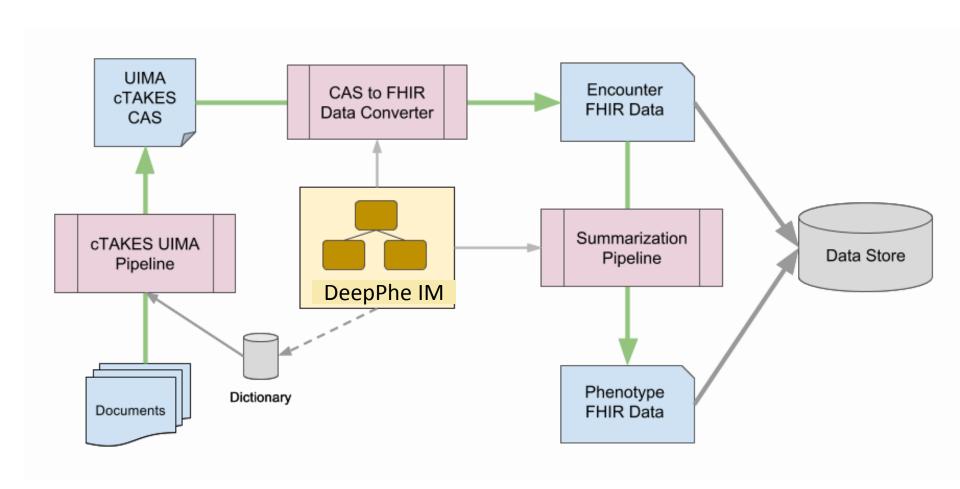
- Summarization across documents of different genre
- Incorporation of structured data with unstructured data



DeepPhe Information Model



Data Flow in DeepPhe



Initial Results

4 breast cancer patients; 48 documents with gold annotations

14 mentions of TNM

".... T STAGE, PATHOLOGIC: pT2; N STAGE, PATHOLOGIC: pN0; M STAGE: Not applicable...."

"... a clinical stage IIIA (T3 N2 Mx) triple negative infiltrating...."

6 mentions of Stage

"...The patient has stage 4 breast carcinoma..."

"...-Sister: Breast cancer (Stage I)

39 mentions of Receptors

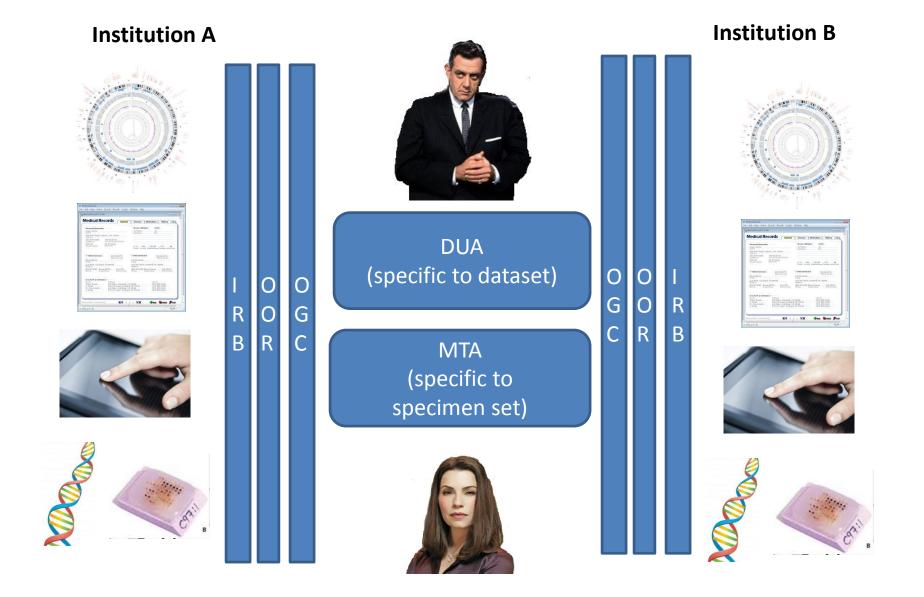
".... ER: Positive 270; PR: Positive 23..."

"... triple negative" breast carcinoma..."

"... REPORTED TO BE NEGATIVE FOR ER, PR, AND HER-2/NEU..."

Туре	Precision	Recall	F1-score
TNM	0.87	0.93	0.90
Stage	1	0.83	0.91
Receptors	1	0.90	0.95

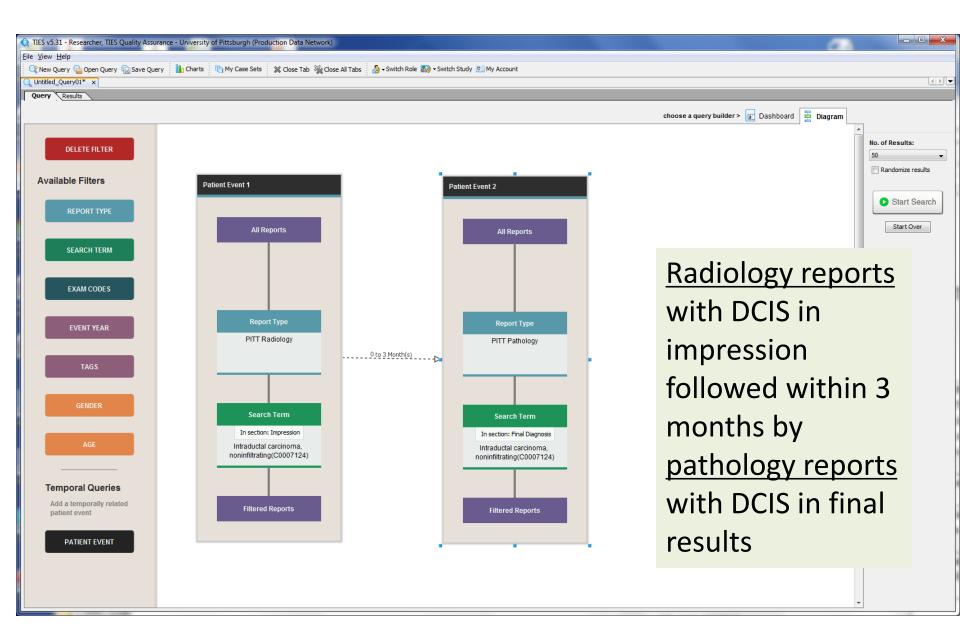
How we share data and biospecimens today

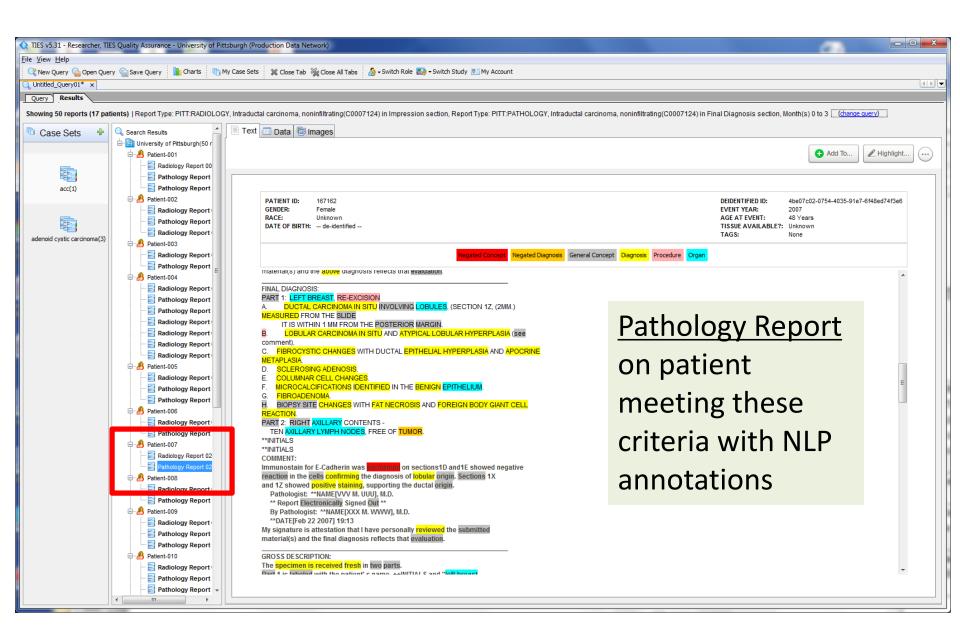


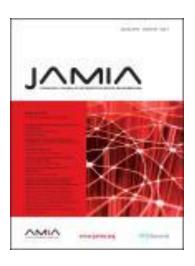
What is TIES?

http://ties.pitt.edu

- An NLP pipeline for de-identifying, annotating and storing clinical documents
- A system for indexing research resources (FFPE, FF, images) with document annotations
- A system for querying large repository of annotated clinical documents and obtaining resources locally, using an honest broker model
- An open source platform to support federated data and biospecimen sharing among networks of cancer centers and other institutions



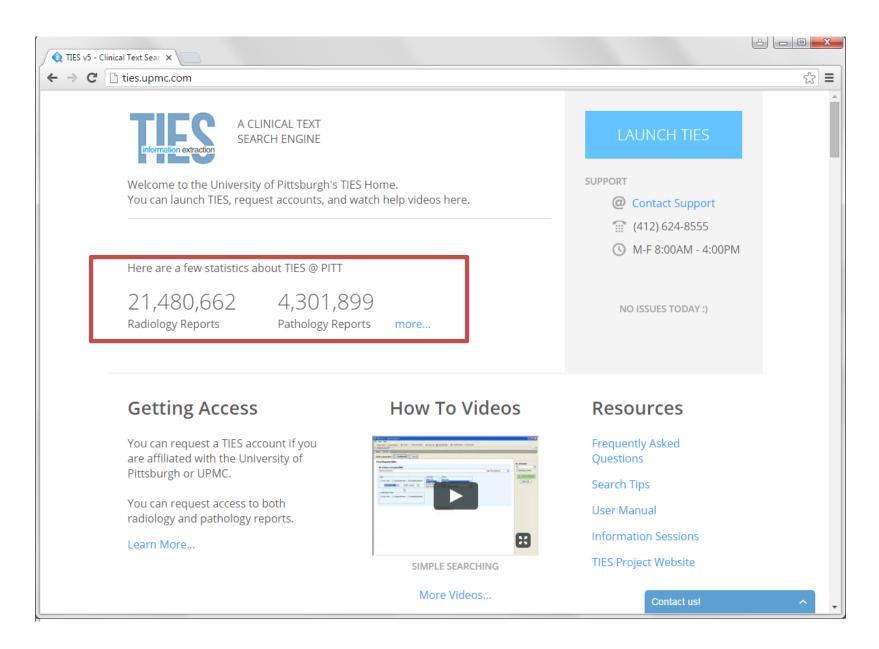




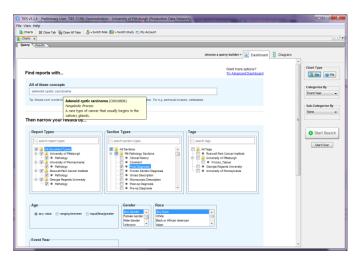
caTIES: a grid based system for coding and retrieval of surgical pathology reports and tissue specimens in support of translational research

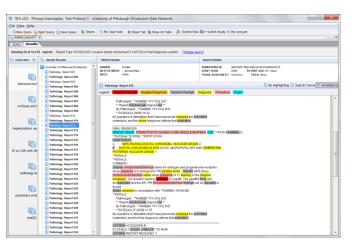
Rebecca S Crowley, 1,2,3 Melissa Castine, 1 Kevin Mitchell, 1 Girish Chavan, 1 Tara McSherry, 4 Michael Feldman 4

 # Comi	# Complexity Query		Response time over three retrievals				Performance metrics			
		Number	Mean	SD	Mean SI	Number	Agreeme	TP FI	P Preci	sion
		Reports	time to		time to all	of Repor	rts nt			
		Retrieved	first		results	or Repo	au			
			results		(sec)	Sets				
			(sec)			(complex	x)			
						Classifie	d			
	Men, 60-80 with prostatic adenocarcinoma on									
1Low	prostatectomy	1792	1.08	3 0.62	4.63 1	92 5	50 0.98	3 49	10.98	
	Women, 30-50 with atypical endometrial									
2Low	hyperplasia	792	0.70	0.19	0.70 0	19 (33 1.00	33	01.00	
3Low	Patients, 20-50 with phaeochromocytoma	54	0.98	5 0.31	0.96 0	31 5	50 0.98	3 49	10.98	
4Low	Patients with hemangiosarcoma of scalp	17	0.49	9 0.13	0.49 0	13	1.00	17	01.00	
5Low	Patients 10-30, with cystosarcoma phylloides	18	0.59	0.07	0.59 0	07 <i>^</i>	18 0.94	16	20.89	
	Patients with superficial spreading melanoma,									
6Low	metastatic	5	0.46	0.08	0.46 0	08	5 1.00	5	01.00	
7Low	Patients with medullary carcinoma in thyroid gland	27	0.59	9 0.26	0.60 0	26 2	27 0.96	26	10.96	
8Low	Patients with adenocarcinoma in brain	156	0.65	5 0.33	0.89 0	44 5	50 1.00	50	01.00	
9Low	Men with invasive ductal carcinoma of breast	29	0.53	3 0.15	0.53 0	15 2	29 1.00	29	01.00	
10Low	Patients, >60 with Hodgkins disease	549	0.64	4 0.17	0.84 0	22 5	50 0.94	34	160.68	
	All Low Complexity Queries	3439	0.67	7 0.20	1.07 1	26 32	29 0.98	308	21	0.94

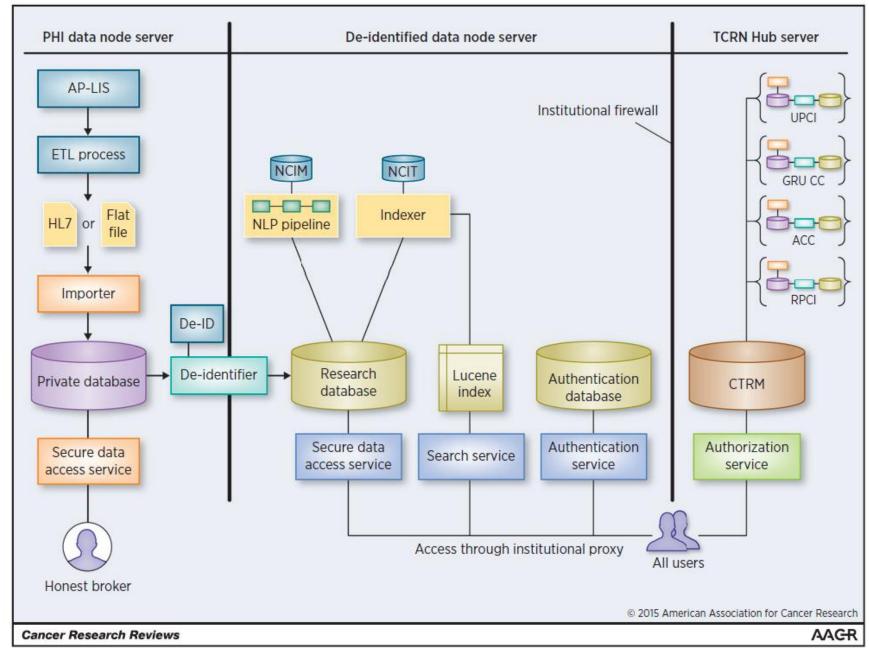


TIES Functionality



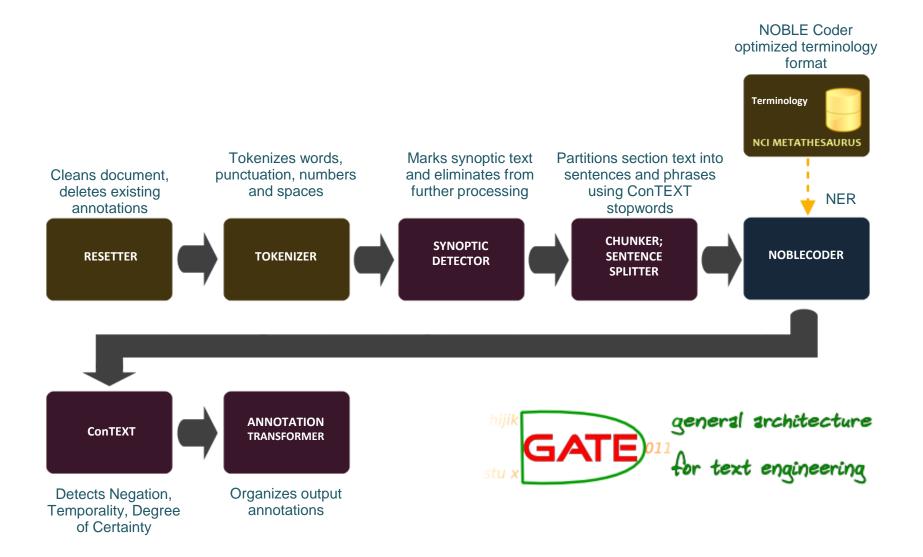


- NLP; Concept annotation with NCIM; ontology indexing with NCIT using Lucene
- Infrastructure to code and recode; parallelize coders
- De-identification, encryption, separation of PHI, auditing, X.509, quarantining
- Honest Broker model built in to software. HBs see identifiers when working with investigator
- Workflow to request FFPE, Frozen Tissue, Radiology Images
- Virtual Slides
- Other datatypes (e.g. Cancer Registry data)



Jacobson et al, Cancer Research 2015

Current TIES NLP Pipeline



BMC Medical Informatics and Decision Making



Research article

Open Access

Security and privacy requirements for a multi-institutional cancer research data grid: an interview-based study

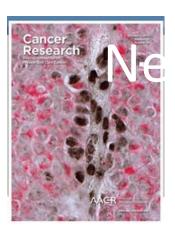
Frank J Manion*1, Robert J Robbins2, William A Weems3 and Rebecca S Crowley4

U Pittsburgh Cancer Institute
Abramson Cancer Center (Penn)
Roswell Park Cancer Institute
GRU Cancer Center
.....And others are preparing to join

http://ties.pitt.edu/tcrn







Resource

A Federated Network for Translational Cancer Research Using Clinical Data and Biospecimens &

Rebecca S. Jacobson¹, Michael J. Becich¹, Roni J. Bollag², Girish Chavan¹, Julia Corrigan¹, Rajiv Dhir¹, Michael D. Feldman³, Carmelo Gaudioso⁴, Elizabeth Legowski¹, Nita J. Maihle², Kevin Mitchell¹, Monica Murphy⁴, Mayurapriyan Sakthivel⁴, Eugene Tseytlin¹, and JoEllen Weaver³

Network Trust Agreements

- Instrument of Adherence
- IRBs agree that use of data for investigators is NHSR, no additional IRB protocol even for record level de-id data
- Establishes governing body

Policies and Processes

- QA and validation
- User authorization
- Auditing
- Incident Reporting
- Joining of new members
- Governance

Table 2. TCRN case statistics for numbers of patients and cases (A) and the number of cases of rare tumors (B) and common cancer categories (C) based on final diagnosis

	GRU	RPCI	ACC	UPCI	Total
A. Case statistics					
Patients	76,404	72,376	465,717	1,840,156	2,454,653
Pathology cases	157,316	156,555	857,681	4,588,017	5,759,569
B. Rare tumors					
Adenoid cystic carcinoma	41	88	404	509	1,042
Adrenocortical carcinoma	5	20	59	63	147
Alveolar soft part sarcoma	3	15	10	25	53
Angioimmunoblastic lymphadenopathy	12	35	58	84	189
Chordoma	5	14	124	245	388
Follicular dendritic cell sarcoma	2	2	8	13	25
Merkel cell carcinoma	9	72	165	196	442
Ovarian granulosa cell tumor	4	10	23	34	71
Phaeochromocytoma	15	38	272	164	489
Pleomorphic xanthoastrocytoma	2	5	12	53	72
Pseudomyxoma peritonei	6	36	46	129	217
Rhabdomyosarcoma	34	70	86	270	460
Sebaceous adenocarcinoma	13	33	26	94	166
Sinonasal undifferentiated carcinoma	2	6	31	27	66
Thymoma	13	45	433	210	701
C. Common cancer categories					
Bladder carcinoma	345	1,618	3,873	6,711	12,547
Breast carcinoma	1,143	9,605	28,262	37,691	76,701
Colorectal carcinoma	465	2,530	6,898	11,608	21,501
Endometrial carcinoma	394	1,815	3,707	7,706	13,622
Esophageal carcinoma	63	1,477	2,452	3,514	7,506
Hepatic carcinoma	153	633	2,912	5,720	9,418
Lung carcinoma	820	4,264	10,208	17,955	33,247
Lymphoma	1,387	6,795	10,605	15,689	34,476
Malignant glial neoplasm	242	292	2,198	4,943	7,675
Malignant melanoma	335	2,675	5,180	7,068	15,258
Ovarian carcinoma	503	2,872	4,659	6,446	14,480
Pancreatic carcinoma	162	740	1,866	3,622	6,390
Prostate carcinoma	903	3,612	18,867	19,445	42,827
Renal cell carcinoma	364	1,319	3,183	10,950	15,816
Thyroid carcinoma	474	1,236	7,681	12,387	21,778

Jacobson et al, Cancer Research 2015

Example of TCRN Pilot Project



UPCI Investigator Yang Liu, PhD

Published OnlineFirst September 17, 2015; DOI: 10.1158/0008-5472.CAN-15-1274

Early Prediction of Cancer Progression by Depth-Resolved Nanoscale Mapping of Nuclear **Architecture from Unstained Tissue Specimens**

Shikhar Uttam¹, Hoa V. Pham¹, Justin LaFace¹, Brian Leibowitz^{2,3}, Jian Yu^{2,3}, Randall E. Brand⁴, Douglas J. Hartman², and Yang Liu^{1,3,4}

Abstract

Early cancer detection currently relies on screening the entire genesis and in human patients with ulcerative colitis, even in at-risk population, as with colonoscopy and mammography. Therefore, frequent, invasive surveillance of patients at risk for developing cancer carries financial, physical, and emotional burdens because clinicians lack tools to accurately predict which patients will actually progress into malignancy. Here, we present a new method to predict cancer progression risk via classified 12 of 15 patients who eventually developed colon nanoscale nuclear architecture mapping (nanoNAM) of unstained tissue sections based on the intrinsic density alteration of nuclear structure rather than the amount of stain uptake. We demonstrate that nanoNAM detects a gradual increase in the density alteration of nuclear architecture during cohorts may eventually advance this method to become a malignant transformation in animal models of colon carcino-

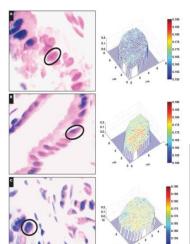
tissue that appears histologically normal according to pathologists. We evaluated the ability of nanoNAM to predict "future" cancer progression in patients with ulcerative colitis who did and did not develop colon cancer up to 13 years after their initial colonoscopy. NanoNAM of the initial biopsies correctly cancer and 15 of 18 who did not, with an overall accuracy of 85%. Taken together, our findings demonstrate great potential for nanoNAM in predicting cancer progression risk and suggest that further validation in a multicenter study with larger routine clinical test. Cancer Res; 75(22); 4718-27. @2015 AACR.

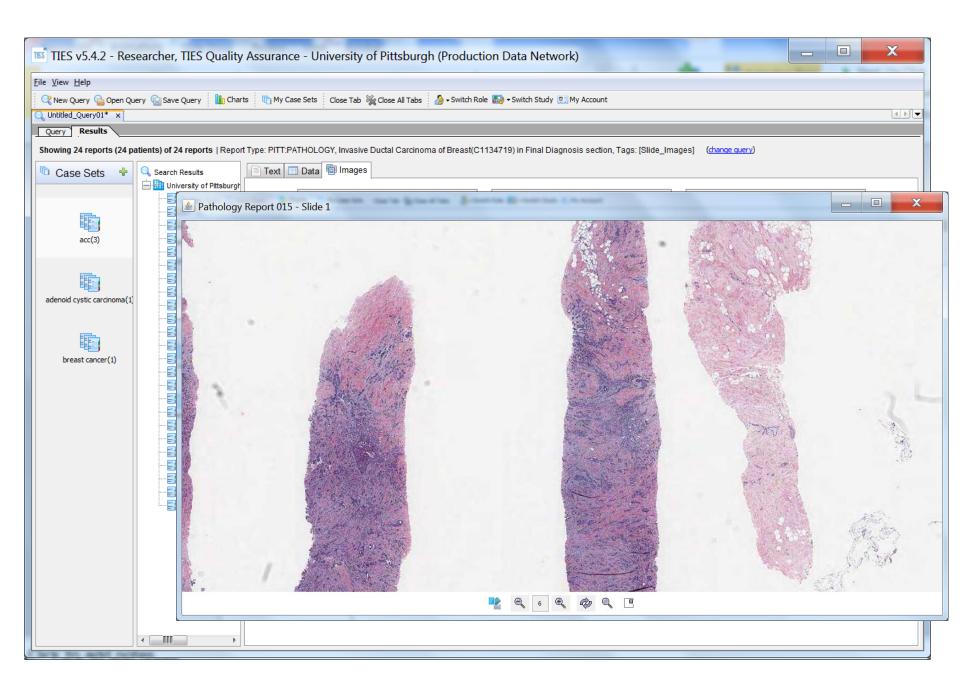
Cancer Research

> Doubled Study N using TCRN

UPMC: 46

Penn: 44





The Future of Cancer Phenotyping



- Deep phenotyping, high throughput phenotyping
- Representing and extracting phentotypes
- Combining text and structured data more effectively
- Sharing of unstructured data, phenotypes, images, even biospecimens across federated networks

- Large scale centralized genotype-phenotype knowledge bases
- Local integration with clinically derived data and data warehouses
- Rapid development and sharing of validated phenotypes across networks
- National data and biospecimen sharing networks

DeepPhe

deepphe.pgh

Harry Hochheiser

Girish Chavan

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Melissa Castine

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deepphe.boston

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Sean Finan

Pei Chen

Timothy Miller

Dmitriy Dligach

Chen Lin

David Harris

Funding

NCI U24 CA132672 Cancer Deep Phenotyping from Electronic Medical Records (Jacobson and Savova, MPIs)

TIES and the TIES Cancer Research Network

TIES Team

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Mayurapriyan Sakthivel

Amanda Rundell

GRU

Roni Bollag

Samir Khleif

Jennifer Carrick

Nita Maihle

And more.....

Funding

Penn

Michael Feldman

Nate DiGiorgio

Tara McSherry

Ioellen Weaver

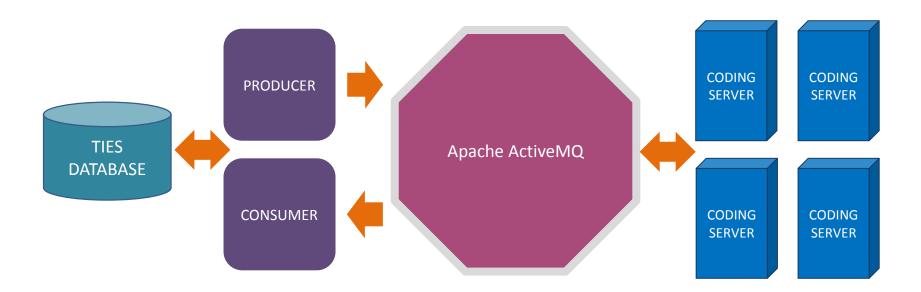
NCI U24 CA180921 Enhanced Development of TIES



Thank You

High throughput coding using Java Messaging Service(JMS)

- Each TIES coding service can be configured to run multiple processes internally to utilize multi-core CPUs effectively
- Additionally, TIES can use Java Messaging to utilize multiple servers for coding a large dataset. This reduces
 the load on the database server by using a JMS provider like ActiveMQ to act as intermediary



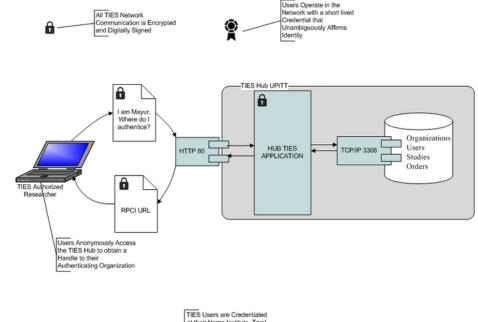
Multi-layered approach to data security

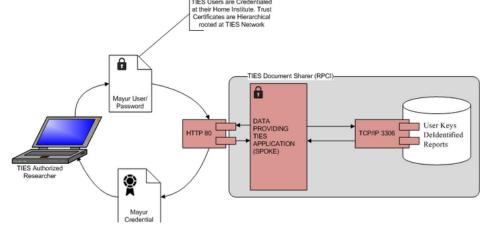
- TIES separates the PHI and de-identified data into separate databases that can be hosted on different servers for additional protection
- OGSA-DAI grid services encrypt all communication between the client and servers using RSA-1024 encryption
- Role based access control allows for data access granularity at three different levels
- Users can quarantine any reports containing PHI, which immediately hides that report from all users until an QA admin reviews it
- All queries and document views are logged by user and study. Auditing view lets you easily retrieve past activity for auditing purposes



Authentication and Authorization

- Authentication happens at user's institution
- Authorization happens at Hub server for the network
- After successful authentication, X.509 proxy certificates with a 12 hour validity are generated and used to communicate with any nodes in the network
- Services are further secured using gridmaps that only allow specific individuals to access them





Structured Data Support

