NLP

Outline

- **Value of the data in clinical text**
- Hyper-simplified linguistics
- Term spotting + handling negation, uncertainty
- ML to expand terms
- pre-NN ML to identify entities and relations
- language models
- Neural methods

Bulk of Valuable Data are in Narrative Text

orange=demographics
blue=patient condition, diseases, etc.
brown=procedures, tests
magenta=results of measurements
purple=time

Mr. Blind is a 79-year-old white white male with a history of diabetes mellitus, inferior myocardial infarction, who underwent open repair of his increased diverticulum November 13th at Sephsandpot Center.

The patient developed hematemesis November 15th and was intubated for respiratory distress. He was transferred to the Valtawnprinceel Community Memorial Hospital for endoscopy and esophagoscopy on the 16th of November which showed a 2 cm linear tear of the esophagus at 30 to 32 cm. The patient's hematocrit was stable and he was given no further intervention.

The patient attempted a gastrografin swallow on the 21st, but was unable to cooperate with probable aspiration. The patient also had been receiving generous intravenous hydration during the period for which he was NPO for his esophageal tear and intravenous Lasix for a question of pulmonary congestion.

On the morning of the 22nd the patient developed tachypnea with a chest X-ray showing a question of congestive heart failure. A medical consult was obtained at the Valtawnprinceel Community Memorial Hospital. The patient was given intravenous Lasix.

Selection of Rheumatoid Arthritis Cohort

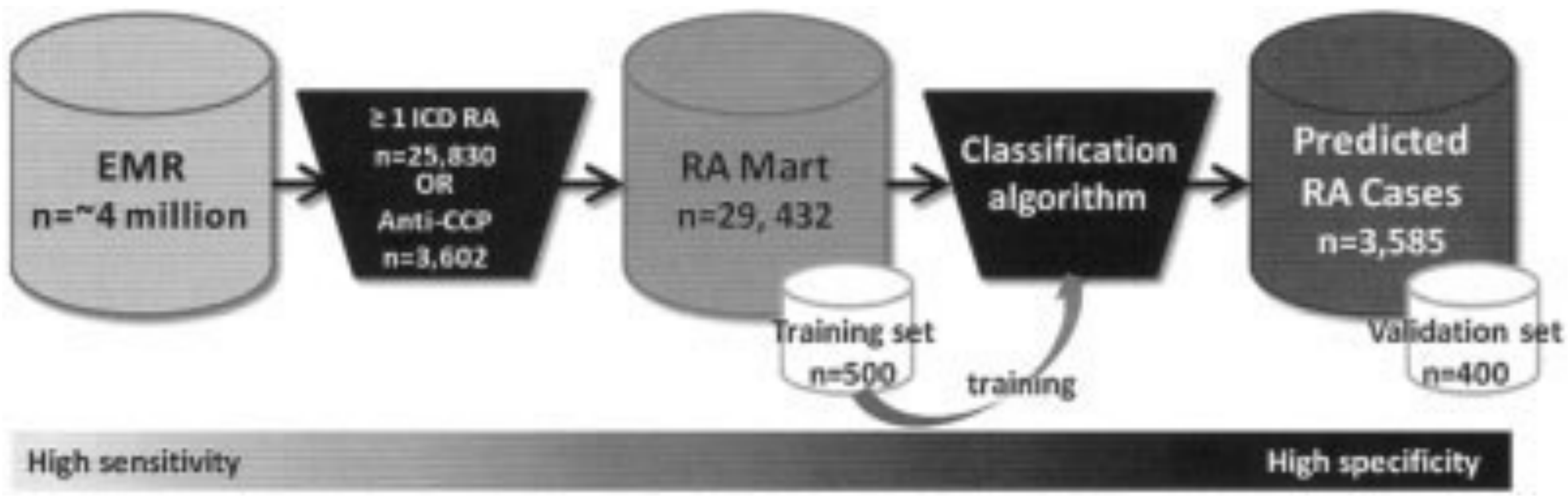
Table 4. Comparison of performance characteristics from validation of the complete classification algorithm (narrative and codified) with algorithms containing codified-only and narrative-only data*

Model	RA by algorithm or criteria, no.	PPV (95% CI), %	Sensitivity (95% CI), %	Difference in PPV (95% CI), %†
Algorithms				
Narrative and codified (complete)	3,585	94 (91–96)	63 (51–75)	Reference
Codified only	3,046	88 (84–92)	51 (42–60)	6 (2–9)‡
NLP only	3,341	89 (86–93)	56 (46–66)	5 (1–8)‡
Published administrative codified criteria				
≥3 ICD-9 RA codes	7,960	56 (47–64)	80 (72–88)	38 (29–47)‡
≥1 ICD-9 RA codes plus ≥1 DMARD	7,799	45 (37–53)	66 (57–76)	49 (40–57)‡

* The complete classification algorithm was also compared with criteria for RA used in published administrative database studies. RA = rheumatoid arthritis; PPV = positive predictive value; 95% CI = 95% confidence interval; NLP = natural language processing; ICD-9 = International Classification of Diseases, Ninth Revision; DMARD = disease-modifying antirheumatic drug.
† Difference in PPV = PPV of complete algorithm − comparison algorithm or criteria.
‡ Significant difference in PPV compared with the complete algorithm.

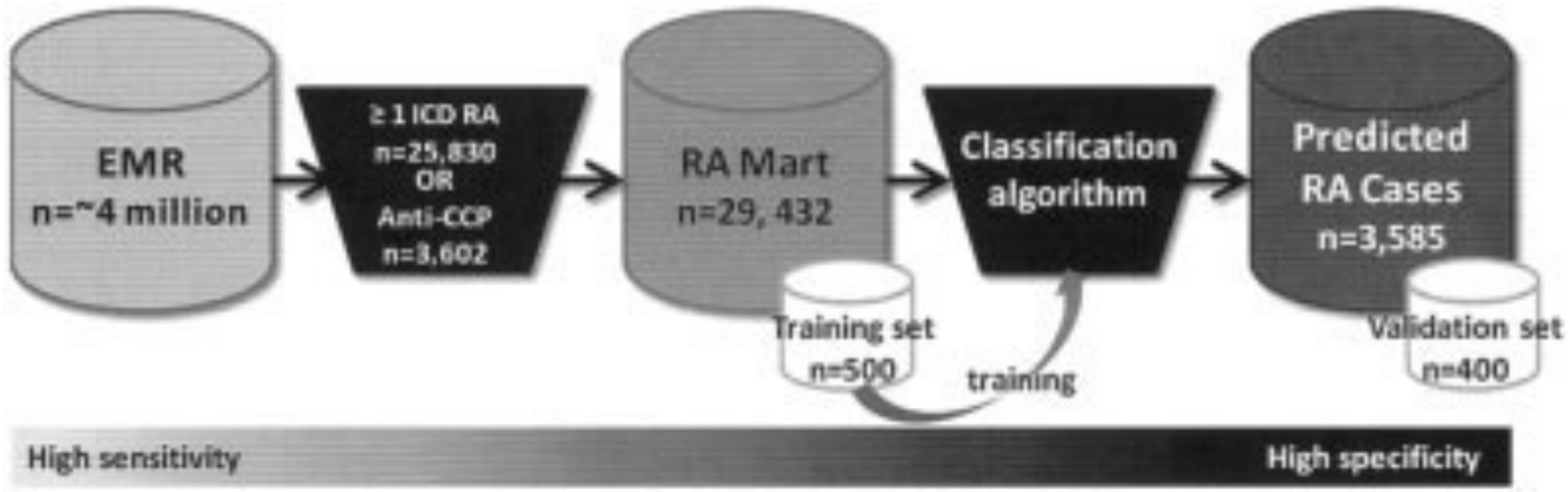
Liao, K. P., Cai, T., Gainer, V., Goryachev, S., Zeng-Treitler, Q., Raychaudhuri, S., Szolovits, P., Churchill, S., Murphy, S., Kohane, I., Karlson, E., Plenge, R. (2010). Electronic medical records for discovery research in rheumatoid arthritis. Arthritis Care & Research, 62(8), 1120–1127. http://doi.org/10.1002/acr.20184

Finding a Cohort of Rheumatoid Arthritis Cases



- Coded data:
  - ICD-9 codes, including RA and related diseases
    - ignore codes within 1 week of previous code
  - electronic prescriptions for
    - DMARDs: methotrexate, azathioprine, leflunomide, sulfasalazine, hydroxychloroquine, penicillamine, cyclosporine, and gold
    - Biologic agents: anti-TNF agents infliximab and etanercept, and abatacept, rituximab, anakinra, etc.
  - anti-cyclic citrullinated peptide (anti-CCP) & rheumatoid factor (RF) labs
  - total number of “facts” in the EMR

Finding a Cohort of Rheumatoid Arthritis Cases



- Narrative text data (processed by HITEx)
  - From health care provider notes, radiology reports, pathology reports, discharge summaries, and operative reports
  - Extracted disease diagnoses (RA, SLE, PsA, and JRA)
  - medications (same as from prescriptions, with the addition of adalimumab)
  - laboratory data (RF, anti-CCP, and the term “seropositive”)
  - radiology findings of erosions on radiographs
- Hand-made lists of equivalent terms
- Negation detection, including special terms, e.g., “RF-”

Zeng QT, Goryachev S, Weiss S, Sordo M, Murphy SN, Lazarus R. Extracting principal diagnosis, co-morbidity and smoking status for asthma research: evaluation of a natural language processing system. BMC Med Inform Decis Mak 2006;6:30.

Table 3. Variables selected for the complete algorithm (narrative and codified EMR data) from the logistic regression in order of predictive value*

Variable	Standardized regression coefficient	Standard error
Positive predictors		
NLP RA	1.11	0.48
NLP seropositive	0.74	0.26
ICD-9 RA normalized†	0.71	0.23
ICD-9 RA	0.66	0.44
NLP erosions	0.46	0.29
Codified RF negative	0.36	0.36
NLP methotrexate	0.3	0.34
Codified anti-TNF‡	0.29	0.3
NLP anti-CCP positive	0.27	0.25
NLP anti-TNF§	0.2	0.36
NLP other DMARDs	0.13	0.34
Negative predictors		
ICD-9 JRA	−0.98	0.9
ICD-9 SLE	−0.57	1.09
NLP PsA	−0.51	0.74

* EMR = electronic medical record; NLP = natural language processing; RA = rheumatoid arthritis; ICD-9 = International Classification of Diseases, Ninth Revision; RF = rheumatoid factor; anti-TNF = anti–tumor necrosis factor; anti-CCP = anti–cyclic citrullinated peptide; DMARDs = disease-modifying antirheumatic drugs; JRA = juvenile rheumatoid arthritis; SLE = systemic lupus erythematosus; PsA = psoriatic arthritis.

† ICD-9 RA normalized = ln (no. of ICD-9 RA codes per subject ≥1 week apart).

‡ Codified anti-TNF = etanercept and infliximab (adalimumab was not available in our EMR).

§ NLP anti-TNF = adalimumab, etanercept, and infliximab.

Algorithm for RA was Portable (!)

- Study replicated at Vanderbilt and Northwestern

	Partners	Northwestern	Vanderbilt
EHR	Local	Epic (inpatient) Cerner (outpatient)	Local
# Patients	4M	2.2M	1.7M
Meds	Structured meds entries (in- and outpatient) and text queries	Structured outpatient meds entries and in- and outpatient text queries	NLP (MedEx) for outpatient medications and structured inpatient records
NLP Queries	Custom RegEx	Custom RegEx from Partners	Generic UMLS concepts, derived from KnowledgeMap web interface

Carroll, R. J., Thompson, W. K., Eyler, A. E., Mandelin, A. M., Cai, T., Zink, R. M., et al. (2012). Portability of an algorithm to identify rheumatoid arthritis in electronic health records. Journal of the American Medical Informatics Association, 19(e1), e162–9. http://doi.org/10.1136/amiajnl-2011-000583

Table 3 Model performance

Algorithm	Testing set											
	Partners			Northwestern			Vanderbilt			Average		
	PPV	Sensitivity	AUC	PPV	Sensitivity	AUC	PPV	Sensitivity	AUC	PPV	Sensitivity	AUC
Published algorithm	88%*	79%*	97%*	87%	60%	92%	95%	57%	95%	90%	65%	95%
Retrained with												
Northwestern	79%	47%	89%	87%	73%	92%	93%	43%	89%	86%	54%	90%
Vanderbilt	85%	74%	97%	82%	40%	88%	97%	81%	97%	88%	65%	94%
Combined	86%	71%	97%	86%	65%	91%	97%	82%	96%	90%	72%	95%
ICD-9 only†												
≥1 RA code	22%	97%	N/A	26%	100%	N/A	49%	100%	N/A	33%	99%	N/A
≥3 RA code	55%	81%	N/A	42%	87%	N/A	73%	98%	N/A	57%	89%	N/A
97% Specificity	80%	49%	88%	80%	36%	84%	93%	43%	93%	84%	43%	88%
Code count for 97% specificity	53			29			48			43.3		

The PPV and sensitivity values reported represent model performance with a specificity set at 97% for logistic regression models.
*These results are from a fivefold cross-validation on the Partners training set. The PPV and sensitivity as published in Liao *et al* was calculated from a separate Partners validation set (PPV 94%, sensitivity 63%).
†ICD-9 cut-off used the count of 714.* codes, excluding codes for juvenile RA (714.3*).
AUC, area under the receiver operating characteristic curve; ICD-9, International Classification of Diseases, version 9 CM; PPV, positive predictive value; RA, rheumatoid arthritis.

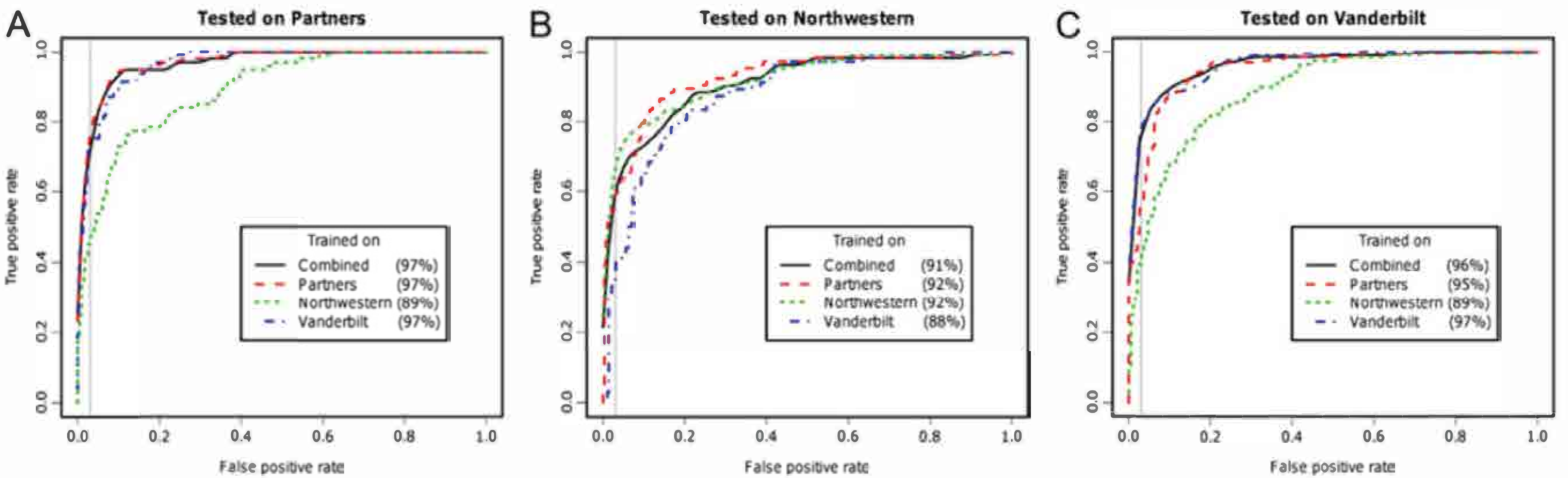


Figure 3 Receiver operating characteristic curves for each test set. The vertical line represents the 97% specificity cut-off used in this study. The test performance at Partners, Northwestern, and Vanderbilt are found in (a), (b), and (c), respectively.

Telegraphic Language

3/11/98 IPN	(date of) Intern Progress Note,
SOB & DOE ↓	the patient's shortness of breath and dyspnea on exertion are decreased,
VSS, AF	the patient's vital signs are stable and the patient is afebrile,
CXR ⊕ LLL ASD no Δ	a recent new chest xray shows a left lower lobe air space density that is unchanged from the previous radiograph,
WBC 11K	a recent new white blood cell count is 11,000 cells per cubic milliliter,
S/B Cx ⊕ GPC c/w PC, no GNR	the patient's sputum and blood cultures are positive for gram positive cocci consistent with pneumococcus, no gram negative rods have grown,
D/C Cef →PCN IV	so the plan is to discontinue the cefazolin and then begin penicillin treatment intravenously.

Typical Goals of MNLP

- for any word or phrase, assign it a meaning (or null) from some taxonomy/ontology/terminology;
  - e.g., “rheumatoid arthritis” ==> 714.0 (ICD9)
- for any word or phrase, determine whether it represents protected health information;
  - e.g., “Mr. Huntington suffers from Huntington’s Disease”
- determine aspects of each entity: time, location, certainty, ...
- having identified two meaningful phrases in a sentence, determine the relationship (or null) between them;
  - e.g., precedes, causes, treats, prevents, indicates, ...
  - note: we also need a taxonomy of relationships
- in a larger document, identify the sentences or fragments most relevant to answering a specific medical question;
  - e.g., where is the patient’s exercise regimen discussed?
- summarization
  - as data sets balloon in size, how to provide a meaningful overview

Two Types of Tasks

- Every word counts
  - De-identification
  - Extraction of all
    - entities
    - time
    - certainty
    - causation and association

- Aggregate judgment
  - E.g., “smoking” challenge
    - Most text may be irrelevant to specific result
  - Cohort selection—does a patient satisfy some set of inclusion and exclusion criteria
    - Often definite presence of a disease, complication, …

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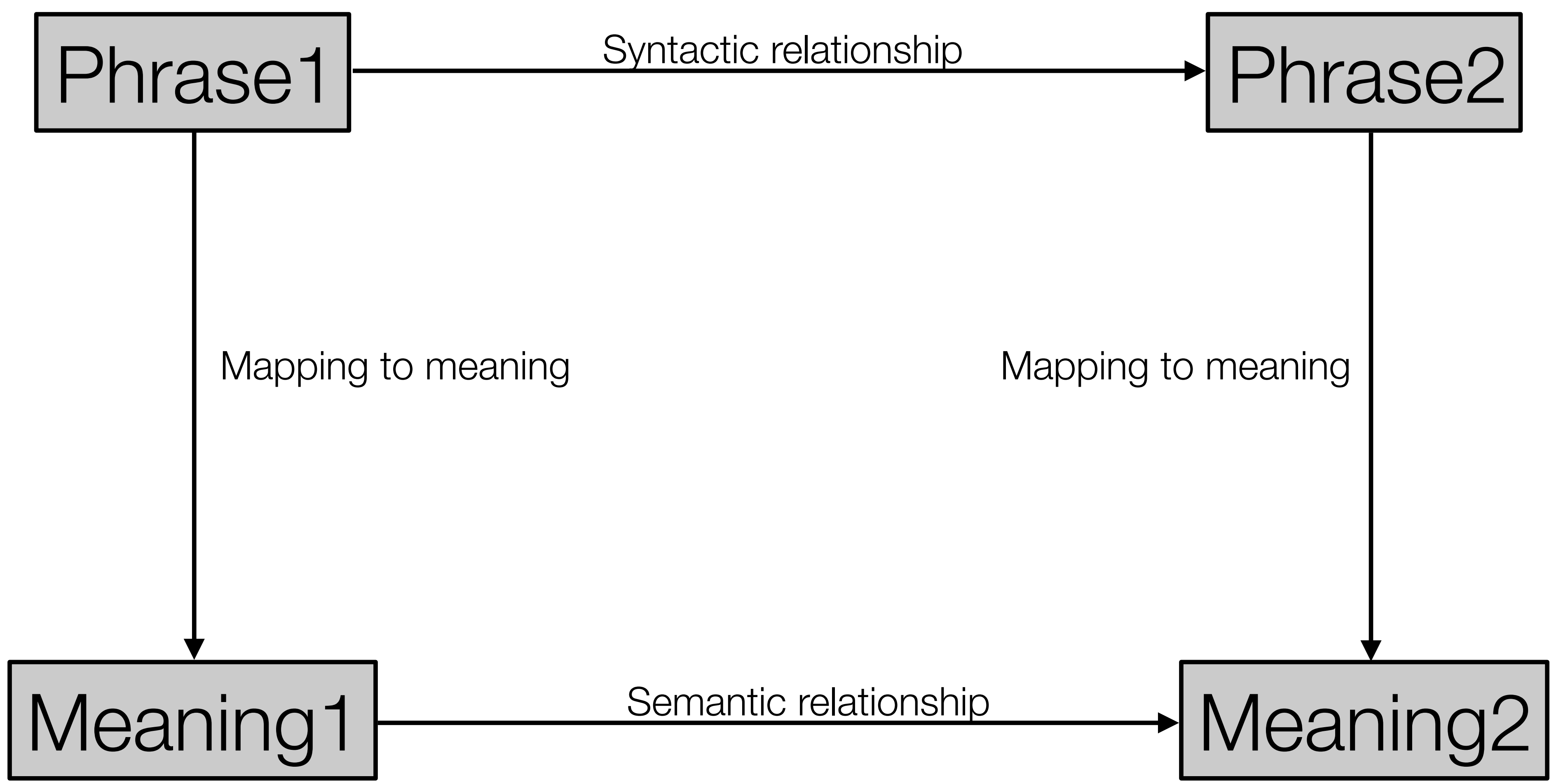
Historical Thought ...

- Frederick B. Thompson, "English for the Computer." *Proceedings of the Fall Joint Computer Conference* (1966) pp. 349-356
- Grammar defined by context-sensitive production rules + transformations
- Semantics defined by mappings:
  - Each grammar rule matches a semantic function
  - Terminal symbols are *referents* or *functions*
  - An environment is (in modern terms) a semantic network of complex interrelationships
  - Meaning is compositional, in terms of the semantic functions
- *Minor* 😆 remaining question: how to represent the "real world"?

Fred Thompson, ~1973

Proposed relationship between syntax and semantics



Formal language semantics

- SRI's DIAMOND/DIAGRAM system (~1980)
- each passage is expressed as a proposition or a conjunction of propositions:
  - a particular procedure for the prevention of hepatitis B could have associated with it the proposition "immunize(GAMMA-GLOBULIN,HEPATITIS-B)"
  - a passage concerned with the etiology of the disease could have the proposition "transmit(TRANSFUSION,HEPATITIS-B)"
  - synonym and hyponym relations
  - … *a language of primitives for the domain*
- French Remède system
  - "medical documentary language using current medical terms and few syntactic rules"
  - taught to doctors to write notes
  - *… not popular*

Walker, D. E., Hobbs, J. R., 1981. Natural Language Access to Medical Text*. (pp. 269–273). Presented at the Proc Annu Symp Comput Appl Med Care.

de Heaulme M, Tainturier C, Thomas D. [Computer treatment of medical reports: example of the "Remède" system (author's transl)]. Nouv Presse Med. 1979 Oct 22;8(40):3223-6. French. PubMed PMID: 534182

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Term Spotting

- Traditionally, lists of coded items, narrative terms and patterns hand-crafted by researcher
- Negation and uncertainty handled by somewhat ad-hoc methods
    - NegEx is widely used, $\exists$ many more sophisticated variants
- Generalize terms
    - Manually or automatically identify high-certainty “anchors”
    - Learn related terms to augment the set of terms
        - From knowledge bases such as UMLS
        - From co-occurrence in EMR data
        - From co-occurrence in publications

Negation

- “Identifying pertinent negatives, then, involves identifying a proposition ascribing a clinical condition to a person and determining whether the proposition is denied or negated in the text.”
- Simpler than general problem of negation in NLP because negation applies mostly to noun phrases indicating diseases, tests, drugs, findings, …
- NegEx
  - Find all UMLS terms in each sentence of a discharge summary
    - “The patient denied experiencing chest pain on exertion” ⇒

      “The patient denied experiencing S1459038 on exertion”
  - Find patterns
    - <negation phrase> *{0,5} <UMLS term>
      - no signs of", "ruled out unlikely", "absence of", "not demonstrated", "denies", "no sign of", "no evidence of", "no", "denied", "without", "negative for", "not", "doubt", versus"
    - <UMLS term> *{0,5} <negation phrase>
      - “declined”, “unlikely”
  - Pseudo-negation: "gram negative", "no further", "not able to be", "not certain if", "not certain whether", not necessarily", "not rule out", "without any further", "without difficulty", "without further”

Chapman WW, Bridewell W, Hanbury P, Cooper GF, Buchanan BG. A simple algorithm for identifying negated findings and diseases in discharge summaries. J Biomed Inform. 2001 Oct;34(5):301-10.

NegEx results

- Baseline:
  - <negation phrase> * <UMLS term>
    - "no", "denies", "not", "without", "*n't", "ruled out", "denied"

	Baseline			NegEx		
	Group 1 sentences (i.e. containing NegEx negation phrases)	Group 2 sentences (i.e., not containing NegEx negation phrases)	All sentences	Group 1 sentences (i.e. containing NegEx negation phrases)	Group 2 sentences (i.e., not containing NegEx negation phrases)	All sentences
n	500	500	1000	500	500	1000
Sensitivity	88.27	0.00	**88.27**	82.31	0.00	77.84
Specificity	52.69	100.00	85.27	82.50	100.00	**94.51**
PPV	68.42	—	68.42	84.49	—	**84.49**
NPV	79.46	96.99	**93.01**	80.21	96.99	91.73

- Extremely simplistic schemes (kind of) work

Generalize Terms

- Use synonymous terms as well as the starting ones
- Take advantage of others related terms
  - hypo- or hypernyms
  - other associated terms
    - e.g., common symptoms or treatments of a disease
- Recursive ML problem: learn how best to identify cases associated with a term
  - “phenotyping”

Available Classification Thesauri Most Available through UMLS

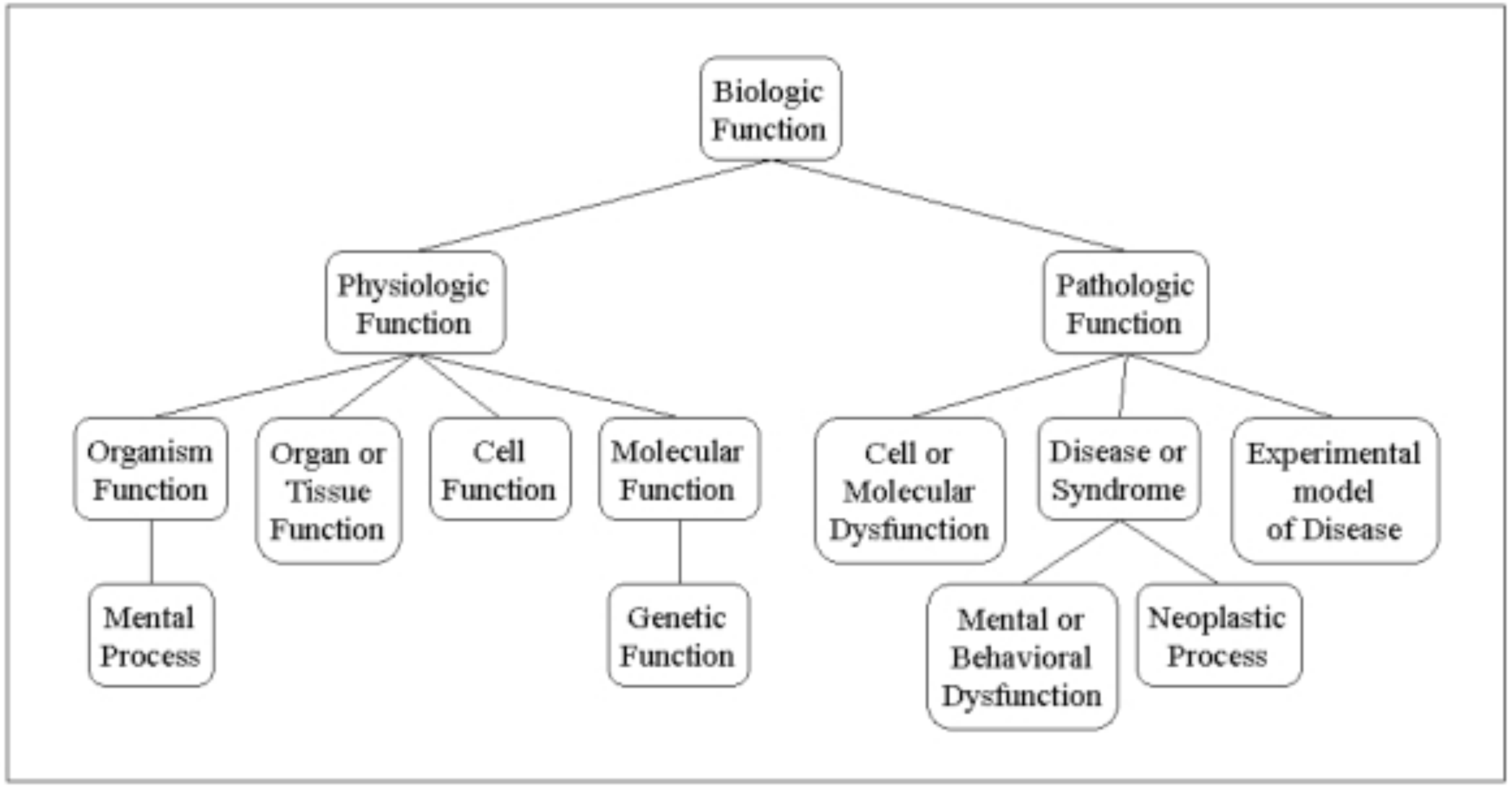
- Unified Medical Language Systems project of NLM; since ~1985
- *Metathesaurus* now (2018ab version) includes 161 source vocabularies
  - MeSH, SNOMED, ICD-9, ICD-10, LOINC, RxNORM, CPT, GO, DXPLAIN, OMIM, ...
- Synonym mappings across vocabularies;
  - e.g., “heart attack” = “acute myocardial infarct” = “myocardial infarction” ...
  - 3,773,462 distinct concepts, represented by concept unique identifier (CUI)
- Jumbled compendium of every hierarchy drawn from every source
- *Semantic Network*
  - Hierarchy of
    - 54 relations
    - 127 types
  - Every CUI assigned ≥1 semantic type

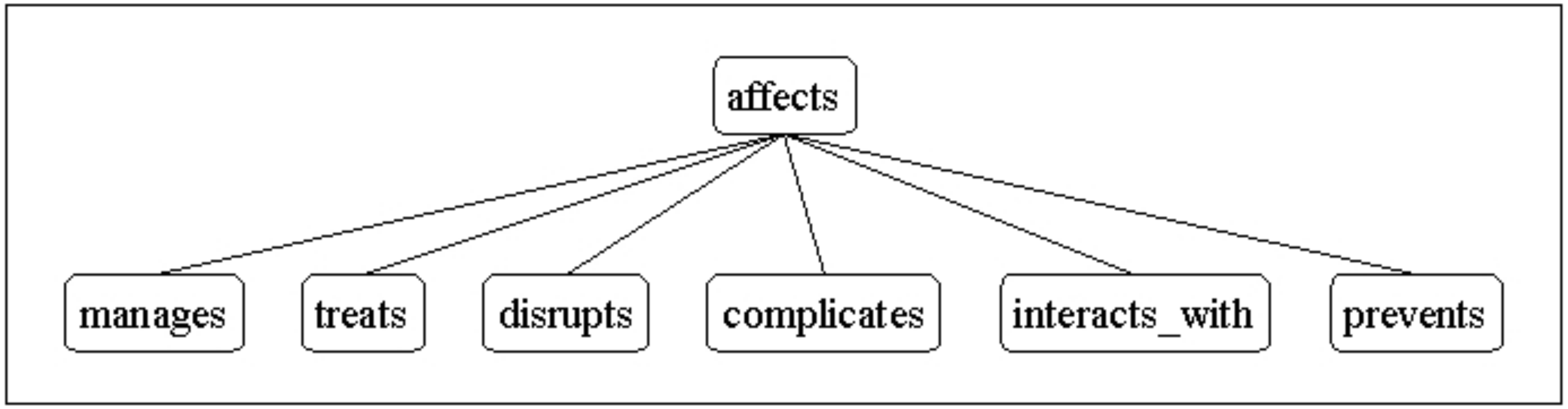
Wealth of UMLS Concepts of Various Types

```
mysql> select tui,sty,count(*) c from mrsty group by sty
order by c desc;
+------+-------------------------------------------+--------+
| tui  | sty                                       | c      |
+------+-------------------------------------------+--------+
| T061 | Therapeutic or Preventive Procedure       | 260914 |
| T033 | Finding                                   | 233579 |
| T200 | Clinical Drug                             | 172069 |
| T109 | Organic Chemical                          | 157901 |
| T121 | Pharmacologic Substance                   | 124844 |
| T116 | Amino Acid, Peptide, or Protein           | 117508 |
| T009 | Invertebrate                              | 111044 |
| T007 | Bacterium                                 | 110065 |
| T002 | Plant                                     |  95017 |
| T047 | Disease or Syndrome                       |  79370 |
| T023 | Body Part, Organ, or Organ Component      |  73402 |
| T201 | Clinical Attribute                        |  60998 |
| T123 | Biologically Active Substance             |  55741 |
| T074 | Medical Device                            |  51708 |
| T028 | Gene or Genome                            |  49960 |
| T004 | Fungus                                    |  47291 |
| T060 | Diagnostic Procedure                      |  46106 |
| T037 | Injury or Poisoning                       |  43924 |
| T191 | Neoplastic Process                        |  33539 |
| T044 | Molecular Function                        |  31369 |
| T126 | Enzyme                                    |  25766 |
| T129 | Immunologic Factor                        |  25025 |
| T059 | Laboratory Procedure                      |  24511 |
| T058 | Health Care Activity                      |  19552 |
| T029 | Body Location or Region                   |  16470 |
| T013 | Fish                                      |  16059 |
| T046 | Pathologic Function                       |  13562 |
| T184 | Sign or Symptom                           |  13299 |
| T130 | Indicator, Reagent, or Diagnostic Aid     |  12809 |
| T170 | Intellectual Product                      |  12544 |
| T118 | Carbohydrate                              |  10722 |
| T110 | Steroid                                   |  10363 |
| T012 | Bird                                      |   9908 |
| T043 | Cell Function                             |   9758 |
...
```

```
select c.cui,c.str from mrconso c join mrsty s on c.cui=s.cui
where c.TS='P' and c.STT='PF' and c.ISPREF='Y' and
c.LAT='ENG' and s.tui='T047';
+----------+------------------------------------------+
| cui      | str                                      |
+----------+------------------------------------------+
| C0000744 | Abetalipoproteinemia                     |
| C0000774 | Gastrin secretion abnormality NOS        |
| C0000786 | Spontaneous abortion                     |
| C0000809 | Abortion, Habitual                       |
| C0000814 | Missed abortion                          |
| C0000821 | Threatened abortion                      |
| C0000822 | Abortion, Tubal                          |
| C0000823 | Abortion, Veterinary                     |
| C0000832 | Abruptio Placentae                       |
| C0000880 | Acanthamoeba Keratitis                   |
| C0000889 | Acanthosis Nigricans                     |
| C0001080 | Achondroplasia                           |
| C0001083 | Achromia parasitica                      |
| C0001125 | Acidosis, Lactic                         |
| C0001126 | Renal tubular acidosis                   |
| C0001127 | Acidosis, Respiratory                    |
| C0001139 | Acinetobacter Infections                 |
| C0001142 | Acladiosis                               |
| C0001144 | Acne Vulgaris                            |
| C0001145 | Acne Keloid                              |
| C0001163 | Vestibulocochlear Nerve Diseases         |
| C0001168 | Complete obstruction                     |
| C0001169 | Acquired coagulation factor deficiency NOS |
| C0001175 | Acquired Immunodeficiency Syndrome       |
| C0001197 | Acrodermatitis                           |
| C0001202 | Acrokeratosis                            |
| C0001206 | Acromegaly                               |
| C0001207 | Hypersomatotropic gigantism              |
| C0001231 | ACTH Syndrome, Ectopic                   |
| C0001247 | Actinobacillosis                         |
...
```

Hierarchy of UMLS Semantic Network Types and Relations





from http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=nlmumls&part=ch05

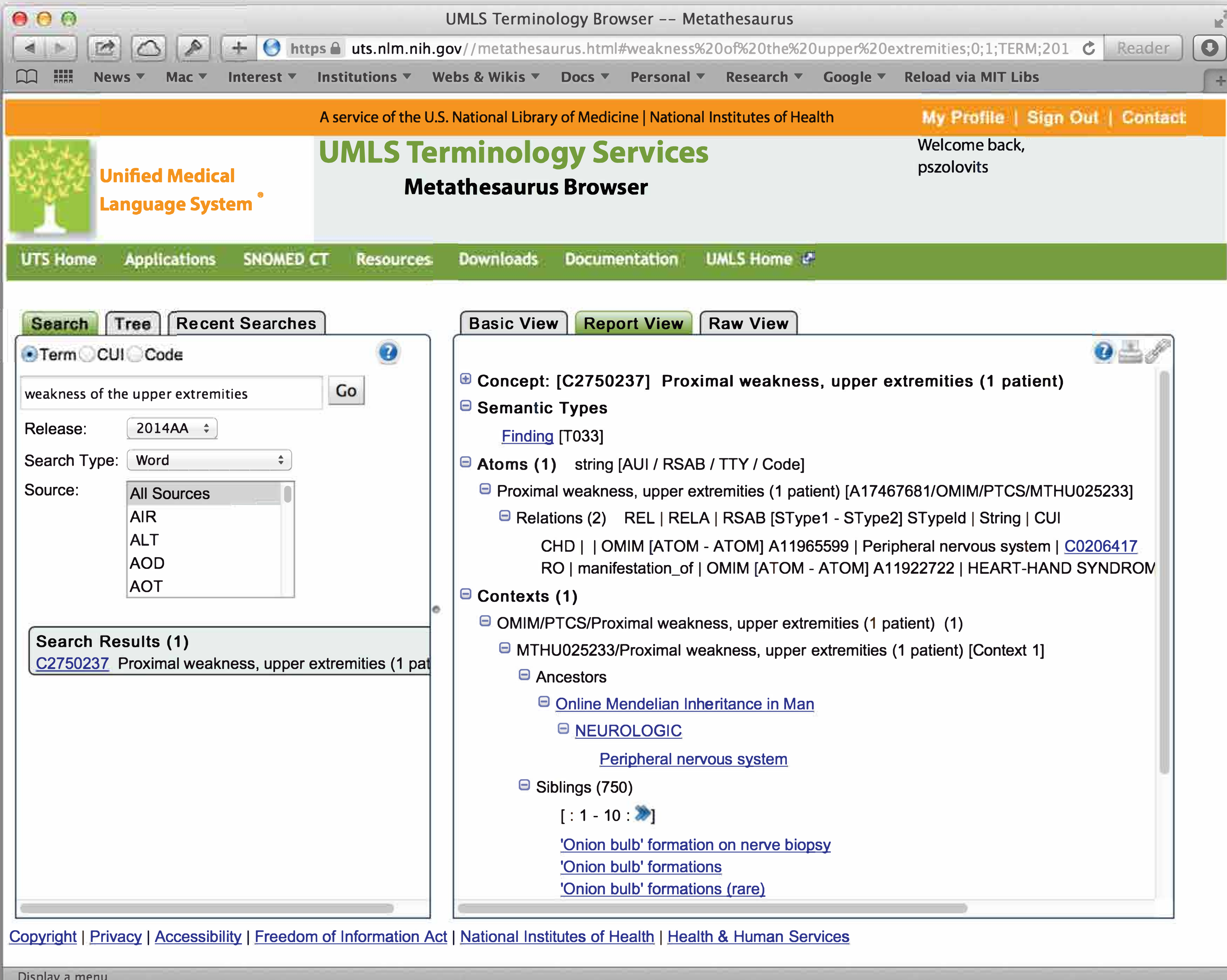
Lexical Variant Generation (LVG) Tools

(from National Library of Medicine)

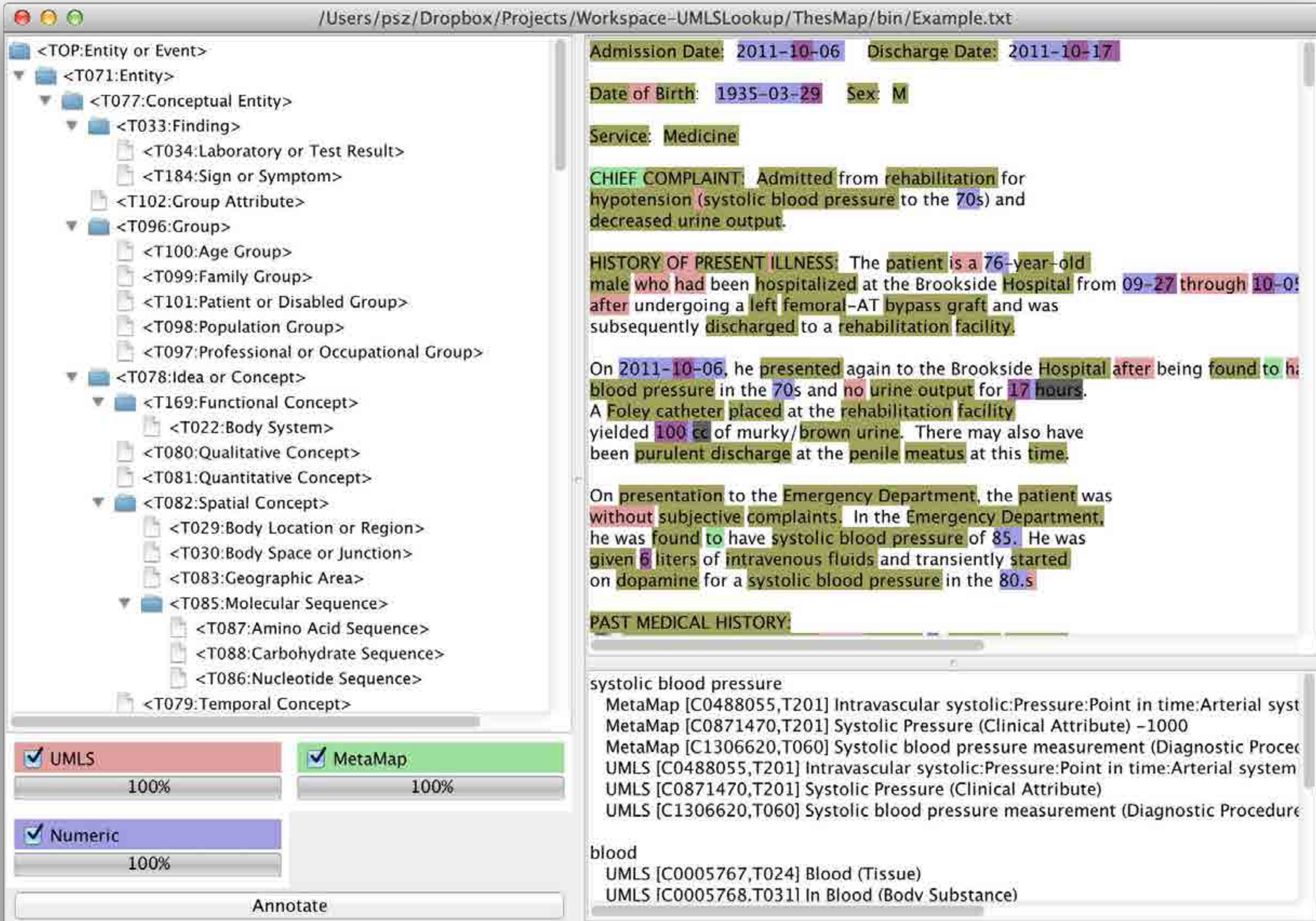
- Normalized words and phrases used as index to UMLS
- Lemmatization of words
  - stripping typical prefixes, suffixes
    - plurals, in-word negation, gerunds
- Discarding “noise” words, punctuation
- Lower-casing
- Alphabetic order of all remaining words

```
Mr. Huntington was admitted to Huntington Memorial Hospital for acute chest pain in March.
Mr. Huntington was admitted to Huntington Memorial Hospital for acute chest pain in March.|acute admit be chest hospital huntington huntington march memorial mr pain
Mr. Huntington was admitted to Huntington Memorial Hospital for acute chest pain in March.|acute admit chest hospital huntington huntington march memorial mr pain was
Mr. Huntington was admitted to Huntington Memorial Hospital for acute chest pain in March.|acute admitted be chest hospital huntington huntington march memorial mr pain
Mr. Huntington was admitted to Huntington Memorial Hospital for acute chest pain in March.|acute admitted chest hospital huntington huntington march memorial mr pain was

Weakness of the upper extremities
Weakness of the upper extremities|extremity upper weakness
```



Courtesy of National Library of Medicine. Image is in the public domain.


/Users/psz/Dropbox/Projects/Workspace-UMLSLookup/ThesMap/bin/Example.txt
<TOP:Entity or Event>
<T071:Entity>
<T077:Conceptual Entity>
<T033:Finding>
<T034:Laboratory or Test Result>
<T184:Sign or Symptom>
<T102:Group Attribute>
<T096:Group>
<T100:Age Group>
<T099:Family Group>
<T101:Patient or Disabled Group>
<T098:Population Group>
<T097:Professional or Occupational Group>
<T078:Idea or Concept>
<T169:Functional Concept>
<T022:Body System>
<T080:Qualitative Concept>
<T081:Quantitative Concept>
<T082:Spatial Concept>
<T029:Body Location or Region>
<T030:Body Space or Junction>
<T083:Geographic Area>
<T085:Molecular Sequence>
<T087:Amino Acid Sequence>
<T088:Carbohydrate Sequence>
<T086:Nucleotide Sequence>
<T079:Temporal Concept>
UMLS
100%
MetaMap
100%
Numeric
100%
Annotate
Admission Date: 2011-10-06 Discharge Date: 2011-10-17
Date of Birth: 1935-03-29 Sex: M
Service: Medicine
CHIEF COMPLAINT: Admitted from rehabilitation for
hypotension (systolic blood pressure to the 70s) and
decreased urine output.
HISTORY OF PRESENT ILLNESS: The patient is a 76-year-old
male who had been hospitalized at the Brookside Hospital from 09-27 through 10-0
after undergoing a left femoral-AT bypass graft and was
subsequently discharged to a rehabilitation facility.
On 2011-10-06, he presented again to the Brookside Hospital after being found to h
blood pressure in the 70s and no urine output for 17 hours.
A Foley catheter placed at the rehabilitation facility
yielded 100 cc of murky/brown urine. There may also have
been purulent discharge at the penile meatus at this time.
On presentation to the Emergency Department, the patient was
without subjective complaints. In the Emergency Department,
he was found to have systolic blood pressure of 85. He was
given 6 liters of intravenous fluids and transiently started
on dopamine for a systolic blood pressure in the 80.s
PAST MEDICAL HISTORY:
systolic blood pressure
MetaMap [C0488055,T201] Intravascular systolic:Pressure:Point in time:Arterial syst
MetaMap [C0871470,T201] Systolic Pressure (Clinical Attribute) -1000
MetaMap [C1306620,T060] Systolic blood pressure measurement (Diagnostic Proce
UMLS [C0488055,T201] Intravascular systolic:Pressure:Point in time:Arterial system
UMLS [C0871470,T201] Systolic Pressure (Clinical Attribute)
UMLS [C1306620,T060] Systolic blood pressure measurement (Diagnostic Procedure
blood
UMLS [C0005767,T024] Blood (Tissue)
UMLS [C0005768,T031] In Blood (Body Substance)