

APPLYING ONTOLOGY AND SEMANTIC WEB TECHNOLOGIES TO CLINICAL AND TRANSLATIONAL STUDIES

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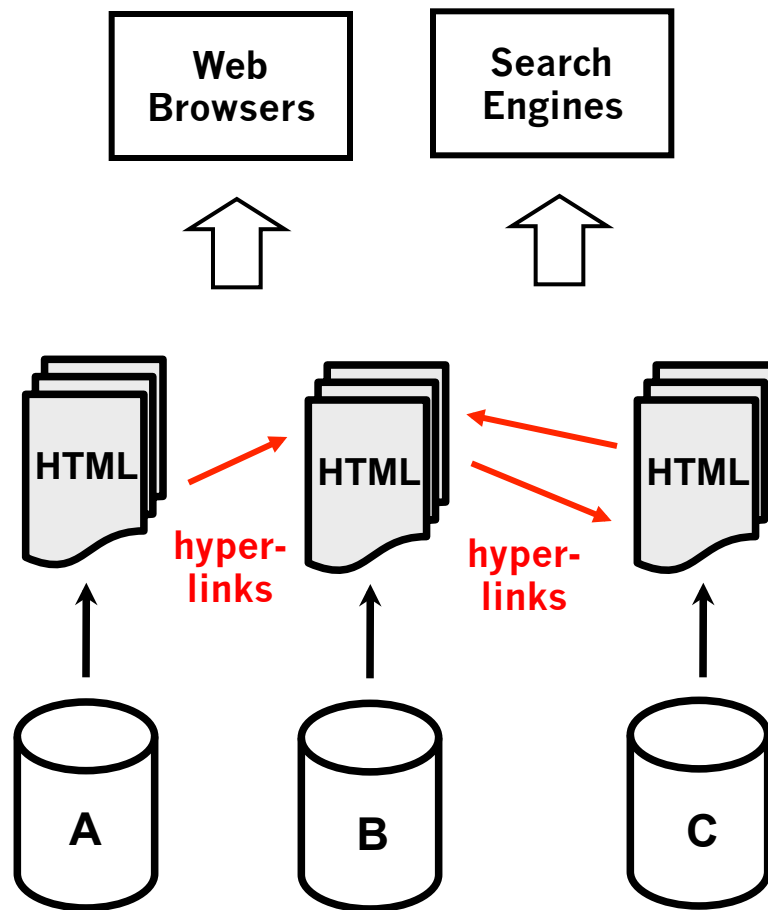
Ontology & Semantic Web

History of the Semantic Web

- Web was “invented” by [Tim Berners-Lee](#) (amongst others)
- TBL’s original vision of the Web was much more ambitious than the reality of the existing (syntactic) Web:
 - “... a goal of the Web was that, if the interaction between person and hypertext could be so intuitive that the **machine-readable** information space gave an accurate representation of the state of people's thoughts, interactions, and work patterns, then **machine analysis** could become a very powerful management tool, seeing patterns in our work and facilitating our working together through the typical problems which beset the management of large organizations.”
- TBL (and others) have since been working towards realising this vision, which has become known as the **Semantic Web**
 - E.g., article in May 2001 issue of Scientific American...



The Syntactic Web (Web of Documents)



Source Chris Bizer

- **Single information space**
- **Built on URIs**
 - globally unique IDs
 - retrieval mechanism
- **Built on Hyperlinks**
 - are the glue that holds everything together

Search by Search Engines

Find the protein
and the amino-acids
information for gene "cdk-4"

Google Search [Advanced Search](#) [Preferences](#)
[Google SafeSearch is ON](#) Personalized based on your web history. [More detail](#)

Web Results 1 - 10 of about **685,000** for **cdk-4** with **Safesearch on**. (0.08 seconds)

Did you mean: [cdk4](#)

Sponsored Links

[Recombinant Human Kinase](#)
Rapid delivery of bulk amounts!
Off the shelf or custom tailored
[www.proqinase.com](#)

[Cd Key 4](#)
Price Compare Cd Key 4.
You want it, we got it!
[BizRate.com](#)

OMIM - CYCLIN-DEPENDENT KINASE 4;
[CDK4](#)
MIM *123829 · Description · Cloning · Gene Structure · Mapping · Gene Function · Molecular Genetics · Animal Model · Allelic Variants ...
[www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=123829 - 2k - Cached - Similar pages](#) -

Gene Result
1: **CDK4** Official Symbol **CDK4** and Name: cyclin-dependent kinase 4 [Homo sapiens] Other Aliases: CMM3, MGC14458, PSK-J3 Other Designations: cell division ...
[www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=gene&list_uids=1019 - Similar pages](#) -
More results from [www.ncbi.nlm.nih.gov](#) »

Cyclin-dependent kinase 4 - Wikipedia, the free encyclopedia
Jul 8, 2008 ... "Direct binding of cyclin D to the retinoblastoma gene product (pRb) and pRb phosphorylation by the cyclin D-dependent kinase **CDK4**". ...
[en.wikipedia.org/wiki/Cyclin-dependent_kinase_4 - 61k - Cached - Similar pages](#) -

CDK4 Gene | CDK4 Protein | CDK4 Antibody - GeneCards
CDK4 Gene in genomic location: bands according to Ensembl, locations according to ... Millipore Mono- and Polyclonal Antibodies for the study of **CDK4** ...
[www.genecards.org/cgi-bin/carddisp.pl?gene=Cdk4 - Similar pages](#) -

CDK4: Home page - 6:18pm
Supporting material for readers and instructors using Distributed Systems: Concepts and Design, Edition 4 by George Coulouris, Jean Dollimore and Tim ...
[www.cdk4.net/ - 11k - Cached - Similar pages](#) -

CDK4 - cyclin-dependent kinase 4 - 6:15pm
Regulation of cyclin D1/ **Cdk4** complexes by calcium/calmodulin-dependent protein Cyclin-dependent kinase 4 (**CDK4**)/cyclin D has a key role in regulating ...
[www.ihop-net.org/UniPub/IHOP/gs/87097.html - 380k - Cached - Similar pages](#) -

The Answer is Here

Home	Genome	Blast / Blat	WormMart	Batch Sequences	Markers	Genetic Maps	Submit	Searches	Site Map
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Find:

WormBase

The Biology and
Genome of
C. elegans.

Gene Summary	Locus Summary	Sequence Summary	Protein Summary	EST Alignments	Genome Browser	Genetic Map	Nearby Genes	Bibliography	Tree Display	XML	Schema	Acedb Image
------------------------------	-------------------------------	----------------------------------	---------------------------------	--------------------------------	--------------------------------	-----------------------------	------------------------------	------------------------------	------------------------------	---------------------	------------------------	-----------------------------

Gene Summary for cdk-4

Specify a gene using a gene name ([unc-26](#)), a predicted gene id ([R13A5.9](#)), or a protein ID ([CE02711](#))

[\[identification\]](#) [\[location\]](#) [\[function\]](#) [\[expression\]](#) [\[gene ontology\]](#) [\[alleles\]](#) [\[similarities\]](#) [\[reagents\]](#) [\[bibliography\]](#)

Identification	IDs:	Main name	Sequence name	Other name(s)	WB Gene ID	
		cdk-4 - (Cyclin-Dependent Kinase family) via person evidence: Michael Krause	F18H3.5	NM_077855 (inferred automatically) NM_001029420 (inferred automatically) XO136 (inferred automatically)	WBGene00000406	
	Concise Description:	cdk-4 encodes two isoforms of a cyclin-dependent serine/threonine protein kinase orthologous to human CDK4 and CDK6 (OMIM:123829 and OMIM:603368 , mutated in cutaneous malignant melanoma) which complex with D-type cyclins to regulate progression through the G1 phase of the cell cycle; CDK-4 activity is essential for G1 progression in postembryonic blast cells and as a result, cdk-4 mutant animals generally arrest during larval stages; the lethality generated by cdk mutations, also seen in <i>Drosophila</i> , can be suppressed by mutations in lin-35/Rb suggesting that, as in other organisms, LIN-35/Rb may be a major target of CDK-4 and hypodermal lineages during mid-to-late embryogenesis, with postembryonic expression detected in hypodermis and cells of the somatic gonad, the vulva, and the intestine. [details]				
	NCBI KOGs*:	Protein kinase PCTAIRE and related kinases [KOG0594]				
	Species:	<i>Caenorhabditis elegans</i>				
		<input type="checkbox"/> Other sequences				
	NCBI:	[AceView: XO136]				
	Gene model(s):	Gene Model	Status	Nucleotides (coding/transcript)	Protein	Amino Acids
		F18H3.5a ^{1,2}	confirmed by cDNA(s)	1029/2854 bp	WP:CE18608	342 aa
		F18H3.5b ^{1,2,3}	partially confirmed by cDNA(s)	1221/1704 bp	WP:CE28918	406 aa
		<input type="checkbox"/> Footnotes				
		<input type="checkbox"/> Other Notes				
		<input type="checkbox"/> History				
Location	Genetic Position:	X:12.69 - (+) 0.007 cM [mapping data]				

Find the protein and the amino-acids information for gene "cdk-4"

What is the Problem?

Consider a typical web page:

The screenshot shows the homepage for the 11th International World Wide Web Conference (WWW 2002) held in Hawaii. The page features a navigation menu on the left with links for Conference Proceedings, Call for Participation, Program, Registration Information, Hotel Accommodation, Conference Committee, Sponsorship/Exhibition Opportunities, Volunteer Information, Information about Hawaii, and Previous & Future WWW Conferences. The main content area includes the conference title, location (Sheraton Waikiki Hotel, Honolulu, Hawaii, USA, 7-11 May 2002), a slogan ("1 LOCATION. 5 DAYS. LEARN. INTERACT."), a list of countries where registered participants are coming from, a "REGISTER NOW" button, a paragraph about the conference's history and purpose, and a section for featured speakers including Tim Berners-Lee and Richard A. DeMillo. The page also includes a URL (http://www2002.org) and a logo for the International World Wide Web Conference Committee.

Markup consists of:

- rendering information (e.g., font size and color)
- Hyper-links to related content

Semantic content is accessible to humans but not (easily) to computers...

What information can we see...

WWW2002

The eleventh international world wide web conference

Sheraton waikiki hotel

Honolulu, hawaii, USA

7-11 may 2002

1 location 5 days learn interact

Registered participants coming from

**australia, canada, chile denmark, france, germany, ghana, hong kong, india,
ireland, italy, japan, malta, new zealand, the netherlands, norway,
singapore, switzerland, the united kingdom, the united states, vietnam,
zaire**

Register now

**On the 7th May Honolulu will provide the backdrop of the eleventh
international world wide web conference. This prestigious event ...**

Speakers confirmed

Tim berners-lee

Tim is the well known inventor of the Web, ...

Ian Foster

Ian is the pioneer of the Grid, the next generation internet ...

Need to Add “Semantics”

- Semantic annotation with respect to a domain ontology
- Ontology is the philosophical study of the nature of being, existence or reality in general, as well as the basic categories of being and their relations
- In computer science and information science, an ontology is a formal representation of the knowledge:
 - concepts within a domain
 - the relationships between these concepts
 - constraints
- It is used to
 - describe the domain
 - reason about the properties of that domain
 - consistency checking

Clinical Informatics using Ontologies

- Big and Complex Data: large-scale deployment of Electronic Health Record (EHR)
- Highly diverse
- New opportunities of secondary use of EHR for clinical and translational studies
- Interoperability of EHR data, clinical knowledge, and application in healthcare IT
- Ontologies and semantic web technologies offer potential solutions

Newsroom

[Health IT in the News](#)

[News Releases](#)

[Events](#)

[Fact Sheets](#)

[Infographics](#)

[Recent Updates](#)

About ONC

The Office of the National Coordinator for Health Information Technology (ONC) is at the forefront of the administration's health IT efforts and is a resource to the entire health system to support the adoption of health information technology and the promotion of nationwide health information exchange to improve health care. ONC is organizationally located within the Office of the Secretary for the U.S. Department of Health and Human Services (HHS).

ONC is the principal federal entity charged with coordination of nationwide efforts to implement and use the most advanced health information technology and the electronic exchange of health information. The position of National Coordinator was created in 2004, through an Executive Order, and legislatively mandated in the Health Information Technology for Economic and Clinical Health Act ([HITECH Act](#)) of 2009.

Media Questions

Contact Peter Ashkenaz if you have media questions. Your queries will be addressed within one business day.

[Get On-the-Ground Support](#)

Email:

Peter.Ashkenaz@hhs.gov 

Telephone: (202) 260-6342

The SHARP

AREA ONE: [Security and Health Information Technology](#) – The University of Illinois at Urbana-Champaign is helping develop technologies and policy recommendations that reduce privacy and security risks and increase public trust.

AREA TWO: [Patient-Centered Cognitive Support](#) – Innovative cognitive research is being led by the University of Texas, Houston to harness the power of health IT to integrate and support physician reasoning and decision-making as providers care for patients.

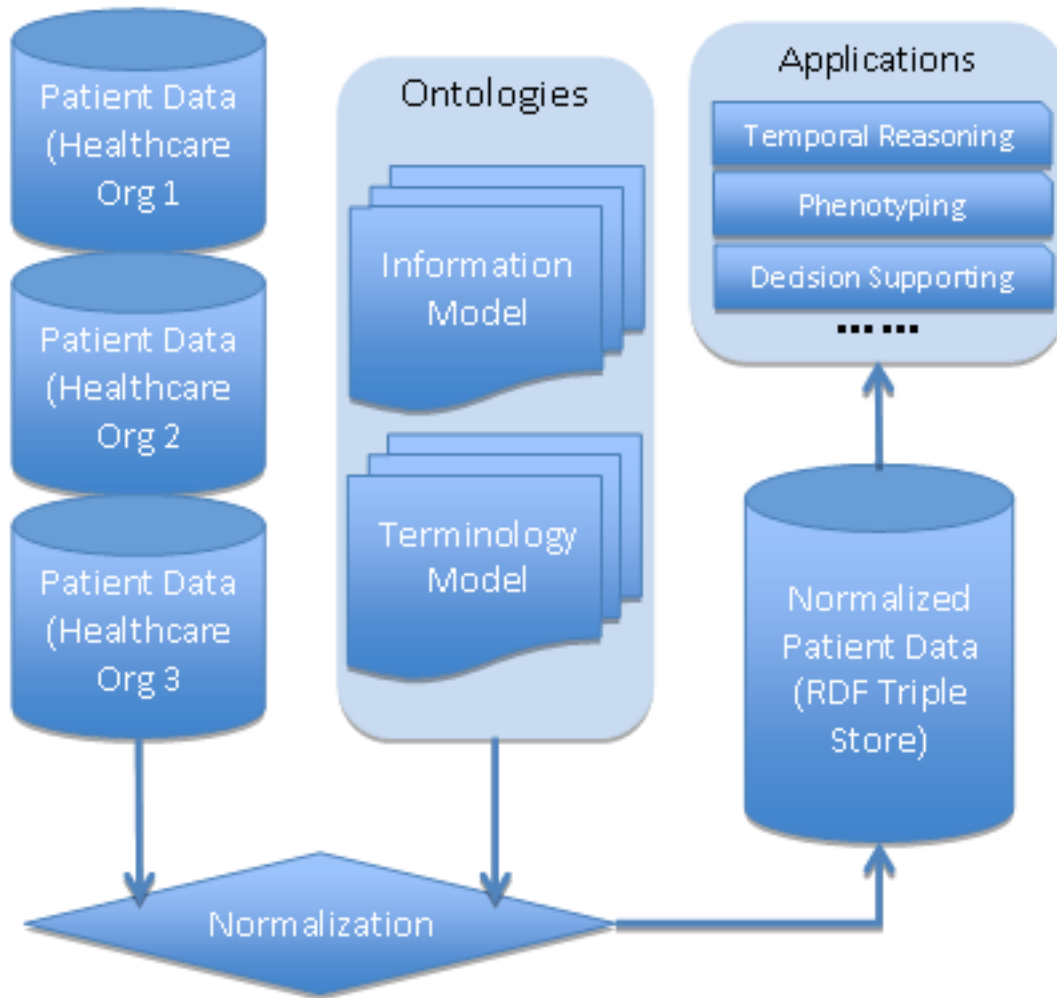
AREA THREE: [Health Care Application and Network Design](#) – Harvard University is leading platform-based research to create new and improved system designs that facilitate information exchange while ensuring the accuracy, privacy, and security of electronic health information.

AREA FOUR: [Secondary Use of EHR Information](#) – Mayo Clinic of Medicine is developing strategies to improve the overall quality of healthcare by leveraging existing EHR data to generate new, environmentally appropriate, best practice suggestions.

Outline

- Semantic Web representation of EHR data
 - Model representation
 - Instance representation
 - Semantic reasoning
- Phenotyping application
- Temporal Relation Modeling, Extraction, and Reasoning (TIMER)

EHR Data Representation



Tao C, et al. Toward semantic web based knowledge representation and extraction from electronic health records. CIKM 2011

Standard Model Representation & Ontology Normalization

- Terminology model:
 - Represent domain knowledge
 - SNOMED CT, LOINC, RxNorm, etc
 - Labetalol is an anti-hypertension drug
- Information model:
 - Provides a consistent architecture for representing healthcare and clinical application-specific concepts in EHR systems
 - Clinical Element Model (CEM)
 - Blood pressure measurements:
 - Systolic and diastolic blood pressure measurements
 - Device
 - Position
 - Inpatient/outpatient

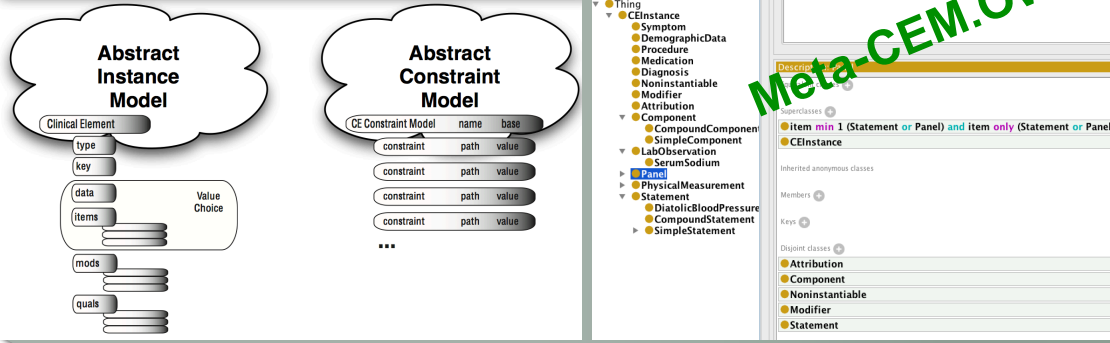
Clinical Element Model (CEM)

- Information model used in SHARPn (Strategic Health IT Advanced Research Projects - Secondary Use of EHR Data)
- Ensure semantic interoperability for:
 - Data representation
 - Data interpretation
 - Data exchange within and across heterogeneous sources and applications
- Represented in CEML/CDL (Constraint Definition Language)
 - Define syntax and grammar
 - Not semantics

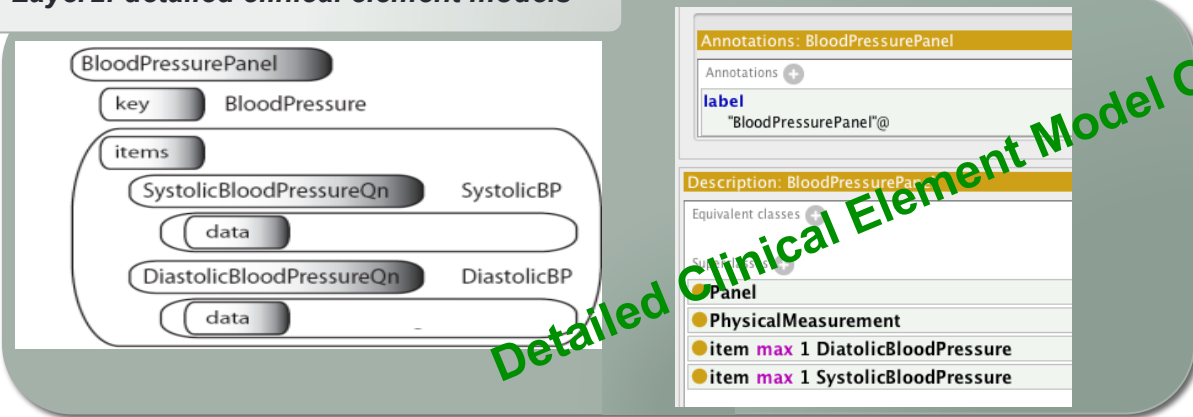
CEM-OWL

- Explicit and formal semantic representation
- Web Ontology Language (OWL) :
 - Define relationships
 - Define classes
 - Define constraints
- Consistency checking
- Link to other domain terminologies
- Semantic reasoning
- Directly using semantic web tools

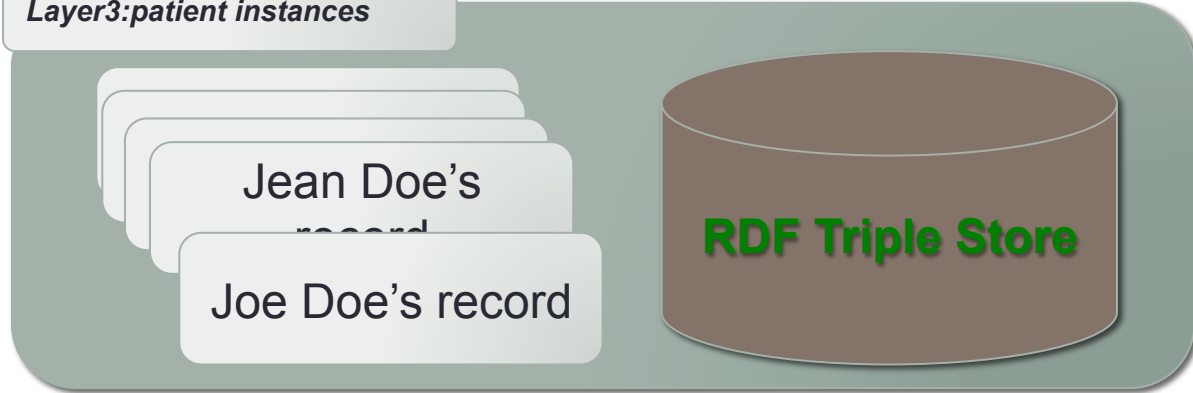
Layer1:meta-ontology



Layer2: detailed clinical element models



Layer3:patient instances



Tao C, et al, A Semantic-Web Oriented Representation of the Clinical Element Model for Secondary Use of EHR Data, JAMIA. 2012

Semantic Reasoning

- Consistency checking
 - Cardinality constraints
 - Data types
 - Property allowed domains and ranges
 - Permissible values in value sets
- Classification and reasoning

Consistency Checking

- ▼ ● Panel
 - **TestPanel**
 - ▶ ● BloodPressurePanel
 - Sequence
 - ▶ ● Attribution
 - ▶ ● Component
 - ▶ ● Modifier
 - Noninstantiable
 - ▶ ● Statement
- ▶ ● OWLList
- 'Physical quality'
- Prefix
- ▶ ● 'Quality value'
- ▶ ● 'Unit of measurement'

The screenshot shows a class hierarchy viewer with three sections: 'Equivalent classes', 'Superclasses', and 'Inherited anonymous classes'. The 'Nothing' class is highlighted in yellow under 'Equivalent classes'. The 'Panel' class and its subclass 'item min 1 Component' are highlighted with a red box under 'Superclasses'. The 'Inherited anonymous classes' section contains a complex logical expression also highlighted with a red box.

Equivalent classes +

- **Nothing**

Superclasses +

- **Panel**
- **item min 1 Component**

Inherited anonymous classes

- (item **some** (Association or Statement) and (item **only** (Association or Statement)))

Consistency Checking

● (item min 0 DiastolicBloodPressure)
and (item max 1 DiastolicBloodPressure)

● (item min 0 SystolicBloodPressure)
and (item max 1 SystolicBloodPressure)

■ item exam1

■ item exam2

■ item exam3

Description: exam1

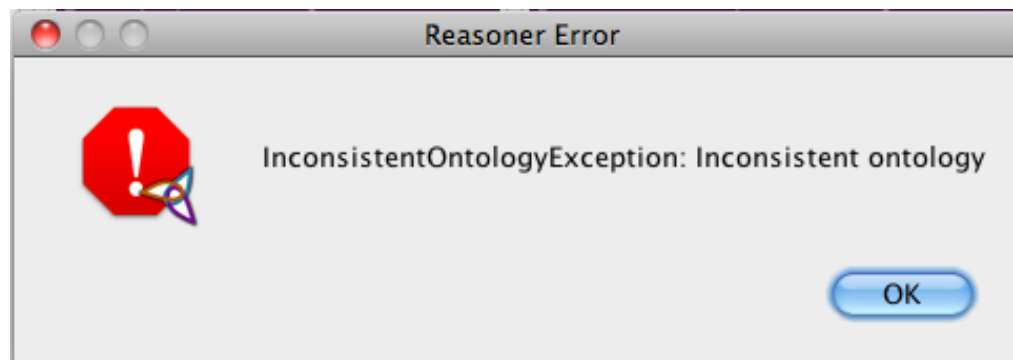
Types +

● DiastolicBloodPressure

Same individuals +

Different individuals +

◆ exam3, exam2



Consistency Checking

Description: BloodPressureBodyLocationPrecoord

Equivalent classes +

- Arm
 - or Finger
 - or Wrist

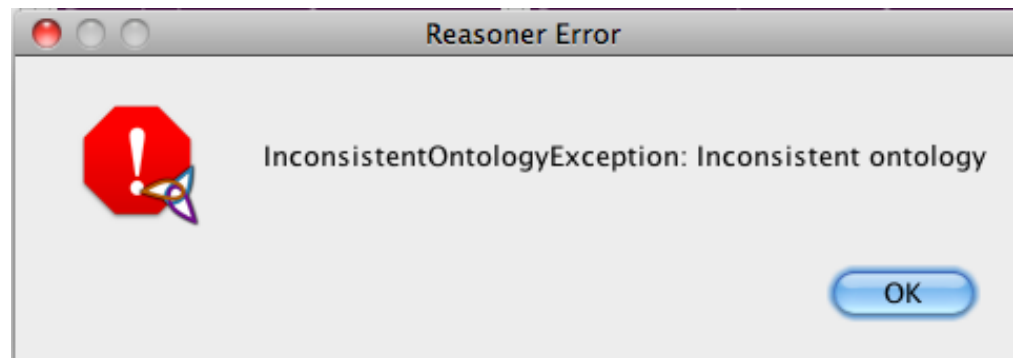
Property assertions: patient0123BP

Object property assertions +

- bloodPressureBodyLocationQual leg
- item exam1
- item exam2

Disjoint classes +

- Arm, Finger, Wrist



Automatic Classification

Semantic Definition of Normal DBP Data

Description: NormalDBPData

Equivalent classes +

● **qualityLiteralValue** some integer [>60, <79]

Two DBP Measurements

Description: DBPdata1	Property assertions: DBPdata1
Types + ● DiastolicBloodPressureData @ X O	Object property assertions + Data property assertions +
Same individuals +	■ qualityLiteralValue 120

Description: DBPdata2	Property assertions: DBPdata2
Types + ● DiastolicBloodPressureData @ X O ■ NormalDBPData	Object property assertions + Data property assertions +
	■ qualityLiteralValue 65

Outline

- Semantic Web representation of EHR data
 - Model representation
 - Instance representation
 - Semantic Reasoning
- **Phenotyping application**
- Temporal Relation Modeling, Extraction, and Reasoning (TIMER)

Electronic health records (EHRs) driven phenotyping

- Overarching goal
 - To develop **automated** techniques and algorithms that operate on normalized EHR data to **identify cohorts of potentially eligible subjects** on the basis of disease, symptoms, or related findings
- National Quality Forum (NQF)
 - More than 600 meaningful use quality measures
 - Quality Data Model (QDM)
 - A structure and grammar to represent quality measures in a standardized format
 - XML-based
 - Not executable

Find Measures

Browse Portfolios

Measures (688)

Portfolios

Compare

□ □ □

Search Term

Search as Phrase

Search

Clear

Measure Steward +

National Quality Strategy Priorities +

Actual/Planned Use +

Care Setting +

Clinical Condition/ Topic Area +

Cross-Cutting Area +

Data Source +

Level of Analysis +

Measure Status +

Measure Type +

Target Population +

eMeasure Available

Page: << < 1 > >>

Export

Show 25 results

Title ↓↑	NQF# ↓↑	Steward ↓↑	Updated ↓↑
(Pediatric) ESRD Patients Receiving Dialysis: Hemoglobin Level < 10g/dL	1667	American Medical Association - Physician Consortium for Performance Improvement (AMA-PCPI)	Jul 09, 2012
30-day all-cause risk-standardized mortality rate following Percutaneous Coronary Intervention (PCI) for patients with ST segment elevation myocardial infarction (STEMI) or cardiogenic shock	0536	Centers for Medicare and Medicaid Services	Jan 02, 2013
30-day all-cause risk-standardized mortality rate following percutaneous coronary intervention (PCI) for patients without ST segment elevation myocardial infarction (STEMI) and without cardiogenic shock	0535	Centers for Medicare and Medicaid Services	Jan 02, 2013
30-Day Post-Hospital AMI Discharge Care Transition Composite Measure (Composite Measure)	0698	Centers for Medicare and Medicaid Services	Sep 10, 2012
Click on the measure title to view the rates included in this composite measure.			
30-Day Post-Hospital HF Discharge Care Transition Composite Measure (Composite Measure)	0699	Centers for Medicare and Medicaid Services	Sep 16, 2012
Click on the measure title to view the rates included in this composite measure.			
30-day Post-Hospital PNA (Pneumonia) Discharge Care Transition Composite Measure (Composite Measure)	0707	Centers for Medicare and Medicaid Services	Jan 16, 2011
Click on the measure title to view the rates included in this composite measure.			
3-Item Care Transition Measure (CTM-3) (Composite Measure)	0228	University of Colorado Health Sciences Center	Jul 01, 2013
Click on the measure title to view the rates included in this composite measure.			
Abdominal Aortic Aneurysm (AAA) Repair	0359	Agency for Healthcare Research	Apr 30, 2012

Phenotype Use Case Example

Resistant Hypertension Phenotyping Algorithm

Has two outpatient (if possible) measurements of Systolic blood pressure > 140 or Diastolic blood pressure > 90 at least one month after taking antihypertensive drugs.

Sample Patient Data

Patient was put on Labetalol 100mg starting from March 1st.

Follow-up BP in 5 weeks: SBP=156, DBP=110

Today's BP measurements: SBP=148, DBP=112 (note date: May 1)

Extract and Represent Clinical Elements & Constraints

Resistant Hypertension Phenotyping Algorithm

Has **two** outpatient (if possible) **measurements** of **Systolic** blood pressure >140 or **Diastolic blood pressure** > 90 at least **one month after** taking antihypertensive drugs.

Sample Patient Data

Patient was put on **Labetalol 100mg** starting from **March 1st**.

Follow-up BP in **5 weeks**: **SBP**=156, **DBP**=110

Today's BP measurements: **SBP**=148, **DBP**=112 (note date: **May 1**)

Example: Diabetes & Lipid Mgmt. - I

Example: Diabetes & Lipid Mgmt. - I

Population criteria

- **Initial Patient Population =**

- AND: "Patient characteristic: birth date" >= 17 year(s) and <= 74 year(s) starts before start of "Measurement period"

- **Denominator=**

- AND: "Initial Patient Population"

- AND:

- OR:

- AND:

- OR: "Encounter: Encounter acute inpatient or ED"

- OR:

- AND: >= 2 count(s) of

- AND: "Encounter: Encounter non-acute inpatient and outpatient"

- AND: FIRST:"Encounter: Encounter non-acute inpatient and outpatient" starts before start of SECOND
:"Encounter: Encounter non-acute inpatient and outpatient"

- AND: "Diagnosis active: diabetes"

- OR:

- OR: "Medication order: Medications indicative of diabetes"

- OR: "Medication dispensed: Medications indicative of diabetes"

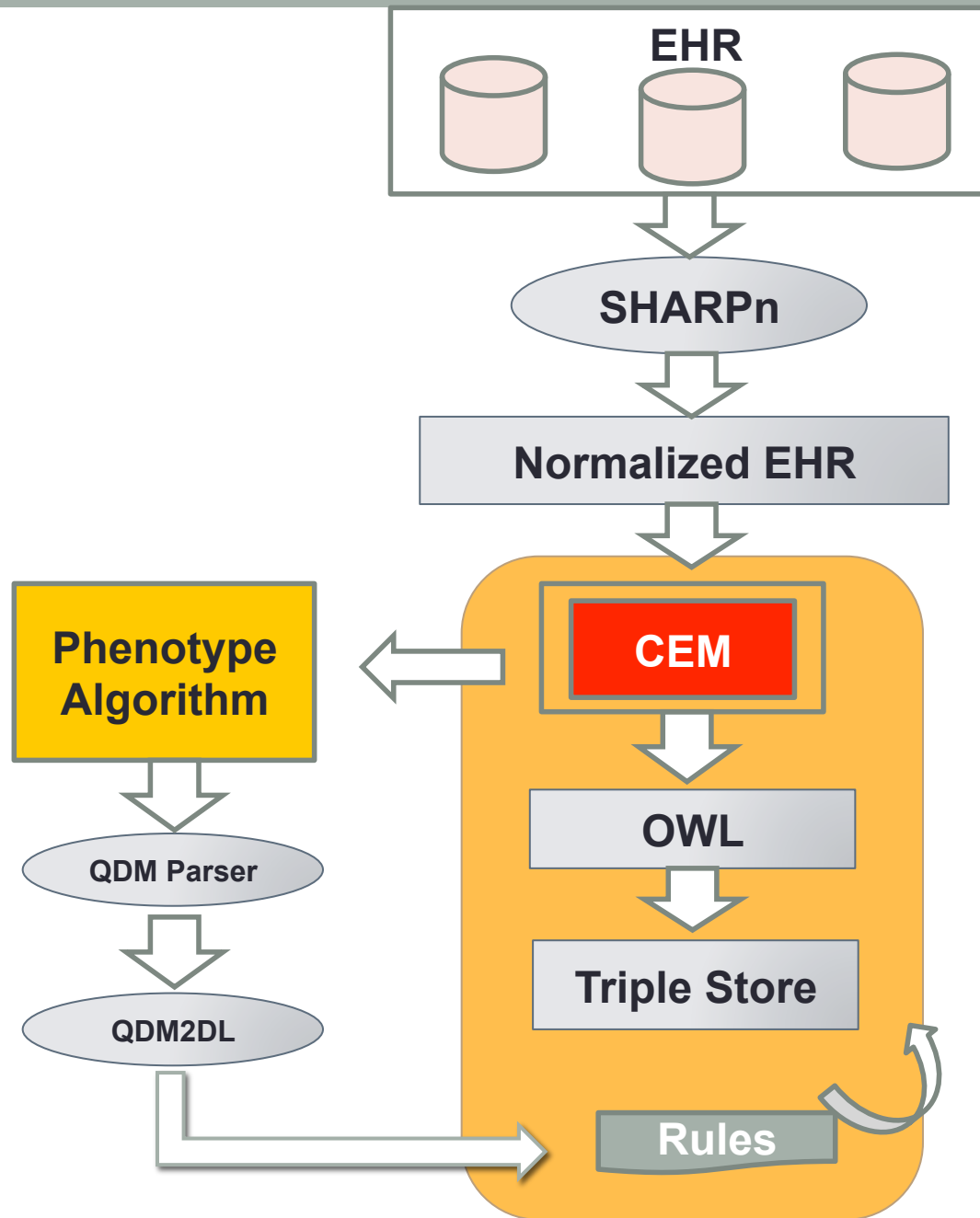
- OR: "Medication active: Medications indicative of diabetes"

- <= 2 year starts before or during "Measurement end date"

Human readable HTML

Phenotyping Application

- Make the measures executable on normalized EHR!
- RDF representation of normalized EHR data
 - Demographic information, laboratory records, medication history, diagnosis, encounters, and symptom descriptions
 - RDF triple store
 - Modeled by CEM-OWL
- SWRL/DL representation of the NQF measures
 - UIMA-based QDM parser
 - QDM2DL API



Shen F, Li D, Liu H, Pathak J, Chute CG, Tao C. A SWRL Implementation of NQF Measures for Querying Electronic Healthcare Records in RDF Triples. Submitted to AMIA-CRI, 2013

1. Value Set Restriction

NQF Operation: Encounter: Encounter Office & Outpatient Consult

Query (class expression)

```
PatientExternalId and itemFor some  
(Encounter and (EncounterHasCode some  
(0001_EncounterCode)) and EncounterHasCodeSys some  
(0001_EncounterCodeSys))
```

2. Logic Operation

NQF Operation:

AND: "Diagnosis, Active: diabetes"

AND:

OR: "Encounter: Encounter acute inpatient or ED"

OR: "Encounter: Encounter non-acute inpatient and outpatient"

Query (class expression)

```
PatientExternalId and itemFor some  
(AdministrativeDiagnosis and DiagnosisHasCode some  
(0064_DiagnosisCode) and DiagnosisHasCodeSys some  
(0064_DiagnosisCodeSys))  
AND  
(PatientExternalId and itemFor some  
(Encounter and EncounterHasCode some  
(0064_EncounterCode) and EncounterHasCodeSys some  
(0064_EncounterCodeSys))  
OR  
(PatientExternalId and itemFor some  
(Encounter and EncounterHasCode some  
(0064_EncounterCode) and EncounterHasCodeSys some  
(0064_EncounterCodeSys))))]
```

3.1. Negation Function

NQF Operation: AND NOT: "Diagnosis, Active: diabetes"

Query (class expression)

```
PatientExternalId and itemFor some  
(AdministrativeDiagnosis and DiagnosisHasCode some  
(0056_DiagnosisCode) and DiagnosisHasCodeSys some  
(0056_DiagnosisCodeSys))
```

3.2. Count Function

NQF Operation: Count >= 2

of: "Encounter: Encounter Office & Outpatient Consult"

Query (class expression)

```
PatientExternalId and itemFor some (Encounter and Count some  
(integer [>="2" ^^integer]))
```

3.3. Order Function

NQF Operation: AND: FIRST: "Encounter: Encounter non-acute inpatient, outpatient, or ophthalmology" >= 1 day(s) starts before start of SECOND : "Encounter: Encounter non-acute inpatient, outpatient, or ophthalmology"

```
Encounter(?enc1), hasVisitDate(?enc1,?value),  
PatientExternalId(?pid), item(?enc1, ?pid),  
Encounter(?enc2), hasVisitDate(?enc2,?value2),  
PatientExternalId(?pid), item(?enc2, ?pid),  
subtractDayTimeDurations(?duration,?value,?value2),lessThanOrEqual(?duration,1)  
→  
PatientExternalId(?pid)
```

4.1 Time comparison between variable and constant without time arithmetic

NQF Operation: Encounter: Encounter ambulatory including pediatrics" during "Measurement period"

Measurement begin time = 2012-01-01T00:00:00
Measurement end time = 2012-12-31T59:59:59

Query (class expression)

```
PatientExternalId and itemFor some  
(SecondaryUsePatient and item some  
(BirthDate and data some  
(TS and qualityLiteralValue some  
dateTime[<="2010-12-31T59:59:59" ^^dateTime])))
```

4.2. Time comparison between variable and constant with time arithmetic

*NQF Operation:
AND: "Patient Characteristic: birth date" >= 2 year(s) starts before start of "Measurement period"*

Time Stamp = 2012-01-01T00:00:00 – 2 years
= 2010-01-01T00:00:00

Query (class expression)

```
PatientExternalId and itemFor some  
(SecondaryUsePatient and item some  
(BirthDate and data some  
(TS and qualityLiteralValue some  
dateTime[<="2010-12-31T59:59:59" ^^dateTime])))
```

4.3. Time comparison between two variables without time arithmetic

NQF Operation: "Diagnosis, Active: Asthma" starts before or during ("Encounter: Encounter Office & Outpatient Consult"

```
AdministrativeDiagnosis(?xatom),  
AttribRecordedTime (?xatttime),  
PatientExternalId(?pid), item(?xatom, ?pid),  
TS(?ts),att(?xatom,?xatttime),data(?xatttime,?ts),TS(  
?ts),qualityLiteralValue(?ts,?value),Encounter(?enc),  
hasVisitDate(?enc,?value2), PatientExternalId(?pid),  
item(?enc, ?pid),lessThanOrEqual(?value,?value2) ->  
PatientExternalId(?pid)
```

4.4. Time comparison between two variables with time arithmetic

*NQF Operation: "Medication, Active: pharyngitis antibiotics"
<= 30 day(s) starts before start of ("Encounter: Encounter ambulatory including pediatrics"*

```
SecondaryUseNotedDrug  
(?xatom), PatientExternalId(?pid),  
item(?xatom,?pid),StartTime(?stime0),TS(?ts0),  
data(?stime0,?ts0),qualityLiteralValue(?ts0,?value),E  
ncounter(?enc), hasVisitDate(?enc,?value2),  
PatientExternalId(?pid), item(?enc,  
?pid),subtractDayTimeDurations(?duration,?value2,?  
value),lessThanOrEqual(?duration,30)  
→PatientExternalId(?pid)
```

NQF Human Readable Statement

[1] AND:

[1.1] OR:

[1.1.1] AND: "Diagnosis, Active: diabetes"

[1.1.2] AND:

[1.1.2.1] OR: "Encounter: Encounter acute inpatient or ED"

[1.1.2.2] OR:

[1.1.2.2.1] AND: Count >= 2 of:AND: "Encounter: Encounter non-acute inpatient, outpatient, or ophthalmology"

[1.1.2.2.2] AND: FIRST:"Encounter: Encounter non-acute inpatient, outpatient, or ophthalmology" >= 1 day(s) starts before start of [1.1.2.2.2.1] SECOND : "Encounter: Encounter non-acute inpatient, outpatient, or ophthalmology"

[1.2] OR: "Medication, Dispensed: Medications indicative of diabetes"

[1.3] <= 2 year(s) starts before or during "Measurement end date"

Rule Representation

1-1.1-1.1.1
(OWL-DL)

1-1.1-1.1.2-
1.1.2.1-1.3
(OWL-DL)

1-1.1-1.1.2-
1.1.2.2-
1.1.2.2.1-1.3
(OWL-DL)

1-1.1-1.1.2-
1.1.2.2-
1.1.2.2.2-
1.1.2.2.2.1-1.3
(SWRL)

1-1.2-1.3
(OWL-DL)

```
( PatientExternalId and itemFor some (AdministrativeDiagnosis and
DiagnosisHasCode some ( 0056_DiagnosisCode) and DiagnosisHasCodeSys
some (0056_DiagnosisCodeSys) and qualityLiteralValue some (dateTime[<=
"2011-12-31T00:00:00"^^dateTime]))
and
(( PatientExternalId and itemFor some (Encounter and EncounterHasCode
some (0056_EncounterCodeIP) and EncounterHasCodeSys some
(0056_EncounterCodeSysIP)) and hasVisitDate some (dateTime[<= "2011-
12-31T00:00:00"^^dateTime]))
or
(( PatientExternalId and itemFor some (Encounter and
EncounterHasCode some (0056_EncounterCodeNIP) and
EncounterHasCodeSys some (0056_EncounterCodeSysNIP)) and Count
some (Integer [>="2" ^^Integer]) and hasVisitDate some (dateTime[<=
"2011-12-31T00:00:00" ^^dateTime]))
and
Encounter(?enc1), hasVisitDate(?enc1, ?value), PatientExternalId(?pid),
item(?enc1,?pid), Encounter(?enc2), hasVisitDate(?enc2, ?value2),
PatientExternalId (?pid), item(?enc2, ?pid),
subtractDayTimeDurations(?duration, ?value, ?value2),
lessThanOrEqual(?duration,1) -> PatientExternalId (?pid)
or
( PatientExternalId and itemFor some (SecondaryUseNotedDrug and
DrugHasCode some (0056_MedicationDispenseCode) and DrugHasCodeSys
some (0056_MedicationDispenseCodeSys) and (qualityLiteralValue some
(dateTime[<= "2011-12-31T00:00:00"^^dateTime]))
```

Outline

- Semantic Web representation of EHR data
 - Model representation
 - Instance representation
 - Semantic Reasoning
- Phenotyping application
- Temporal Relation Modeling, Extraction, and Reasoning (TIMER)

Introduction

- Time is essential in clinical research
 - Uncover temporal pattern
 - Disease level
 - Patient level
 - Explain past events
 - Predict future events
- Challenges
 - Vast amount of data
 - Data embedded in narratives
 - Many temporal relations are not *explicitly* stated in the clinical narratives, but rather needs to be inferred

Temporal Relation Reasoning (Example)

- *Patient's INR value is below normal (Event 1) today. (note date: 01/26/07)*
- *He has had the chills and body aches (Event 2) before the abnormal test. (Event 3)" (note date: 01/26/07)*
- *On Jan. 30, 2007, patient started Coumadin dosing plan of 1.0 mg (Event 4).(note date: 02/09/07)*
- *Question: "did the patient experience body aches before he started the Coumadin dosing plan?"*

Temporal Relation Reasoning (Example)

- *Patient's INR value is below normal (Event 1) today. (note date: 01/26/07)* *Event1 = Event3*
- He has had the *chills and body aches (Event 2) before the abnormal test. (Event 3)*” (note date: 01/26/07)
- On Jan. 30, 2007, patient started *Coumadin dosing plan of 1.0 mg (Event 4).*(note date: 02/09/07)
- *Question: “did the patient experience body aches before he started the Coumadin dosing plan?”*

Temporal Relation Reasoning (Example)

- *Patient's INR value is below normal* (Event 1) today. (note date: 01/26/07)
- He has had the *chills and body aches* (Event 2) before *the abnormal test.* (Event 3)" (note date: 01/26/07)
- On Jan. 30, 2007, patient started *Coumadin dosing plan of 1.0 mg* (Event 4).(note date: 02/09/07)
- *Question: "did the patient experience body aches before he started the Coumadin dosing plan?"*

Event1 = Event3

+

Event2 before Event3

→

Event2 before Event1

Temporal Relation Reasoning (Example)

- *Patient's INR value is below normal (Event 1) today. (note date: 01/26/07)*
- *He has had the chills and body aches (Event 2) before the abnormal test. (Event 3)" (note date: 01/26/07)*
- *On Jan. 30, 2007, patient started Coumadin dosing plan of 1.0 mg (Event 4).(note date: 02/09/07)*
- *Question: "did the patient experience body aches before he started the Coumadin dosing plan?"*

Event1 = Event3

+

Event2 before Event3

→

Event2 before Event1

Event1 01/26/07 +

Event4 01/30/07

→

Event1 before Event4

Temporal Relation Reasoning (Example)

- *Patient's INR value is below normal (Event 1) today. (note date: 01/26/07)*
- *He has had the chills and body aches (Event 2) before the abnormal test. (Event 3)" (note date: 01/26/07)*
- *On Jan. 30, 2007, patient started Coumadin dosing plan of 1.0 mg (Event 4).(note date: 02/09/07)*
- *Question: "did the patient experience body aches before he started the Coumadin dosing plan?"*

Event1 = Event3

+

Event2 before Event3

→

Event2 before Event1

Event1 01/26/07 +

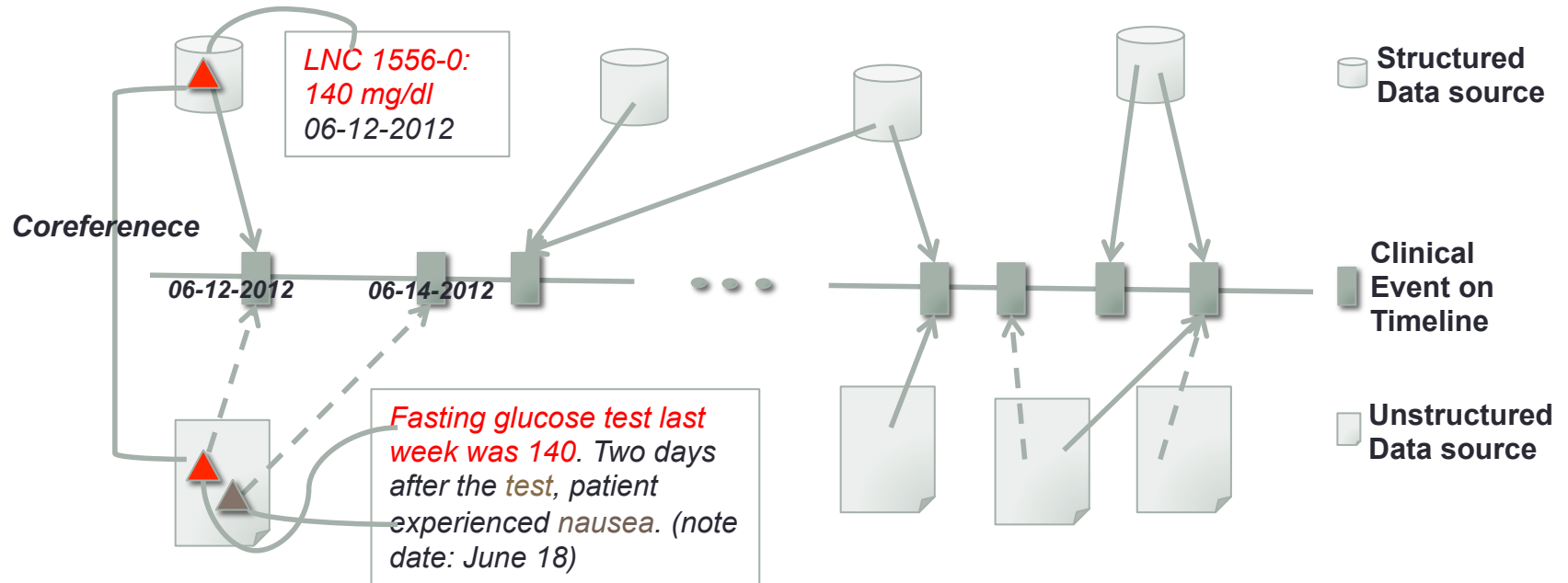
Event4 01/30/07

→

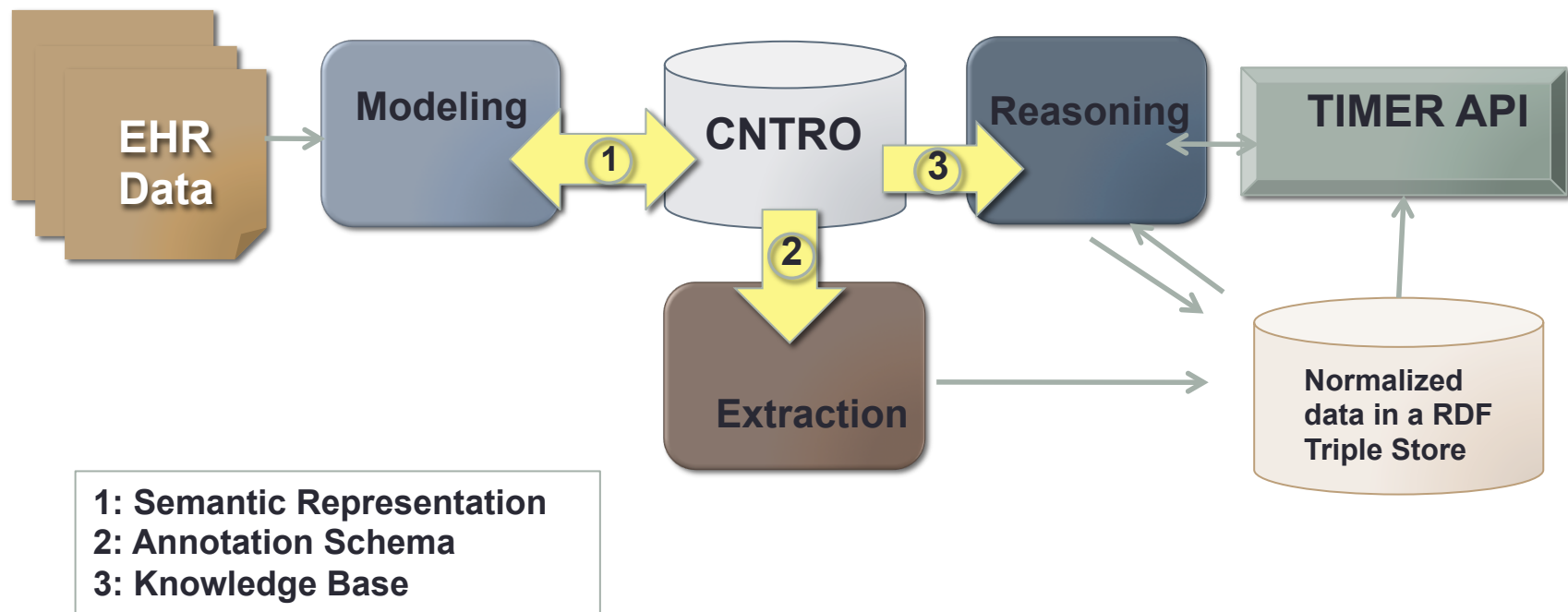
Event1 before Event4

Event2 before Event4

Temporal Reasoning Example

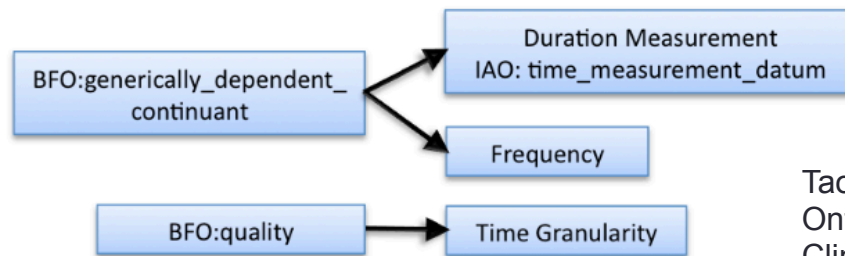
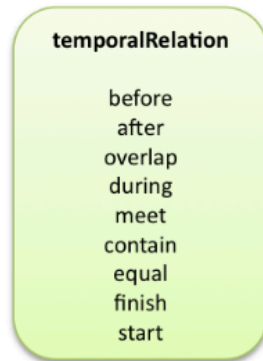
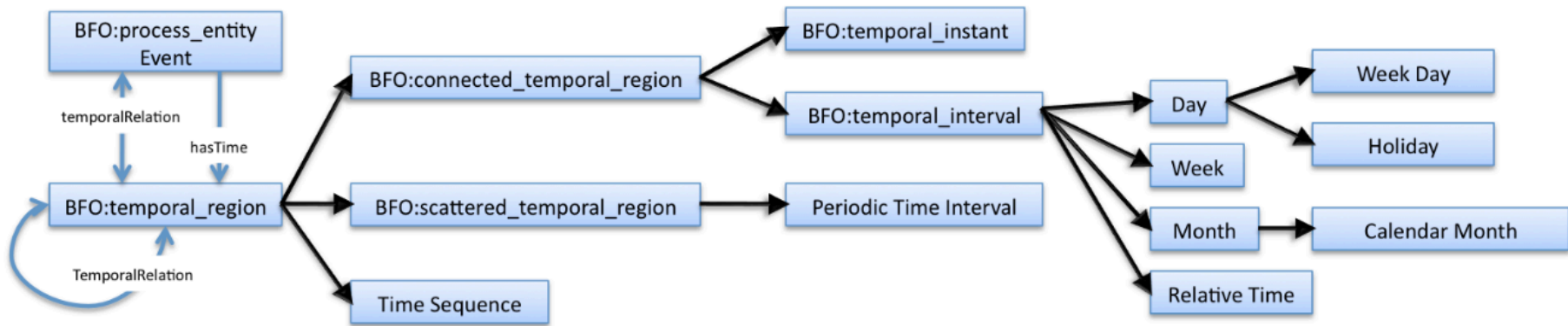


TIMER (Temporal Information Modeling, Extraction, & Reasoning)



CNTRO

Clinical Narrative Temporal Relation Ontology



Tao C, et al. CNTRO: A Semantic Web Ontology for Temporal Relation Inferencing in Clinical Narratives. AMIA. 2010

Tao C, et al.. CNTRO 2.0: A Harmonized Semantic Web Ontology for Temporal Relation Inferencing in Clinical Narratives. AMIA-CRI. 2011

Available at BioPortal

Semantator: Information Extraction & Semantic Annotation

Semantator1:

File Annotate Create Highlight Help

PT RECVD **1ST ENGERIX-B DOSE (DELT) 3-29-90 AM. SAME DAY EXPER RED AREA AT SOI, NAUSEA. FOLLOWING DAY ACHES SUBSIDING 4-1-90; NAUSEA CONTINUED. 3-31-90 FLU-LIKE SYMPTOMS. 4-4-90 RASH AT LF AXILLARY AREA NOT AT SOLTREATMENT TYLENOL BENADRYL**

Individuals by type: '1ST ENGERIX-B DOSE' [] [] [] []

- TimeInstant (6)
- Event (7)
 - ◆ RASH
 - ◆ 'FLU-LIKE SYMPTOMS'
 - ◆ NAUSEA
 - ◆ 'ACHES SUBSIDING'
 - ◆ NAUSEA
 - ◆ 'RED AREA AT SOI'
 - ◆ '1ST ENGERIX-B DOSE'
- 49610 (1)
- Influenza_AE (1)
 - ◆ 'FLU-LIKE SYMPTOMS.'

Property assertions: '1ST ENGERIX-B DOSE'

Object property assertions +

- hasValidTime 3-29-90

Data property assertions +

Negative object property assertions +

Negative data property assertions +

Song D, Chute CG, Tao C. Semantator: annotating clinical narratives with semantic web ontologies. AMIA-CRI. 2012

Tao C, et al. Semantic Annotator for Converting Biomedical Text to Linked Data, submitted to Journal of Biomedical Informatics

Information Extraction & Semantic Annotation

Semantator:

- A GUI for users to browse, query, & edit annotated results in the original context
- Manual annotation
- Semi-automatic annotation
- Reasoning: consistency checking
- Inter-annotator agreements

[http://informatics.mayo.edu/CNTRO/index.php/
Semantator](http://informatics.mayo.edu/CNTRO/index.php/Semantator)

Temporal Relation Reasoning

- Temporal Representation Normalization
- OWL DL Reasoning
- SWRL-based Reasoning

Tao C, et al. Time-Oriented Question Answering from Clinical Narratives Using Semantic-Web Techniques, ISWC 2010

Implementation Status

- *findEvent(searchText)*
 - returns a list of events that match the searching criteria.
- *GetEventFeature(event, featureflag)*
 - returns a specific time feature for a given event.
 - Sample query:
 - When was the patient diagnosed with diabetes?
 - When did the patient start his chemotherapy?

Implementation Status

- *getDurationBetweenEvents(event1, event2)*
 - returns the time interval between two events.
 - Sample query: How long after the patient was diagnosed colon cancer did he start the chemotherapy?
- *getDuration(event)*
 - returns the duration of a given event.
 - Sample query: How long did the symptoms of rectal bleeding last?

Implementation Status

- *getTemporalRelationType(event1, event2)*
 - returns the temporal relations between two events if it can be retrieved or inferred.
 - Sample query: Was the CT scan after the colonoscopy?
- *getTemporalRelationType(event1, time)*
 - returns the temporal relations between an event and a specific time if it can be inferred or retrieved.
 - Sample query: Is there any behavior change within a week of the test?

Implementation Status

sortEventsByTemporalRelationsOrTimeline(events)

- returns the order (timeline) of a set of events.
- sample query:
 - What is the tumor status timeline as indicated in the patient's radiology note?
 - What is the treatment timeline as recorded in oncology notes?
 - When was the first colonoscopy done?
 - When was the most recent glucose test?

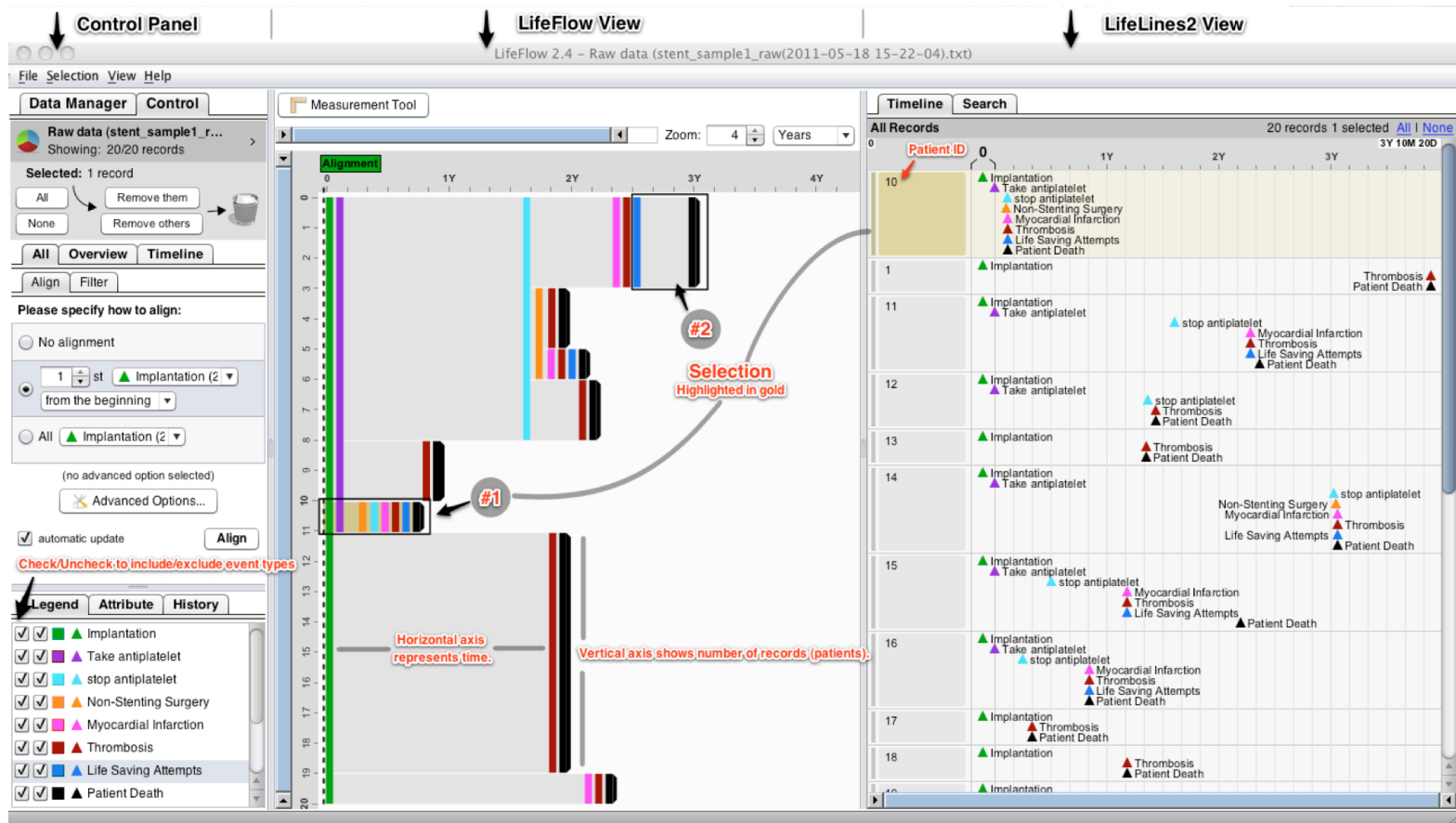
TIMER Application

- Late stent thrombosis (LST) adverse event
- Complaint files from Manufacturer and User Facility Device Experience (MAUDE) database
- Detect potential temporal patterns within complaint files of similar adverse events

Clark KK, Sharma DK, Chute CG, Tao C. Application of a temporal reasoning framework tool in analysis of medical device adverse events. AMIA 2011

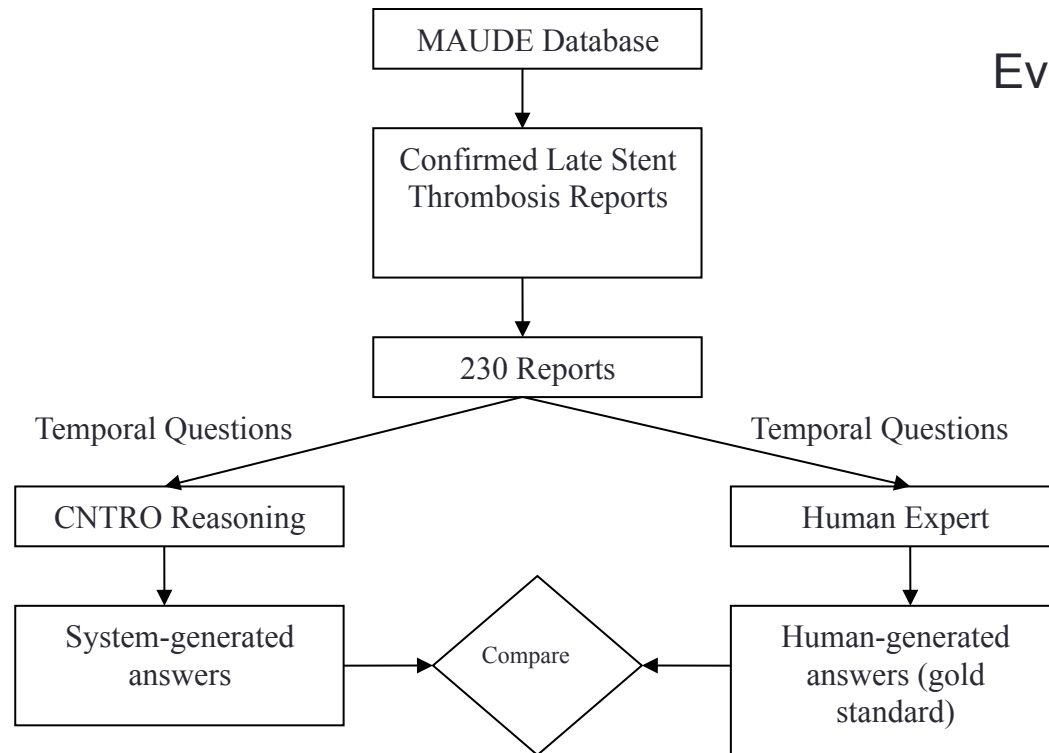
Clark KK, Sharma D, Qin R, Chute CG and Tao C. Ontology-based temporal analysis for medical device adverse event— a use case study on Late Stent Thrombosis. SWAT4LS 2013

Visualization: Connect with LifeFlow



Tao C, Wongsuphasawat K, Plaisant C, Shneiderman B, et al. Towards event sequence representation, reasoning and visualization for EHR data. IHI'12 - Proceedings of the 2nd ACM SIGHT IHI. 2012

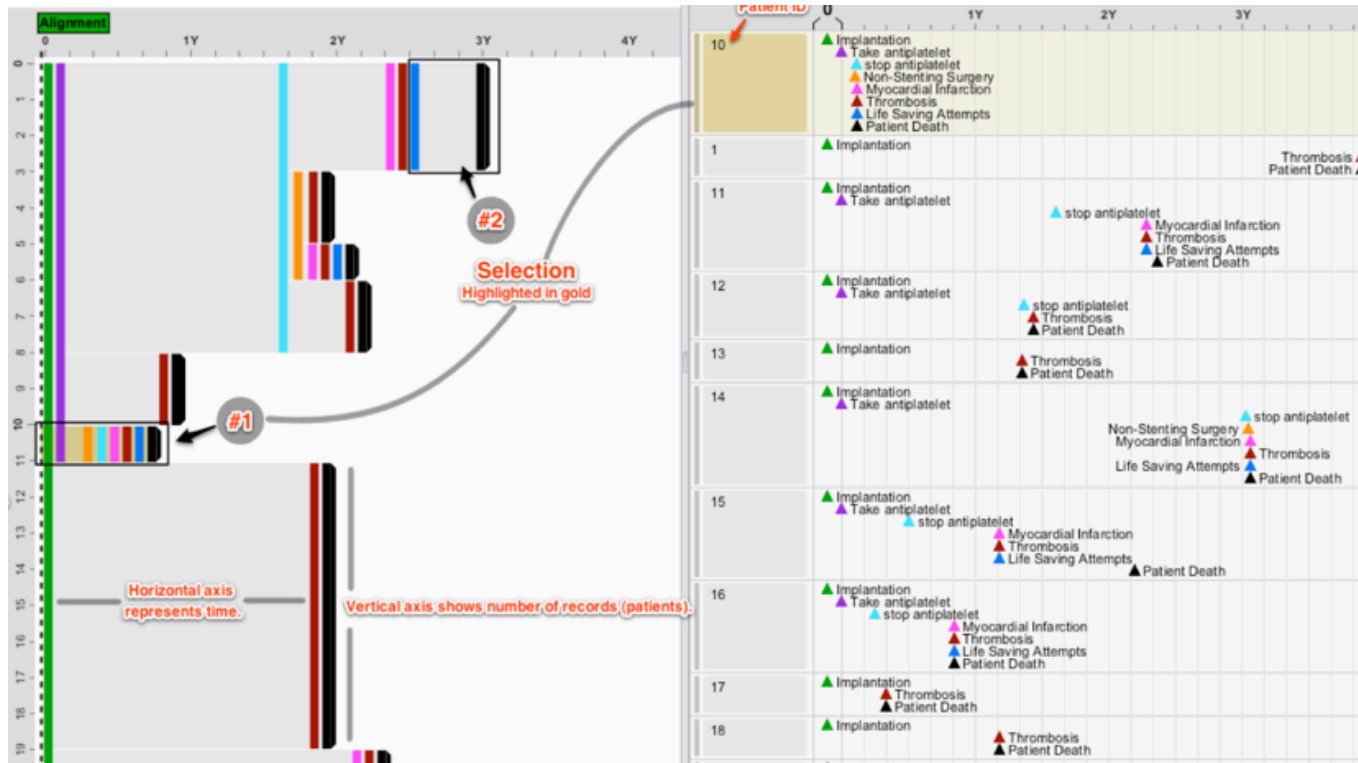
TIMER Application



Evaluation Results:

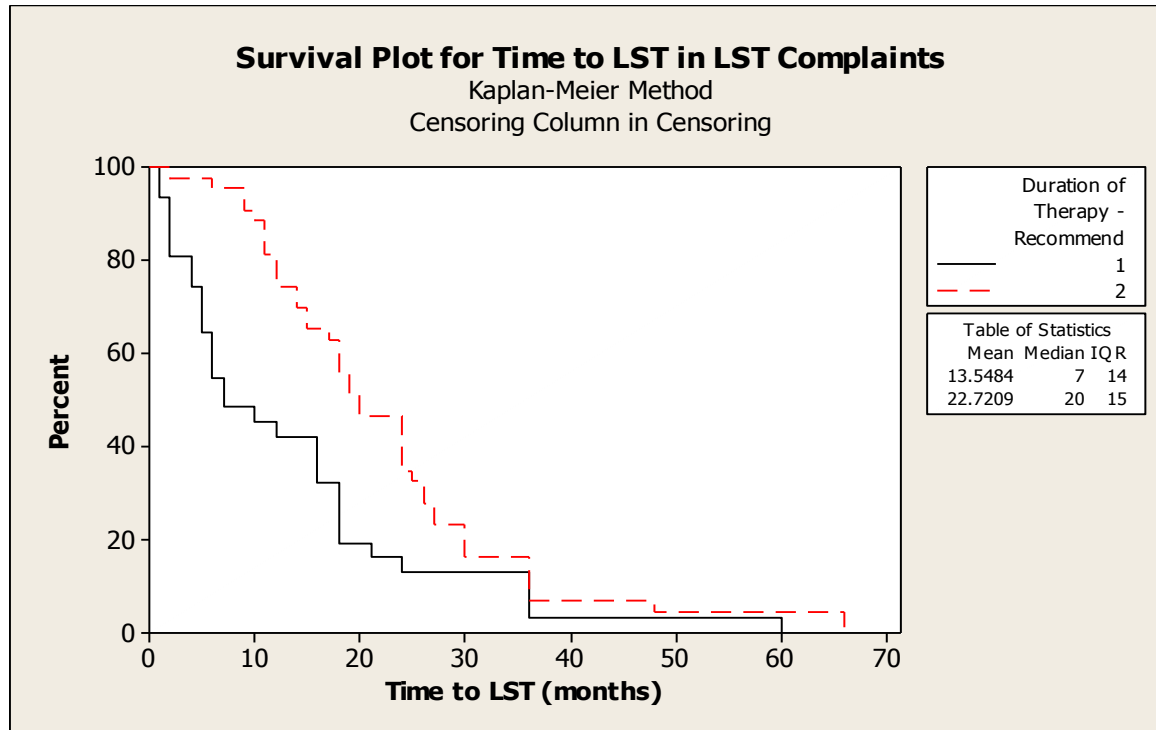
- Timeline: 87.4%
- Duration calculation: 89%

TIMER Application: Temporal Pattern



Event sequence pattern matches previously identified common temporal patterns within LST AEs.

TIMER Application: Statistical Analysis



Survival analysis of shorter duration of antiplatelet therapy (group 1) and longer duration of antiplatelet therapy (group 2) in late stent thrombosis complaints

- Consistent with other relevant studies
- Guidance on Antiplatelet Therapy After Stenting is 12 months
- Early discontinuation could associate with significantly higher rates of LST

Summary

- Ontologies and semantic web technologies can provide a viable and interoperable solution for
 - Modeling of clinical data
 - Conducting scalable querying over the data
 - Inferring new knowledge
- Supports clinical and translational research
 - Decision support
 - Phenotyping
 - Biomedical data network analysis

