# Semantics for Healthcare and the Life Sciences

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26th May, 2006
Edinburgh, UK

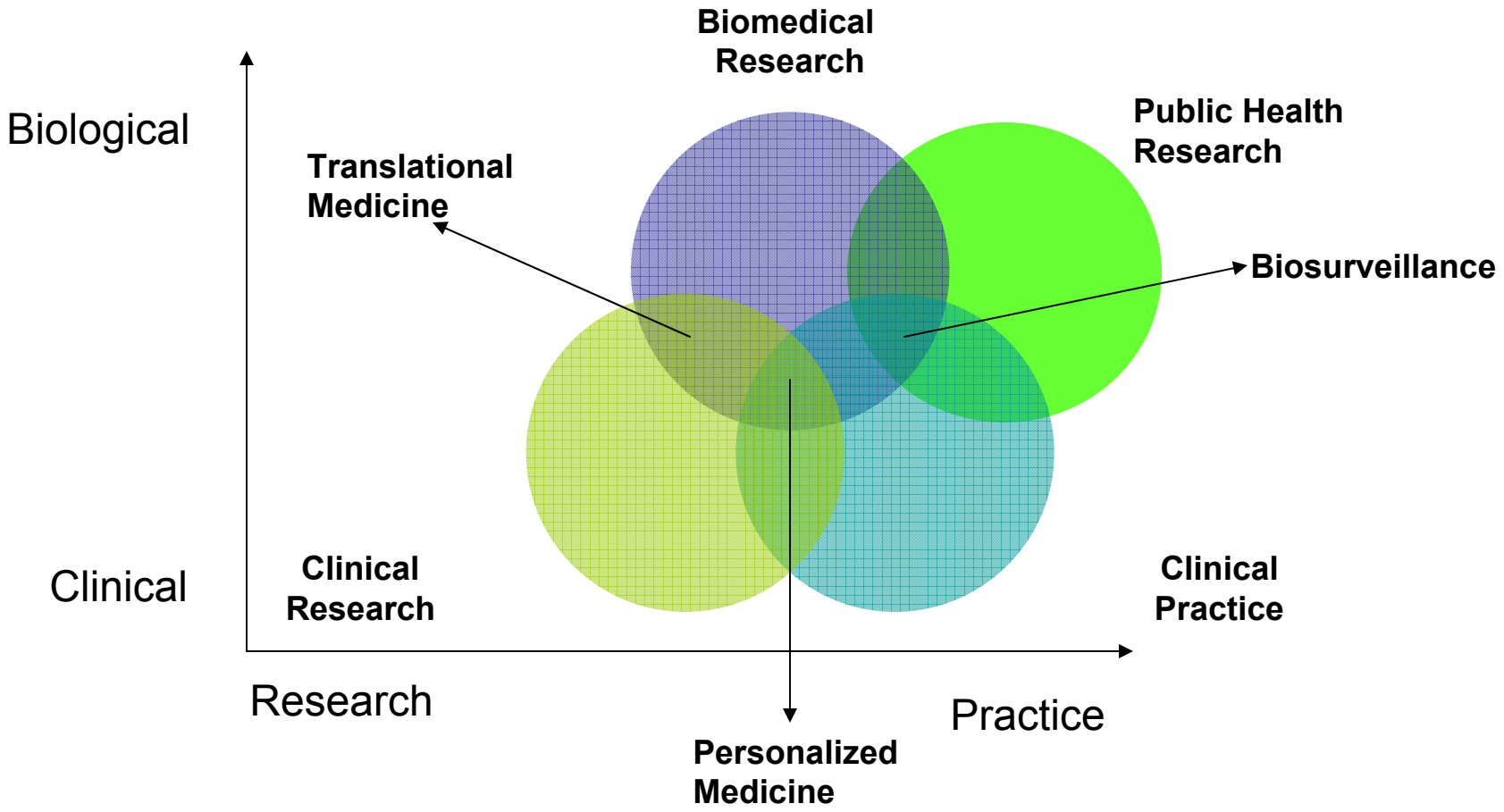
# Outline

- The Bench ↔ Bedside Vision ☑
- Role of Data, Knowledge and Semantics in the HCLS Ecosystem
- Functional Requirements
  - Metadata-based Semantic Annotation
  - *Recombinant Data:* Information Aggregation and Integration
  - Ontology-driven Decision Support
  - Knowledge Update and Maintenance
- Conclusions

# The Bench ↔ Bedside Vision

- Healthcare and Life Sciences: Framework ☑
  - An Information/Knowledge Perspective
- Current Challenges
- The Healthcare Life Sciences (HCLS) Ecosystem
- HCLS Ecosystem: Business Drivers

# Healthcare and Life Sciences: Framework



# HCLS Framework: Biomedical Research

- Systems Biology/Physiology
  - Organism as an integrated an interacting network of genes, proteins and biochemical reactions
  - Human body as a system of interacting organs
- Molecular Cell Biology/Genomic and Proteomic Research
  - Gene Sequencing, Genotyping, Protein Structures
  - Cell Signaling and other Pathways
- Biomarker Research
  - Discovery of genes and gene products that can be used to measure disease progression or impacts of drugs on patients
- Pharmaco-genomics
  - Impact of genetic inheritance on effects of drugs on patients
- Drug Discovery and Translational Research
  - Use of preclinical research to identify promising drug candidates

# HCLS Framework: Clinical Research

- Clinical Trials
  - Determination of efficacy, impact and safety of drugs for particular diseases
- Pharmaco-vigilance/ADE Surveillance
  - Monitoring of impacts of drugs on patients, especially safety and adverse event related information
- Patient Cohort Identification and Management
  - Identifying patient cohorts for drug trials is a challenging task
- Translational Research
  - Test theories emerging from pre-clinical experimentation on disease affected human subjects
- Development of EHRs/EMRs for both clinical research and practice
  - Currently EHRs/EMRs focussed on clinical workflow processes
  - Re-using that information for clinical research and trials is a challenging task

# Clinical Practice

- Electronic Medical/Health Record
  - Integration of Structured and Unstructured Information
  - Design of EHRs/EMRs for both clinical research and practice
- Computerized Physician Order Entry
  - Computerized aids for submitting medication and lab orders
- Clinical Disease Support
  - Physican perpective:
    - Therapeutic Decision Support, Drug Drug Interactions
- Structured Clinical Documentation
  - Templated forms to aid structured observation capture and storage into the electronic medical record
- Enterprise Terminological Services
  - Standardization of definitions and codes for conditions, findings, observations, labs, therapies, diagnoses, etc.
- Disease Management
  - Portals containing information relevant to a particular disease condition, e.g., diabetes
- Personalized Medicine
  - Personalizing therapeutic recommendations based on genetic profile of patient

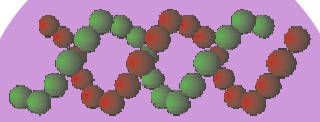
# Public and Consumer Health

- Epidemiology/Bio-surveillance
  - Monitoring of disease occurrences for unusual patterns
  - Indicative of epidemics, terrorist attacks
- Bio-sensors
  - E.g., detection of cancer causing agents in ground water (ORNL)
- Consumer Health Portals
  - Health Information Prescription
  - Electronic Prescription
- Disease Management
  - Portals containing reminders and alerts for patients for upcoming physicals, labs, etc.
- Personalized Health Records
  - Presentation of patient health related information in a language understandable to the lay person
- Clinical Decision Support:
  - Patient Perspective – help in choosing a good doctor
  - Population perspective – help deploy appropriate resources in appropriate areas

# A Convergence of Need (CLEF)


Management & Policy


Evidence based health care



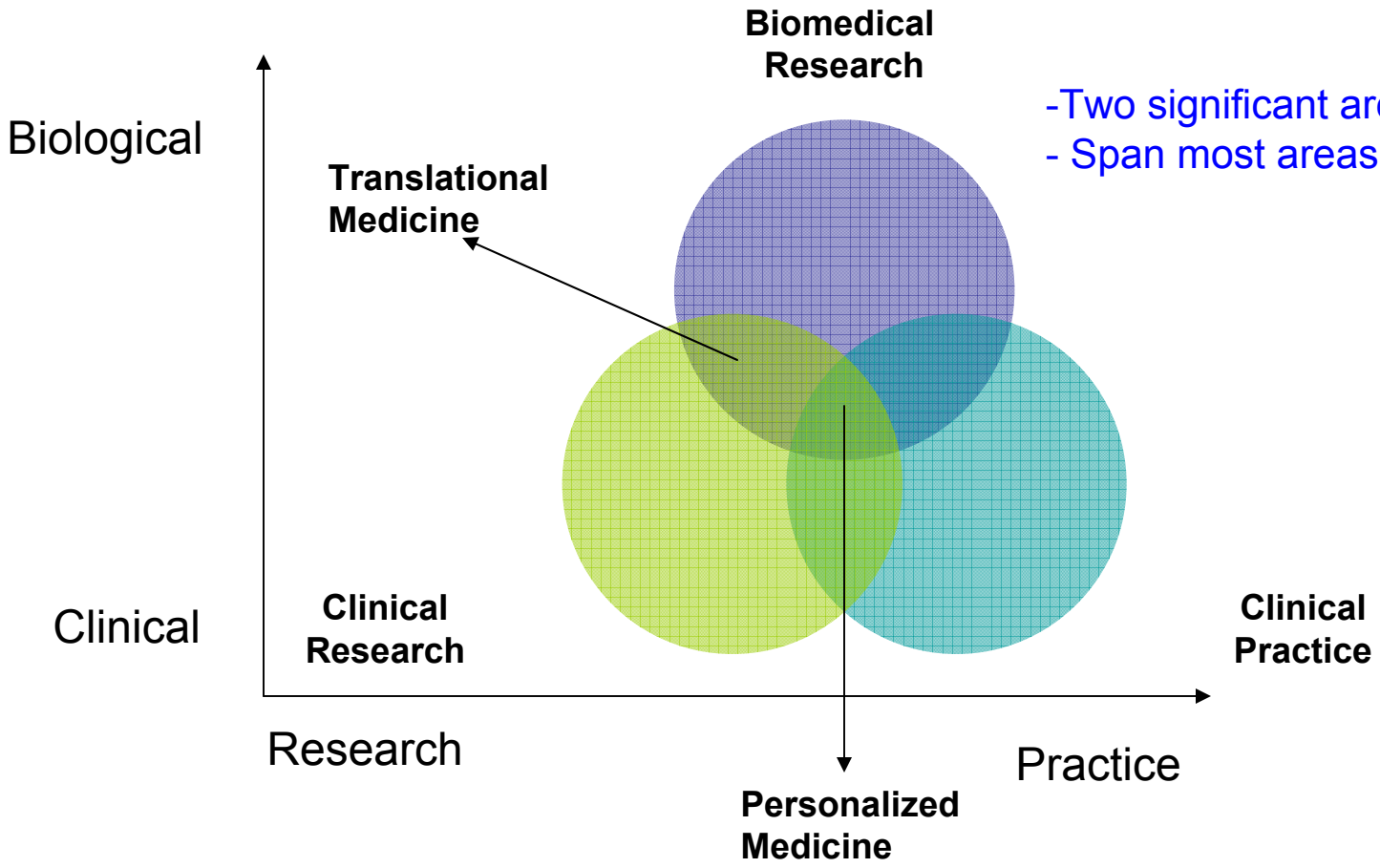
Post genomic research

**Need for more and better clinical information**

Clinical Practice, Audit & Governance

Clinical trials recruitment

# Translational Research and Personalized Medicine




-Two significant areas of HCLS activity
- Span most areas of activity

# Translational Research

- Improve communication between basic and clinical science so that more therapeutic insights may be derived from new scientific ideas - and vice versa.
- Testing of theories emerging from preclinical experimentation on disease-affected human subjects.
- Information obtained from preliminary human experimentation can be used to refine our understanding of the biological principles underpinning the heterogeneity of human disease and polymorphism(s).
- http://www.translational-medicine.com/info/about
- NIH Roadmap activity
  - http://nihroadmap.nih.gov

# Personalized Medicine

- Propagation of insights from Genomic research into clinical practice

- Impact of new Molecular diagnostic tests hitting the market
  - How can they be incorporated into clinical care?
  - How does one update current clinical guidelines to incorporate the use of these tests
  - How can one enable novel clinical decision support?

- How can phenotypic characteristics and genomic markers be used to:
  - Stratify patient populations
  - “Personalize” clinical care
    - Genetic test results as risk factors
    - Therapeutic use of genomic markers

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- Current Challenges ☑
- The Healthcare Life Sciences (HCLS) Ecosystem
- HCLS Ecosystem Business Drivers

Hygieia, G. Klimt

# Healthcare and Life Sciences: Current Challenges

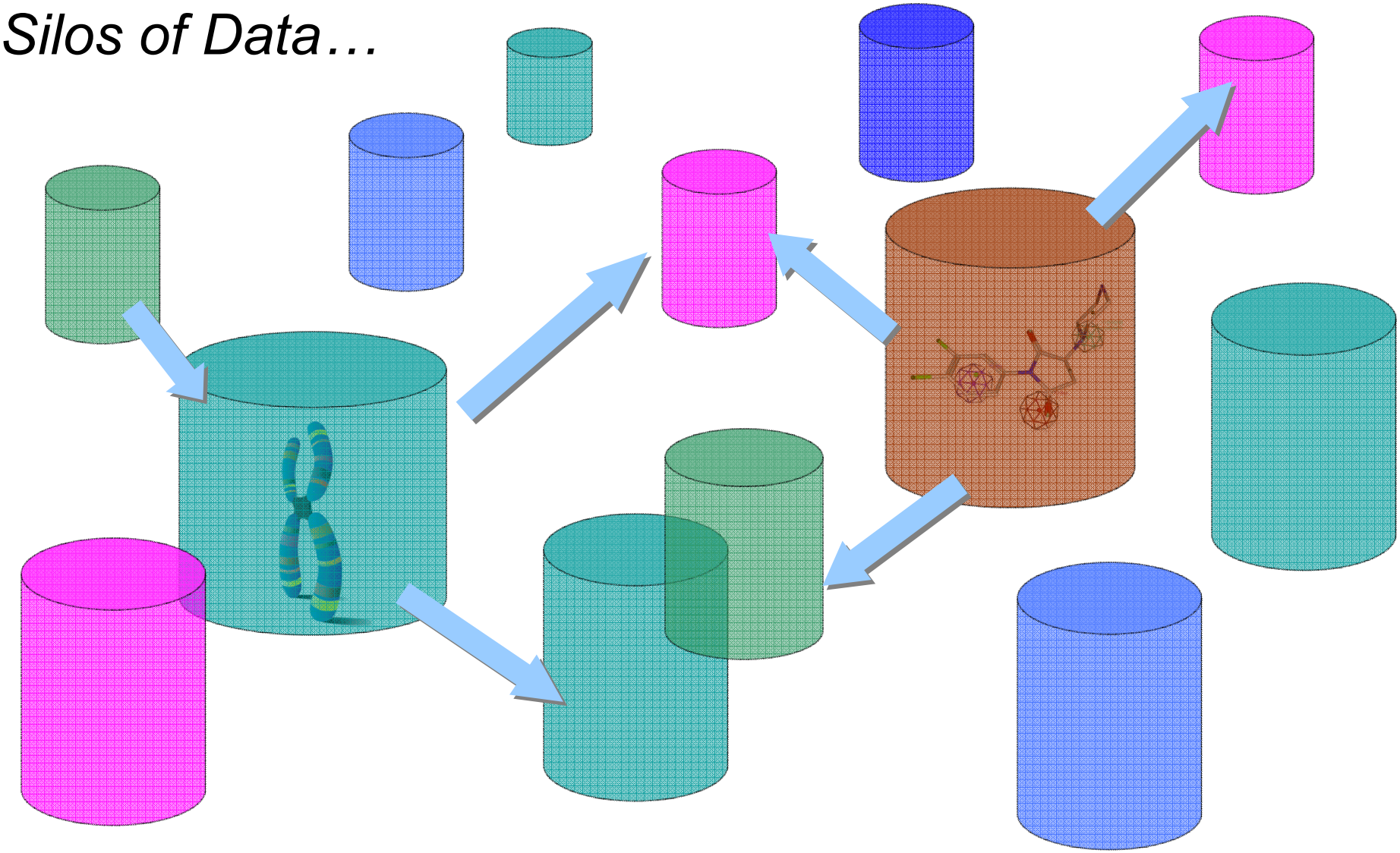
- *Health*
- *Practice*
- *Safety*
- *Prevention*
- *Knowledge*

# Current Challenges: Biomedical Research

- Bridging between the genome and phenome
- Integrating information across medical specialties, across model organisms, between biological and clinical
- Lack of Data/Knowledge Provenance, Rich Annotations
- Lack of creation, management and inferencing with biomarker evidence.
- Drug Discovery Process
  - How to break away from current “Conveyor Belt Model” and adopt the “Translational Research Model” gaining and sharing insights throughout the process
  - Issues related to safety, efficacy and adverse event detection do not seem to have the attention of the biomedical research community

# Distributed Nature of R&D

*Silos of Data…*



# Current Challenges: Clinical Practice

- Medical literature doubling every 19 years
- 2 Million facts needed to practice
- Limited decision support functionality implemented by current vendor products
  - A typical drug order recommendation, accounts for, at best, Age, Weight, Height, Labs, Other Active Meds, Allergies, Diagnoses
- There are 3000+ molecular diagnostic tests on the market, genomics and personalized medicine will increase the speed of change of evidence exponentially

Covell DG, Uman GC, Manning PR.
Ann Intern Med. 1985 Oct;103(4):596-9

# Current Challenges: Clinical Decision Support

- How do we supply meaningful decision support that both improves quality of care for patients and quality of life for clinicians (and self-managing patients)?
- How do we implement scalable decision support in presence of a large number of decision variables to be introduced by genomic knowledge?
- How do we affordably develop, acquire and maintain the knowledge bases required to deliver meaningful decision support?
- How do we adapt to ever changing clinical knowledge and incorporate new knowledge into clinical decision support knowledge bases?

# Current Challenges: Clinical Knowledge Management

- The rate of change for contraindication definition today is very slow, yet it's a challenge for most EHRs to provide decision support for contraindication or indication management
- With the advent of molecular medicine, this rate of change could become more rapid, possibly daily
- Change in a contraindication definition can lead to changes in associated clinical decision support rules, order sets and templates and other related content areas.
- How does one create knowledge editing tools and software infrastructure that can be used by subject matter experts, knowledge engineers and informaticians to rapidly create and manage different types of clinical knowledge?

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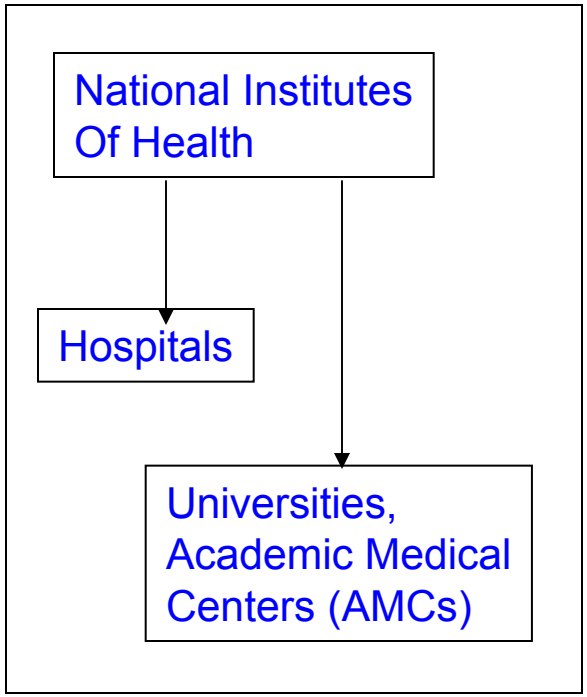
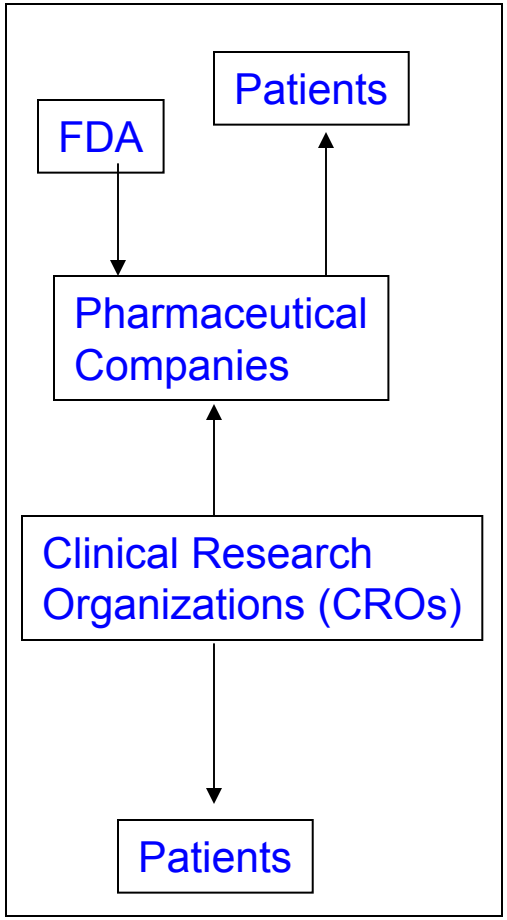
# Ecosystem: Current State

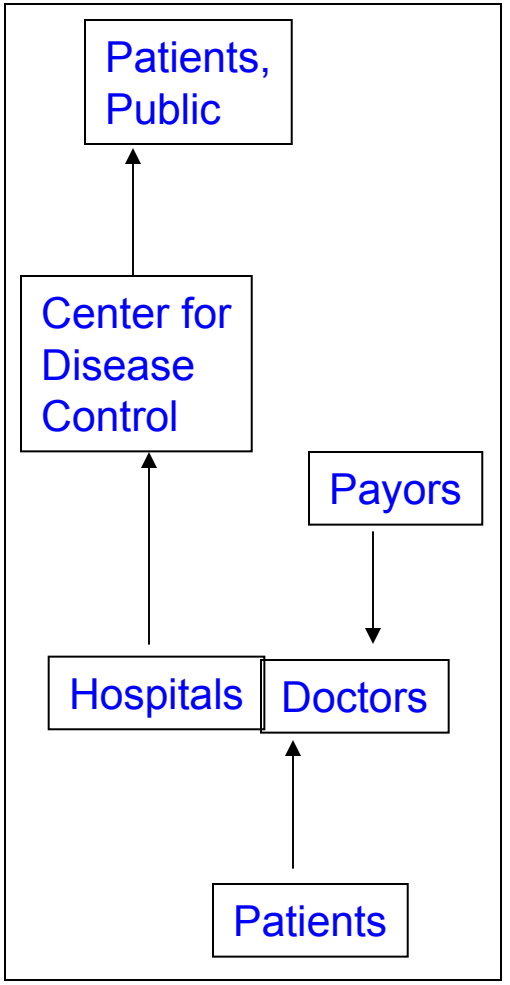
Characterized by silos with uncoordinated supply chains leading to inefficiencies in the system




Biomedical Research
Clinical Practice

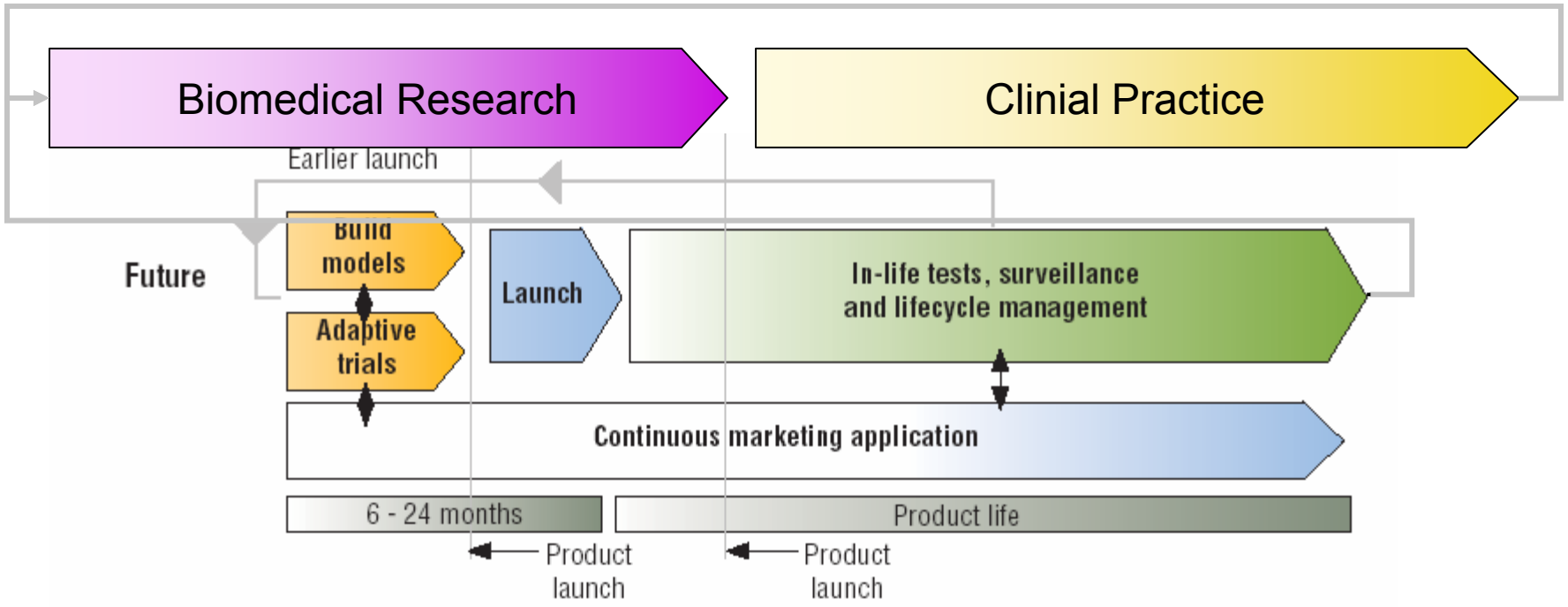



Clinical Trials/Research

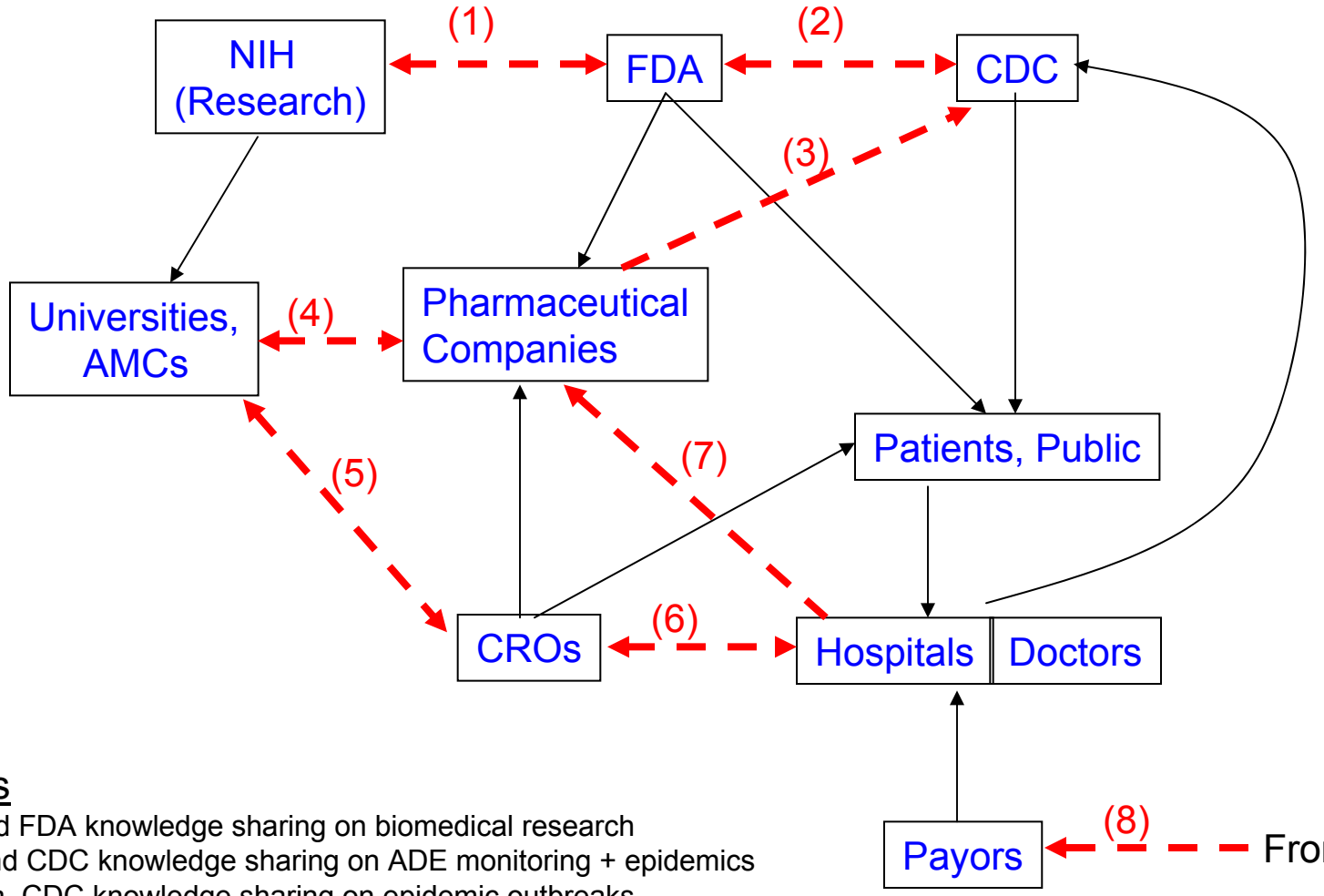



Clinical Practice

# Ecosystem: Goal State



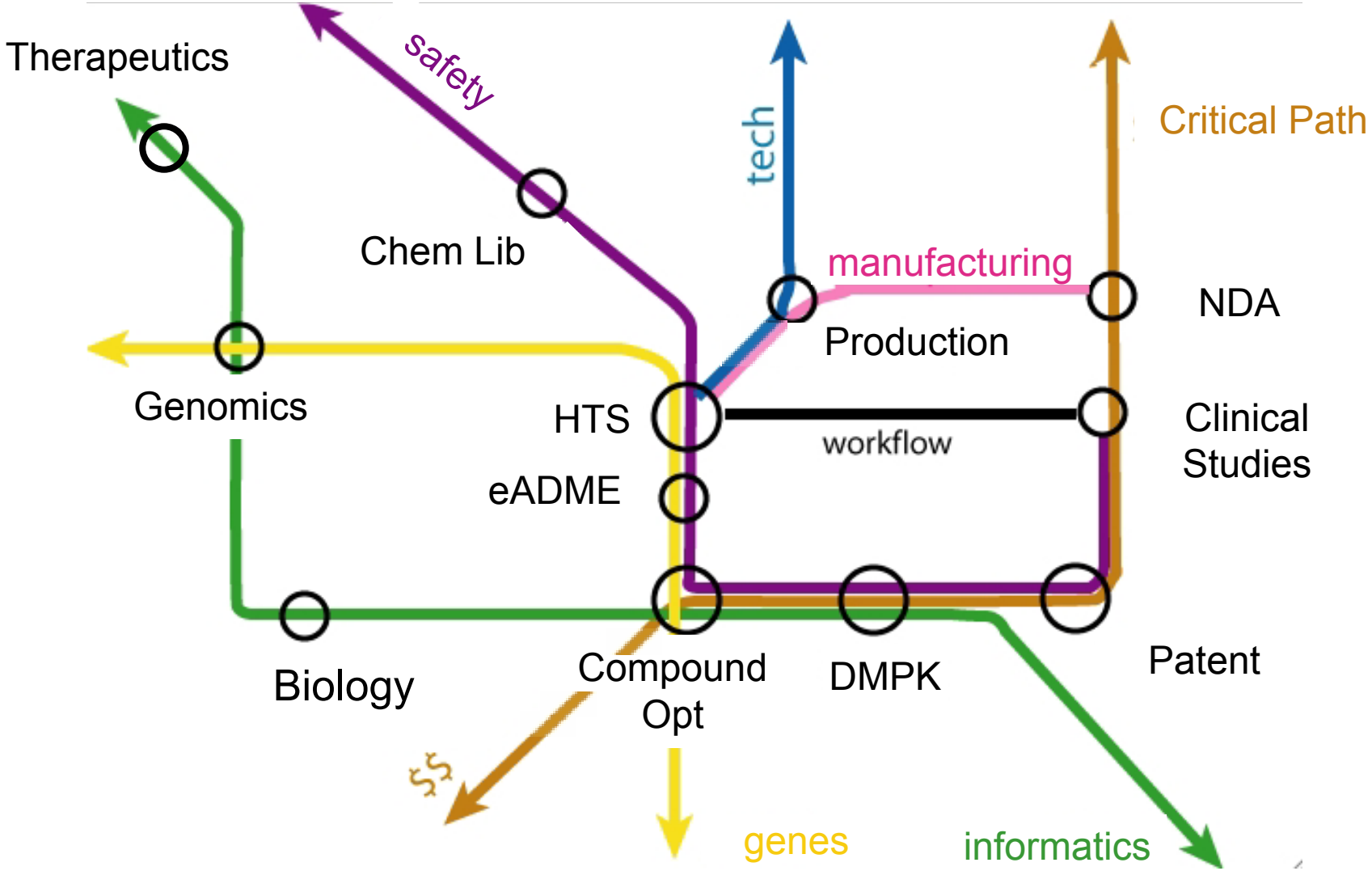
# Ecosystem: Goal State




## Synergies

(1) NIH and FDA knowledge sharing on biomedical research
(2) FDA and CDC knowledge sharing on ADE monitoring + epidemics
(3) Pharma, CDC knowledge sharing on epidemic outbreaks
(4) AMCs, Pharma knowledge sharing on clinical and biomedical research
(5) Universities/AMCs, CROs knowledge sharing on clinical resarch and trials
(6) CROs, Hospitals knowledge sharing on identifying patient cohorts
(7) Pharma, Hospitals knowledge sharing on post market drug surveillance
(8) Payors get information regarding new conditions, drug efficacies from FDA and CDC

# Drug Discovery Application Space



# Roadmap

- Need to support a “virtual” view of Goal Ecosystem State.
  - Alignment of key players unlikely
- Need to enable rapid and precision information and knowledge sharing across all players in the Ecosystem.
- Ability to characterize information flows and enable “semantic” standards to achieve this
- Potential role for semantic web technologies
- Governmental Initiatives
  - NIH Roadmap Initiative
  - FDA Critical Path

IMPACT: Likely to leverage efficiencies of operation and scale across the HCLS Ecosystem.

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# Ecosystem: Economic, Business and Social Drivers

- Biomedical Research
  - Strong public sector funding for long term research initiatives
- Drug Discovery + Clinical Trials
  - Costly, lengthy, siloized process
  - Lack of economic drivers for certain disease areas
  - Increased spending has corresponded to lesser number of submissions to FDA.
  - Need for data and guidelines to drive adoption of new diagnostic tests in the market and support from payors
- Healthcare
  - Delay in Innovation Adoption
    - Consequent impacts on Patient Safety and Quality of Care
  - Patient Safety: Impact of Medical Errors
  - Pay for Performance
  - Economic and Patient Safety Impacts of Rapid Knowledge Change
  - Electronic Health Record: National  Initiative (NHIN, NHS)

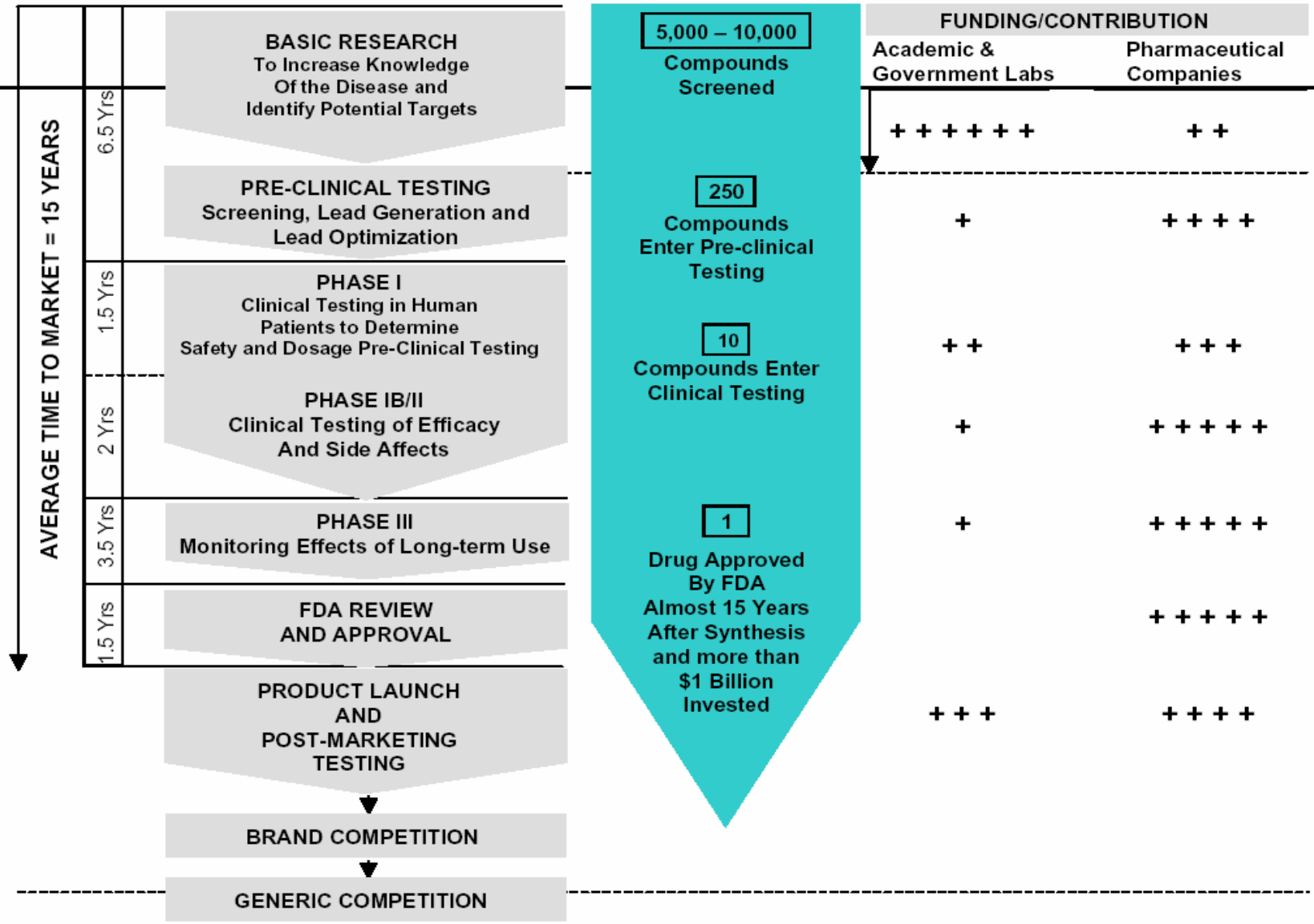
# Biomedical Research: Socio-Economic Drivers

- NIH Funding Initiatives
  - Program Announcements (PAs) that seek to initiate new programs of research in various disease and translational areas
  - Request for Applications (RFAs) touching on various fields of biomedical and clinical research typically within the context of a program
  - SBIR/STTR: Small Business, Technology Transfer grants
  - Types of Grants
    - R01: PI Lead Research Grant
    - R03: Small Research Grant
    - R21: Exploratory Research Grant
    - R34: Clinical Trial Planning Grant
    - R56: High Priority, Short Term Project Grant
- Other Funding Agencies: AHRQ, DoD, DoE, Other Foundations
- Sample Funding Opportunities
  - “Innovations in Biomedical Computational Science and Technology”
  - “Translational Research in the Social Neuroscience of Mental Health”

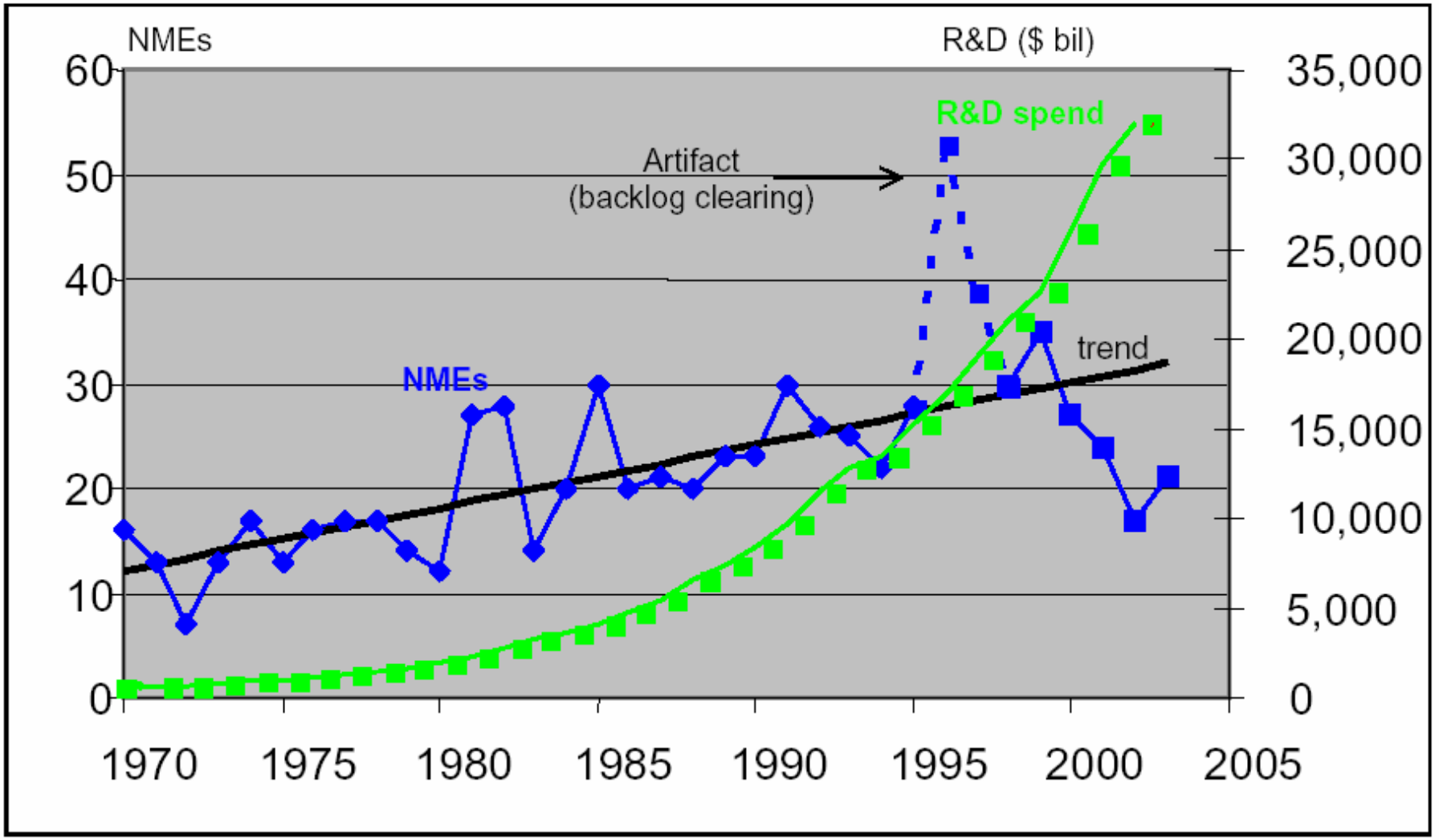
# Drug Discovery: Economic Drivers

- Need to find new uses for existing therapies, e.g., antibiotics
- Insufficient economic drivers for certain disease areas
- Post-market surveillance is weak
- Higher spending on Biomedical Research doesn't translate into larger number of drug and biological product submissions
- Increase in investment required for a successful drug launch
- Need for better data and guidelines for using molecular diagnostic tests, e.g., Roche P450 test

# Business Drivers: How Medicines make it to the Market

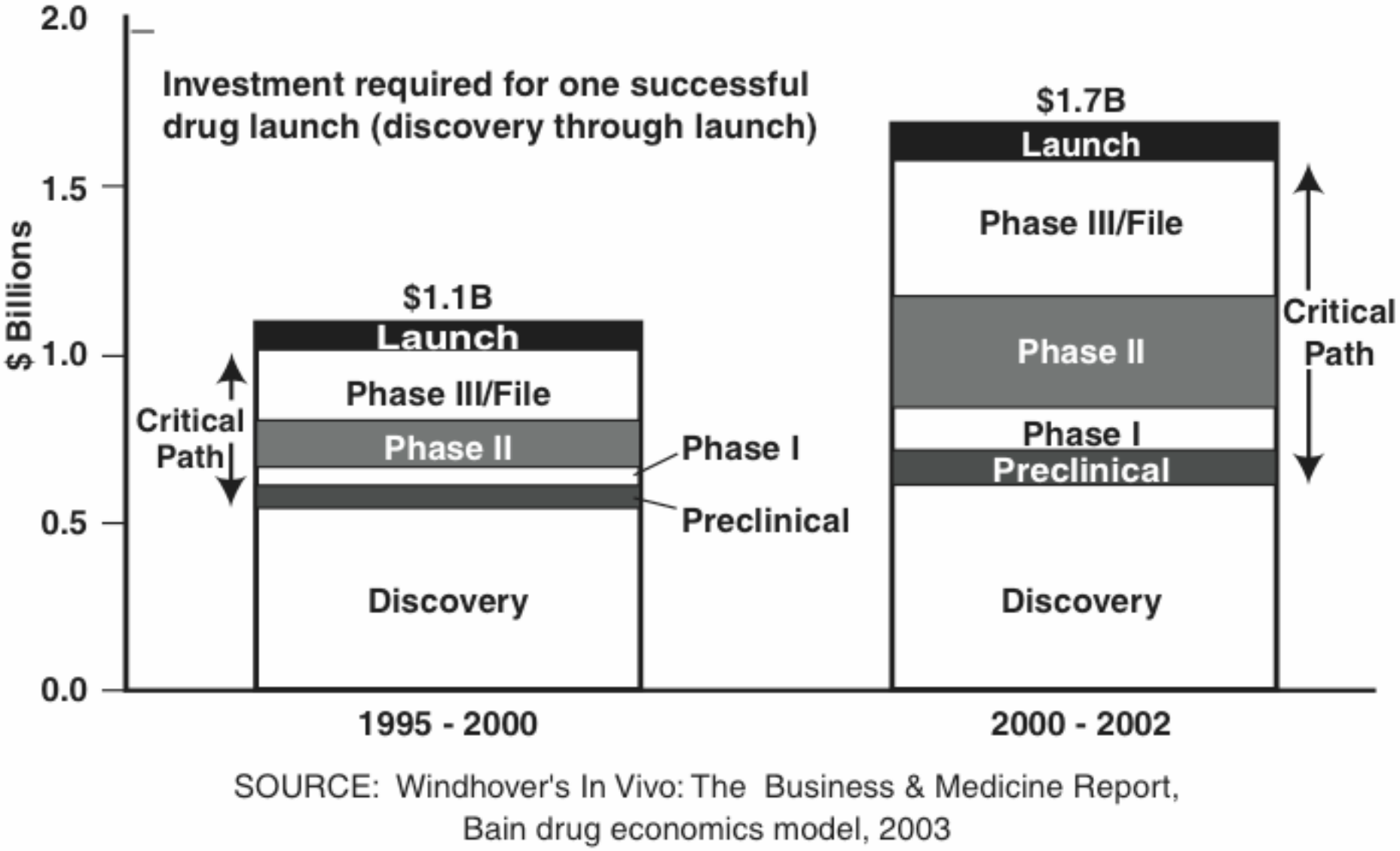


# The Pharma R&D Productivity Conundrum




*Source: FDA and PhRMA*

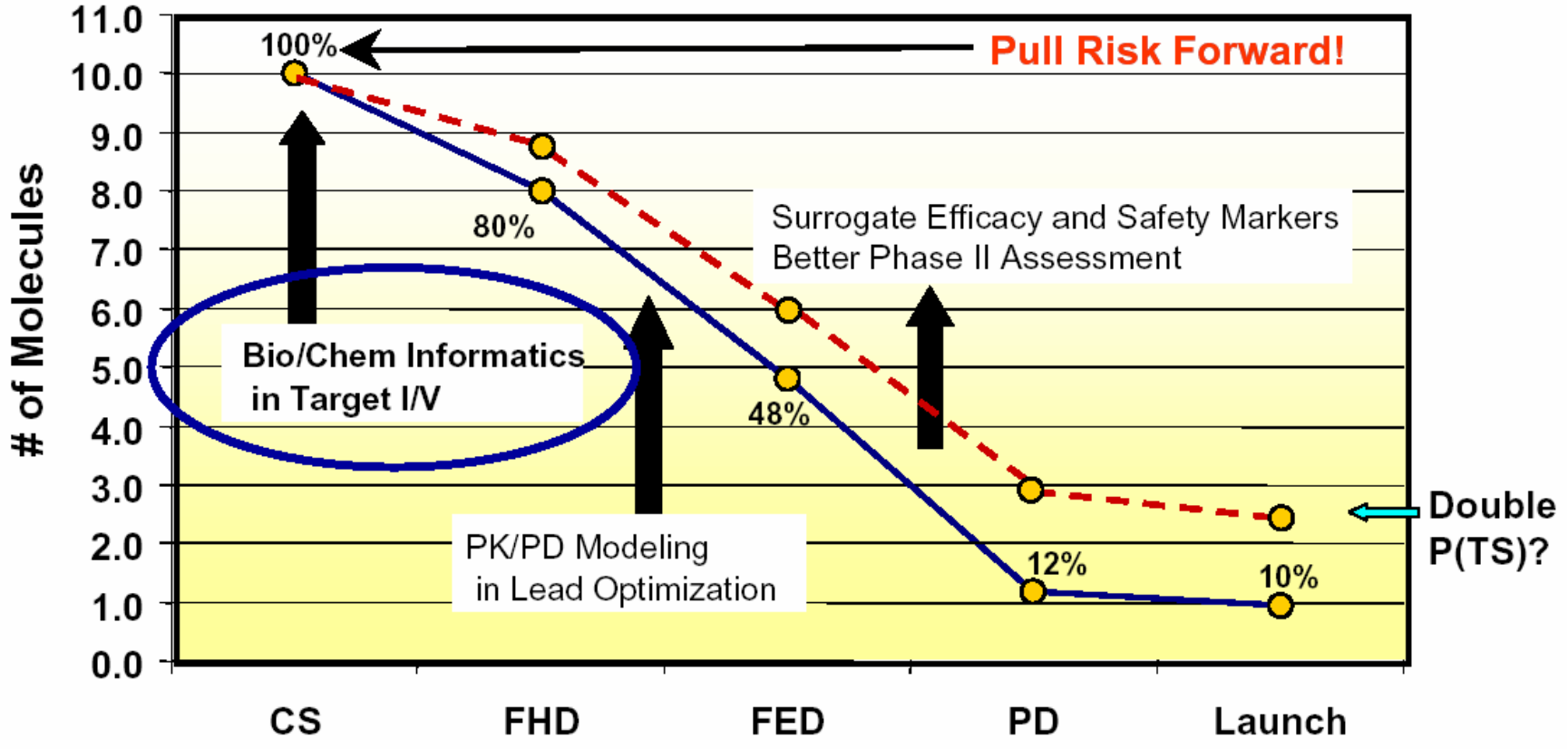
# Business Drivers: Drug Discovery




SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

from *Innovation or Stagnation*, FDA Report March 2004

# Reducing the Development Attrition Curve



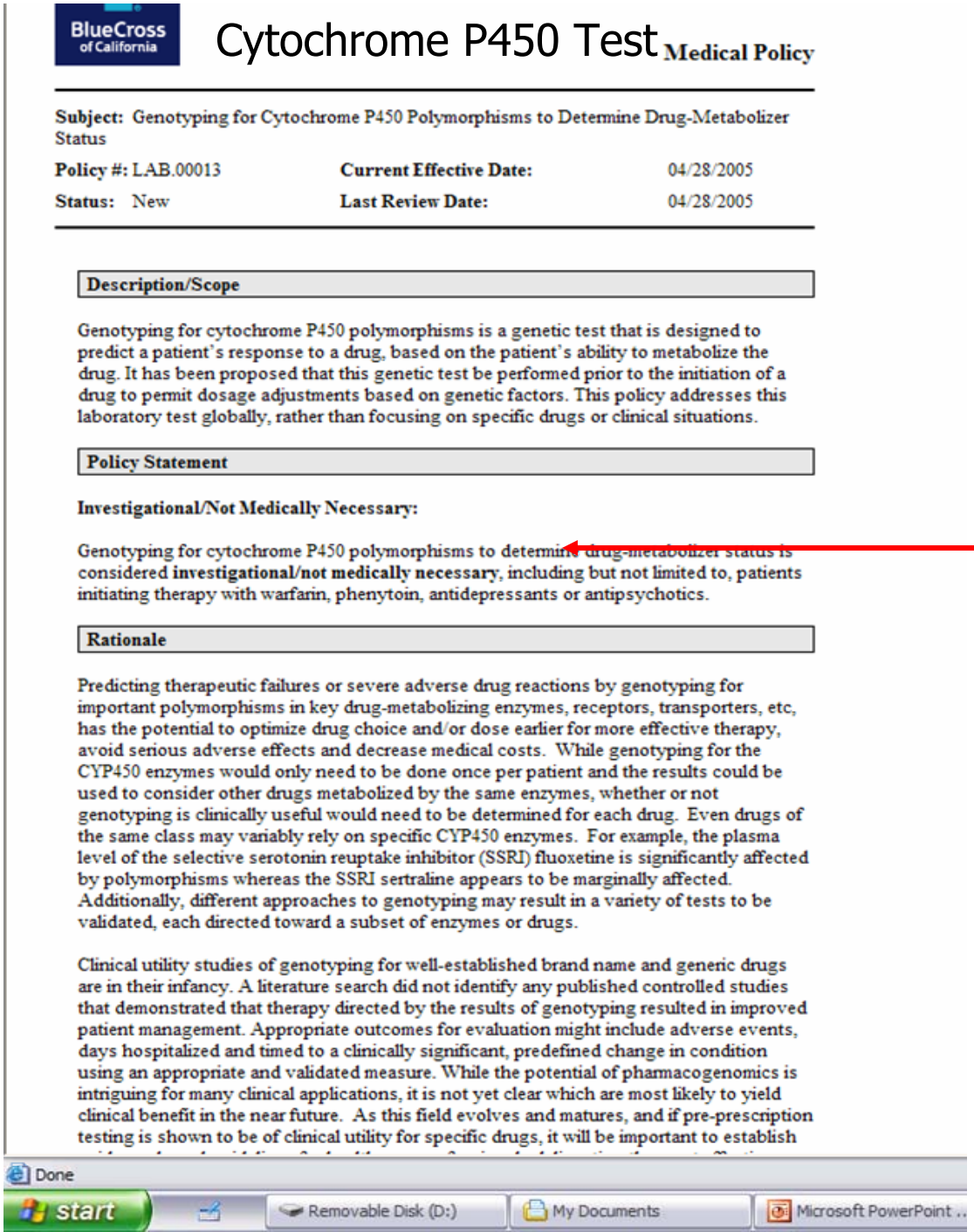
# Drug Discovery: Business Drivers

**The Cytochrome P450 test…**
**new data to drive drug choice and dose**
**When do you order this test?**
**How do you use the test result?**

WSJ.com THE WALL STREET JOURNAL. ONLINE

## Leading the News: Roche Test Promises to Tailor Drugs to Patients --- Precise Genetic Approach Could Mean Major Changes In Development, Treatment

June 25, 2003
Roche Holding AG is launching the first gene test able to predict how a person will react to a large range of commonly prescribed medicines, one of the biggest forays yet into tailoring drugs to a patient's genetic makeup.
The test is part of an emerging approach to treatment that health experts expect could lead to big changes in the way drugs are developed, marketed and prescribed. For all of the advances in medicine, doctors today determine the best medicine and dose for an ailing patient largely by trial and error. The fast-growing field of "personalized" medicine hopes to remove such risks and alter the pharmaceutical industry's more one-size-fits-all approach in making and selling drugs.



BlueCross of California

# Cytochrome P450 Test Medical Policy

**Subject:** Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-Metabolizer Status

**Policy #:** LAB.00013 **Current Effective Date:** 04/28/2005

**Status:** New **Last Review Date:** 04/28/2005

## Description/Scope

Genotyping for cytochrome P450 polymorphisms is a genetic test that is designed to predict a patient's response to a drug, based on the patient's ability to metabolize the drug. It has been proposed that this genetic test be performed prior to the initiation of a drug to permit dosage adjustments based on genetic factors. This policy addresses this laboratory test globally, rather than focusing on specific drugs or clinical situations.

## Policy Statement

**Investigational/Not Medically Necessary:**

Genotyping for cytochrome P450 polymorphisms to determine drug-metabolizer status is considered **investigational/not medically necessary**, including but not limited to, patients initiating therapy with warfarin, phenytoin, antidepressants or antipsychotics.

## Rationale

Predicting therapeutic failures or severe adverse drug reactions by genotyping for important polymorphisms in key drug-metabolizing enzymes, receptors, transporters, etc, has the potential to optimize drug choice and/or dose earlier for more effective therapy, avoid serious adverse effects and decrease medical costs. While genotyping for the CYP450 enzymes would only need to be done once per patient and the results could be used to consider other drugs metabolized by the same enzymes, whether or not genotyping is clinically useful would need to be determined for each drug. Even drugs of the same class may variably rely on specific CYP450 enzymes. For example, the plasma level of the selective serotonin reuptake inhibitor (SSRI) fluoxetine is significantly affected by polymorphisms whereas the SSRI sertraline appears to be marginally affected. Additionally, different approaches to genotyping may result in a variety of tests to be validated, each directed toward a subset of enzymes or drugs.

Clinical utility studies of genotyping for well-established brand name and generic drugs are in their infancy. A literature search did not identify any published controlled studies that demonstrated that therapy directed by the results of genotyping resulted in improved patient management. Appropriate outcomes for evaluation might include adverse events, days hospitalized and timed to a clinically significant, predefined change in condition using an appropriate and validated measure. While the potential of pharmacogenomics is intriguing for many clinical applications, it is not yet clear which are most likely to yield clinical benefit in the near future. As this field evolves and matures, and if pre-prescription testing is shown to be of clinical utility for specific drugs, it will be important to establish

Done

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- Payors won't pay for this test
- No data on it's value
- Worse, no knowledge base on how to use the test result
- No titration algorithms
- No substitution algorithms
- Test could be as ubiquitous as serum creatinine level for renal function
- Must plan for this in the early discovery process, not after it's on the market

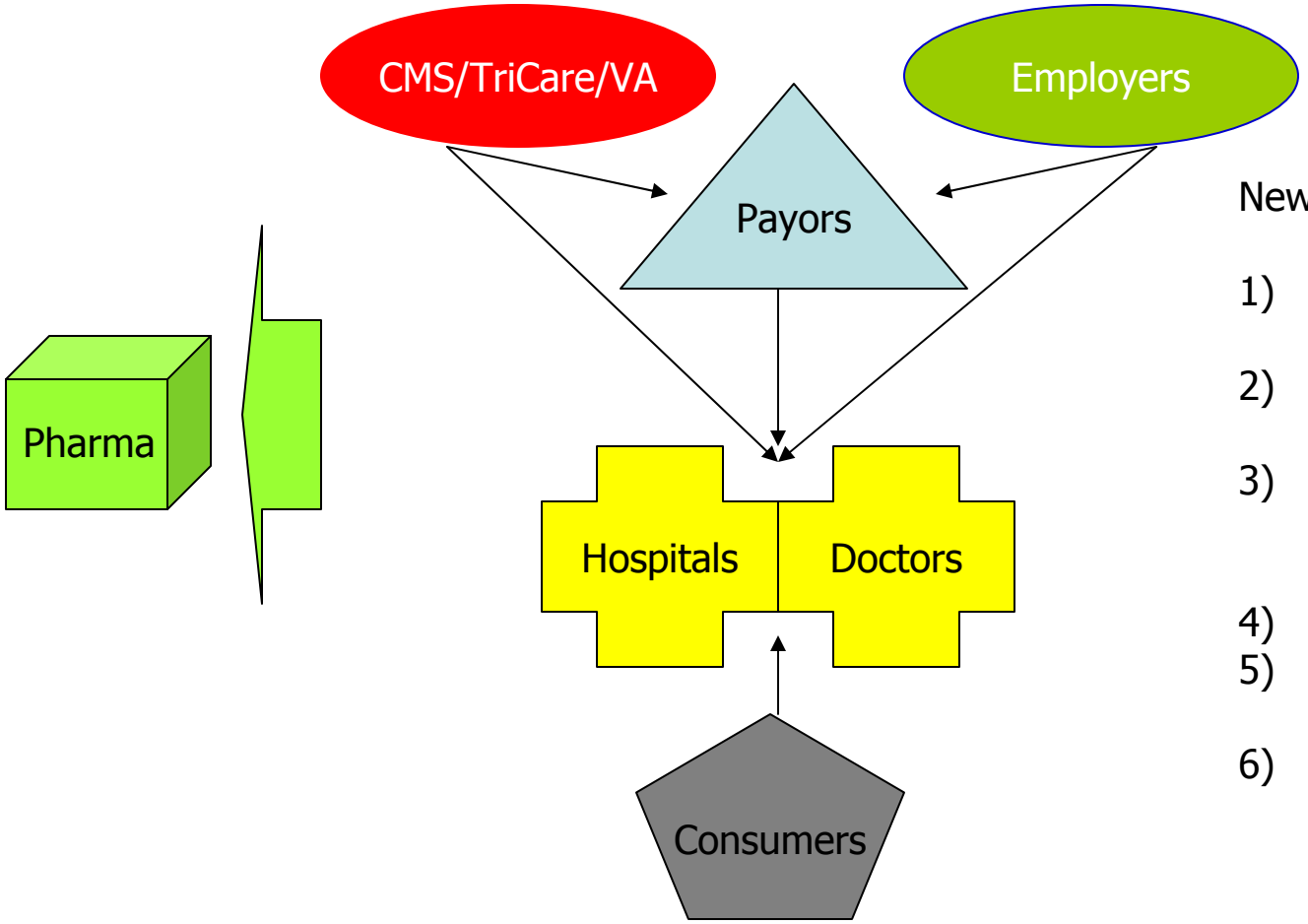
# Clinical Practice: Business Drivers

- As much as a 17 year innovation adoption curve from discovery into accepted standards of practice
- Patient safety is a big issue:
  - Even if a standard is accepted, patients have a 50:50 chance of receiving appropriate care, a 5-10% probability of incurring a preventable, anticipatable adverse event
- Healthcare inflation is an issue -- past market utilization management measures have not succeeded
- Economic and social costs of chronic diseases such as diabetes
- Quality measures drive reimbursement

# Clinical Practice: Patient Safety is an issue!


- Medical Errors kill between 44,000 and 98,000 people each year
- 7.3% of hospital admissions incur preventable medication errors
  - 66% of these were not intercepted
  - 25% resulted in patient harm
  - 360 preventable Adverse Drug Events for a hospital with 20,000 annual admissions, almost 1 ADE per day

# Clinical Decision Support: Business Drivers




New Healthcare Business Climate in the US:

1) Give consumers greater financial responsibility
2) Reduce Hospitalizations and cost per hospitalization
3) Increase quality performance – value based purchasing
4) Reduce drug expenditures
5) Reduce imaging study expenditures
6) Increase wellness/reduced sick days

# Clinical Practice: Business Drivers

Today's Globe Opinion Magazine Education Science NECN Special reports Obituaries

HOME > NEWS > LOCAL > MASS.

## State posts data on doctors

The Boston Globe

### Website provides surgery statistics

**By Liz Kowalczyk, Globe Staff | February 1, 2006**

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Today's Globe Opinion Magazine Education Science NECN Special reports Obituaries

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## Plan would tie copayments to doctors' rankings

The Boston Globe

### Lower fee for using 'best value' physicians

**By Jeffrey Krasner, Globe Staff | January 27, 2006**

The agency that oversees health insurance for 144,000 state workers wants to launch a program to control runaway healthcare expenses: a ranking of doctors' quality and efficiency that would be tied to lower copayments for patients who seek care from higher-rated doctors.

The Group Insurance Commission this morning will examine proposals it requested from Harvard Pilgrim Healthcare, Tufts Health Plan, Health New England, Fallon Community Health Plan, and other insurance companies. A key feature of each proposal is variable copayments. For example, under the Harvard Pilgrim and Tufts scenarios patients would pay $15 to visit a doctor who is rated highly and $25 to see one with a lower rating.

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Dolores L. Mitchell, executive director of the commission, said ranking doctors would be an important step toward making medical care more transparent and keeping premiums down.

"We're saying to our members, these specialty doctors and primary-care physicians represent the best value, and we'll reward you if you use them," Mitchell said.

But many of the state's physicians oppose the idea, saying there is no widely accepted measure of quality care or efficiency. They also warn about the risks of adopting a new program with such a large group of beneficiaries without first conducting pilot studies.

- Employers and consumers are now paying for performance
- They will not wait for the data to be right or fair because they believe if they wait, it never will be
- Instead, they are using the process of rewarding performance to force the healthcare providers to "make the data right"
- Defined Contribution lays even greater purchasing responsibility at the door of the consumer
- Pay for performance and defined contribution will increase EHR adoption

# Business Drivers: EMR

- Pay for performance will provide motivation for capturing and storing accurate data
  - Will “force” the providers to make the data “right”
  - EMRs will provide a cost-effective tool for this
- Need for computing quality measures that will drive reimbursment
- Provides the substrate for implementing decision support
- Socio-governmental driver: Federal Government initiatives and incentives
  - NHIN effort in the US
  - NHS modernization in the UK

# Diabetes: Economic and Social Impacts

- Epidemic, associated with obesity
- Estimated avg $21,000/year per diabetic employee in absenteeism, disability and medical costs (study of 6 employers with 375,000 employees)
- Creation of Quality measures that drive reimbursment
  - Maintain HbA1c <7 (diet, oral agents and/or insulin)
  - If Renal Disease and no contraindication, should be on ACE inhibitor or ARB
  - If lipid disorder and no contraindication, should be on a statin like lipitor

# When Knowledge Changes…


Feb. 1, 2006 5:37pm

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Q&A: Understand Risks From Pain Relievers

To assist patients with the recall of one of the three COX-2 drugs yanked from the market, Merck offers the following information

E-MAIL THIS STORY | PRINTABLE VERSION

## Merck Yanks Vioxx From Shelves

NEW YORK, Sept. 30, 2004

(CBS/AP)

1 2 3

PREVIOUS IMAGE NEXT IMAGE

**(CBS/AP)** Vioxx, the blockbuster arthritis drug heavily promoted on TV and taken by tens of millions of people, was pulled from the market by its maker Thursday after a study found it doubled the risk of heart attacks and strokes.

Experts advised patients to immediately stop taking Vioxx and talk to their doctors about alternatives.

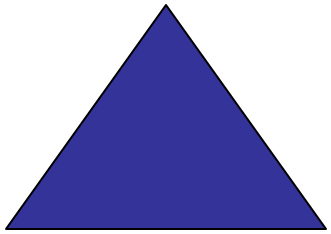
"Given the availability of alternative therapies, and the questions raised by the data, we

How quickly can you change the content of your rules, order sets, templates, and reports?

# CDS + Knowledge Acquisition: Business Drivers

**Clinical Standardization**

*Standards of Practice,*
*Role/Venue Requirements*
*Billing/Regulatory Requirements*



**Improvisation**

*Patient Preferences*

**User Personalization**

*End-user role, workflow preferences*
*Learning and User-defined*

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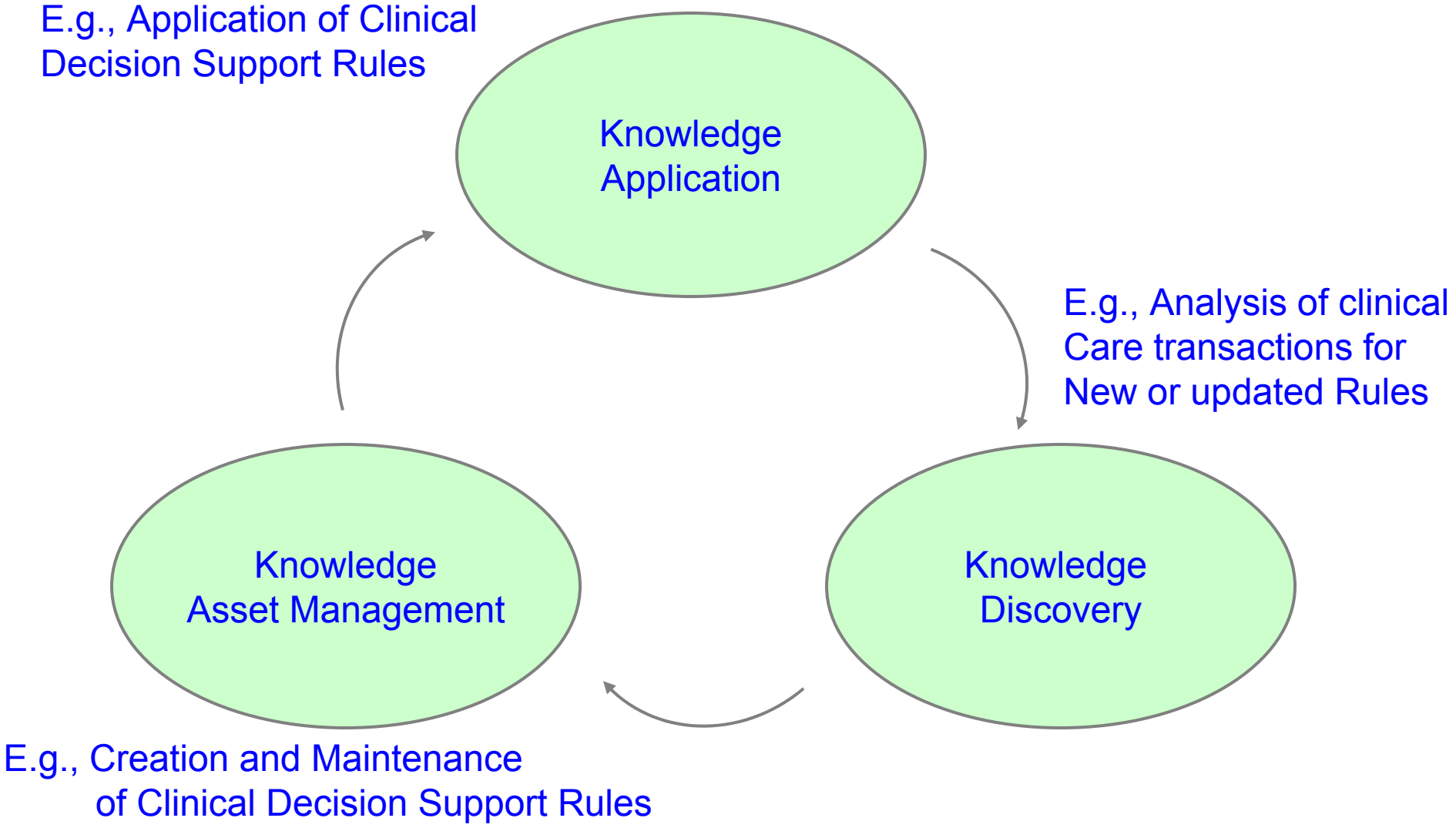
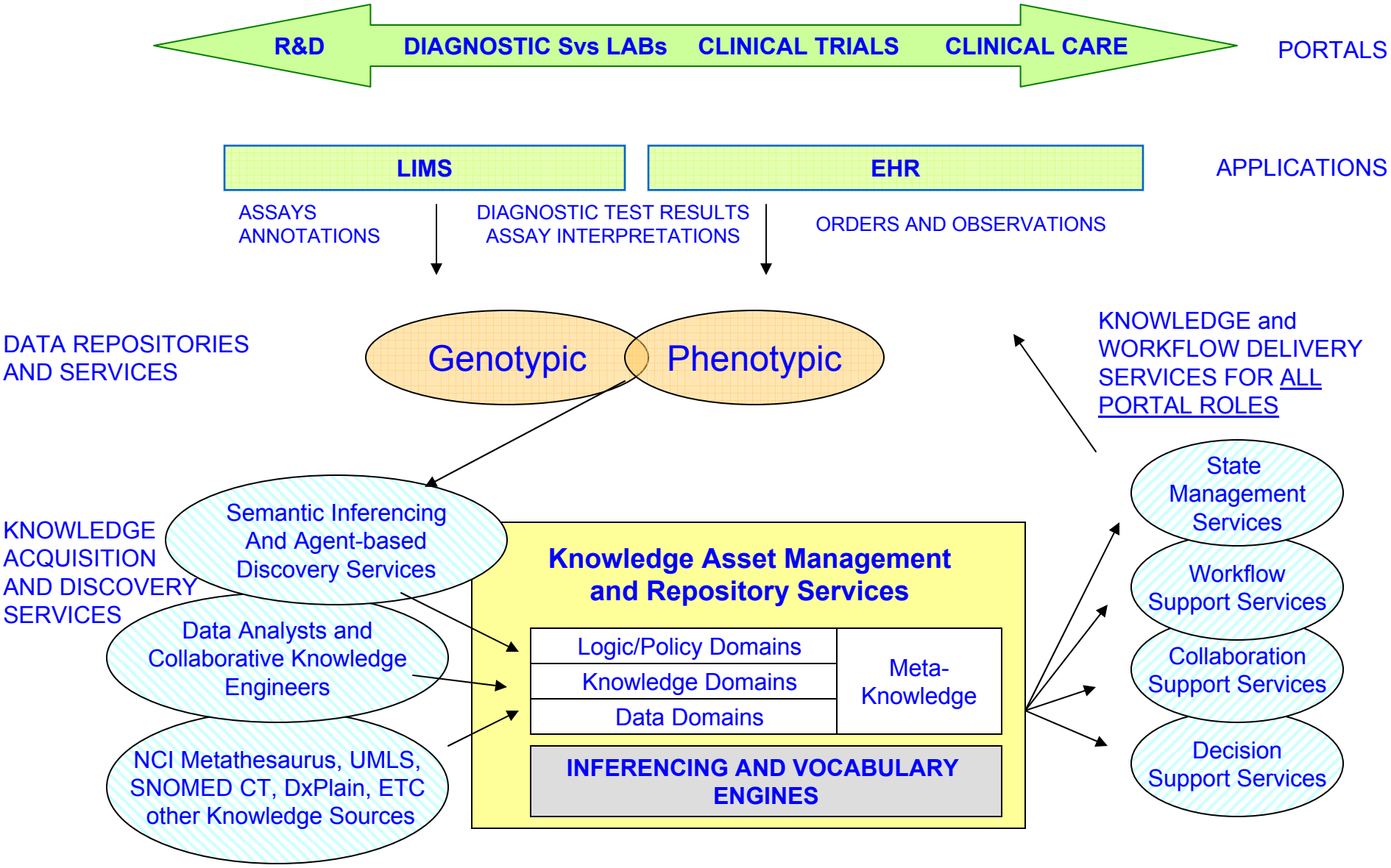
# Role of Data, Knowledge and Semantics in the HCLS Ecosystem

- Knowledge Feedback Loop
- Bench ↔ Bedside Vision:
  - Knowledge Dependent Architecture
  - Use Case Flows
    - Personalized Medicine
    - Drug Discovery and Development
- The Data Semantics Continuum
- The Knowledge Semantics Continuum

# HCLS: The Knowledge Feedback Loop



# Bench ↔ Bedside: Knowledge Dependent Architecture



# Bench ↔ Bedside:
# Use Case Flow based on Shared Semantics

*Patient Encounter*

**Personalized Medicine Decision Support Services and Knowledge Repository**

Test ordering and documentation guidance

Clinical Trials Referral

Structured Test Result Interpretations

**Tissue-bank**

Therapeutic ordering and documentation guidance

***Knowledge Acquisition, Discovery And Management Services for Clinical Care***

**Integrated Genotypic and Phenotypic Research Clinical Data Repository**

***R&D Discovery Services***

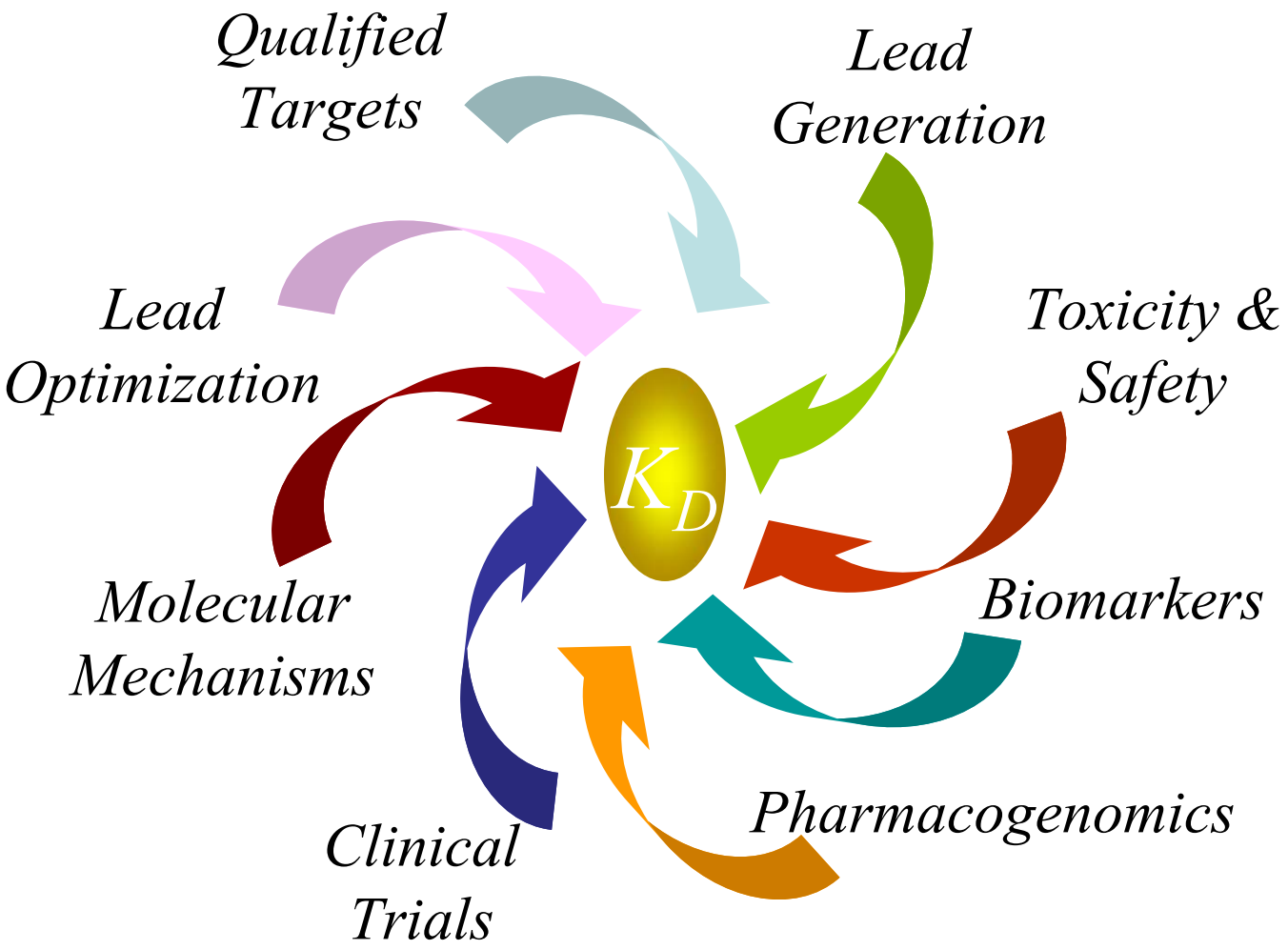
**Structured Research Annotations**

**Bench R&D**

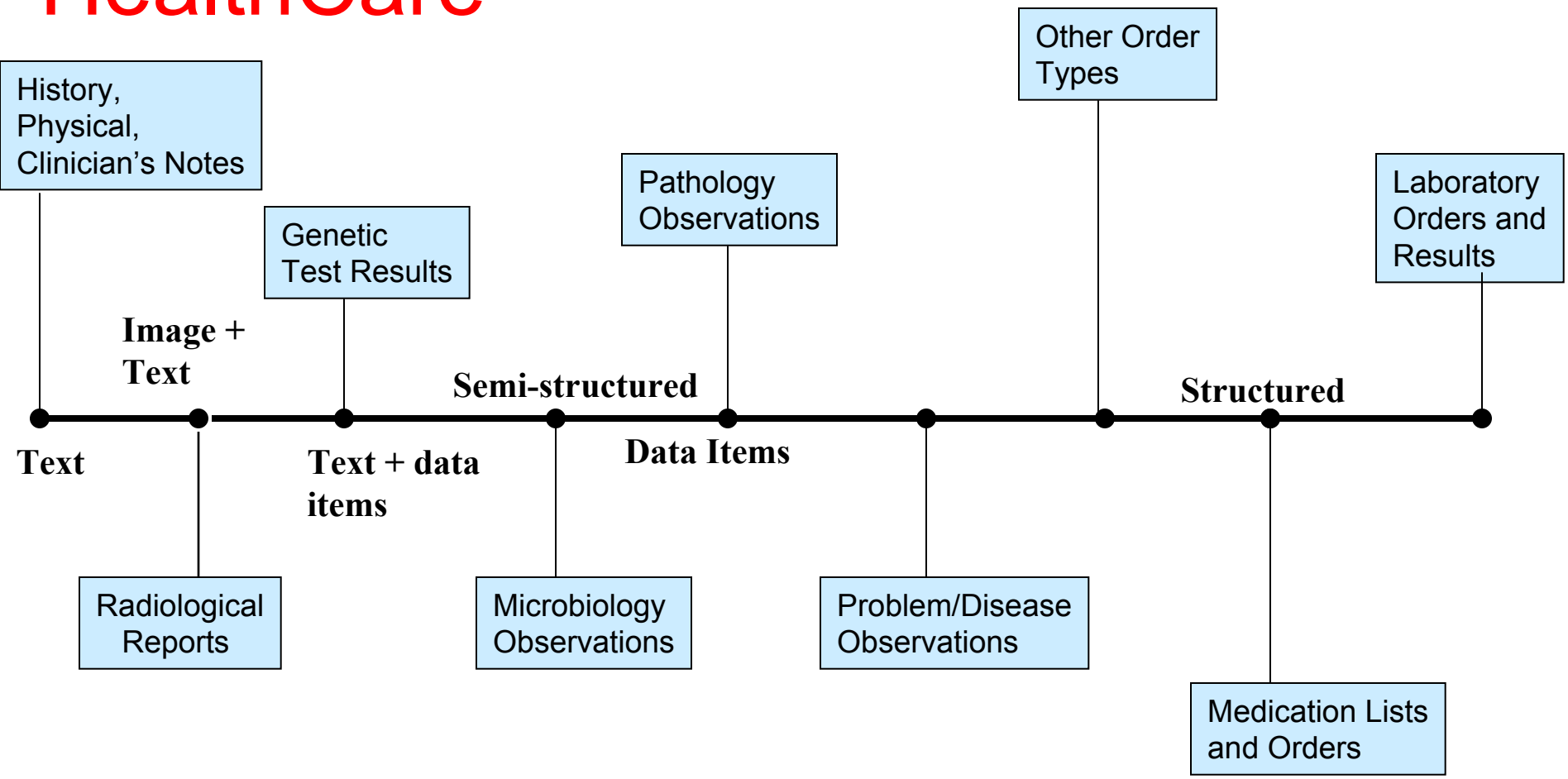
**Clinical Trials 1- 4**

**Pharmacovigilance**

# Use Case Flow:
# Drug Discovery and Development



# The Data Semantics Continuum: HealthCare



# Healthcare Data: Clinician Notes

HISTORY OF PRESENT ILLNESS: <X> had a fall on September, 15, bruised and cut her face and lip and required some sutures. A review of her laboratory tests reveals an albumin, creatinine ratio of 139 the test done in 06/04. She is currently on 75 mg of captopril and plans are to retest microalbumin. Again, revisit in three months. Nocturia one to two times nightly. She does have occasional paresthesias in her upper extremities.

MEDICATIONS: 500 mg of metformin one in the morning, one at noon and 1000 mg in the evening and Avandia 4 mg a day. In addition, to her captopril she is on Norvasc.

REVIEW OF SYSTEMS: No chest pain, shortness of breath, or cardiovascular symptoms at this time. She has not had her eyes examined for the past year and will make an appointment at the BI-Deaconess Medical Center.

PHYSICAL EXAMINATION: No change. Her weight is 223 pounds. Blood pressure 122/80, pulse 75 regular. Blood sugar this morning 121.

PLAN: Revisit in three months, continue medication.

_____

<Y>, M.D.

Dictated By: <Y>

eScription document:1-5763294 UF

DD: 10/05/04
DT: 10/05/04
DV: 10/05/04"

Mostly unstructured data divided into broad sections

Opportunity: Identification and tagging using standardized concepts

# Healthcare Data: Radiological Report

Exam Number: random number
Report Status: Final
Type: CT SCAN ABDOMEN W/O CONTRAST
Date/Time: date:time
Ordering Provider: TURCHIN, ALEXANDER M.D.
Report Below from Associated Order A07439985: CT SCAN PELVIS W/O CONTRAST

HISTORY: Please evaluate whether the right adrenal mass and the pancreatic
REPORT
HISTORY: 5 cm right adrenal mass. Pancreatic mass.
TECHNIQUE: CT scan of the abdomen and pelvis was performed following the administration of oral contrast. Intravenous contrast was not administered.
PRIOR STUDIES: CT scan abdomen and pelvis dated <Date>.
FINDINGS:
LUNG BASES: Subsegmental atelectasis is seen in the right lung base and slight atelectatic changes are noted in the left base. Small area of high attenuating material is seen in the medial aspect of the right lower lobe which may be related to prior aspiration. This finding is unchanged.
ABDOMEN: Evaluation of the solid abdominal viscera is limited without intravenous contrast material. The liver, gallbladder, spleen, and left adrenal gland are unremarkable. There is a 4.4 x 2.7 cm cystic mass in the pancreatic body, essentially unchanged from the prior examination. The pancreatic duct is normal in caliber.
PELVIS: Heavy vascular calcifications are seen in the abdominal aorta and its major branches.
OSSEOUS STRUCTURES: Left hip enthesopathy is noted. There are no suspicious lytic or blastic lesions. Degenerative changes are seen throughout the thoracolumbar spine.
IMPRESSION:
1. 4.6 x 2.9 cm cystic mass within the pancreatic body. Differential diagnostic considerations include cystic neoplasms such as serous microcystic adenoma or mucinous macrocystic adenoma. Further evaluation with an MRI examination is recommended.
2. Stable right adrenal mass which may also be evaluated during the time of the pancreatic MRI.
3. Several indeterminate left renal cystic lesions.

END OF IMPRESSION:
eScription document:5-7347531 ABBWH
RADIOLOGISTS:
SIGNATURES: GIRSHMAN, JEFFREY, MD(R)
MORTELE, KOENRAAD, MD(T)

Still primarily unstructured data.
However sections are more finely defined (e.g., Findings – Lung Bases, Abdomen, Osseous Structures, etc.) and presence of “facts”, e.g., type of report.

Opportunity:
Grounding of facts in standardized Ontologies
Tagging of sections and fragments of unstructured text using standardized concepts

# Healthcare Data: Pathology Observations

Accession Number: randomnumber
Report Status: Final
Type: CytologySpecimen
Type: FINE NEEDLE ASPIRATION, Right THYROID
Procedure Date: date:time
Ordering Provider: BRIAN W KIM M.D.
CASE: randomnumber
PATIENT: patientname
Cytotechnologist: Janet A Cronin, CT(ASCP)
Pathologist: Xiaohua Qian, M.D., Ph.D.
FINE NEEDLE ASPIRATION, RIGHT THYROID
FINAL CYTOLOGIC INTERPRETATION
INTERPRETATION:
NO MALIGNANT CELLS IDENTIFIED.
DIAGNOSIS:
Benign-appearing follicular cells and colloid.
Cyst lining cells.
The findings are consistent with a benign thyroid nodule.
CLINICAL DATA
GROSS DESCRIPTION
50cc colorless.
MATERIALS
Total slides: 2
By his/her signature below, the senior physician certifies that he/shepersonally conducted a microscopic examination of the described specimen(s) andrendered or confirmed the diagnosis (es) related thereto.
Final Diagnosis by Xiaohua Qian M.D., Ph.D.,
Electronically signed on 4/25/2006

Very Structured in Nature
A collection of data items and
Some free text.

Opportunity:
Link “properties” and “values” to standardized Namespaces and concepts
Tagging for fragments of unstructured text.

# Healthcare Data: Microbiology Observations

Specimen: randomnumber
Collected date:time
Received  date:time
Ordering Provider:
Specimen Group:  NOSE/NASOPHARYNX
Specimen Type:  NARES FOR MRSA  MRSA CULTURE
Reported: date:time
NO METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS ISOLATED

Mostly structured items

Opportunity: Link “properties” and values to standardized namespaces and contexts.

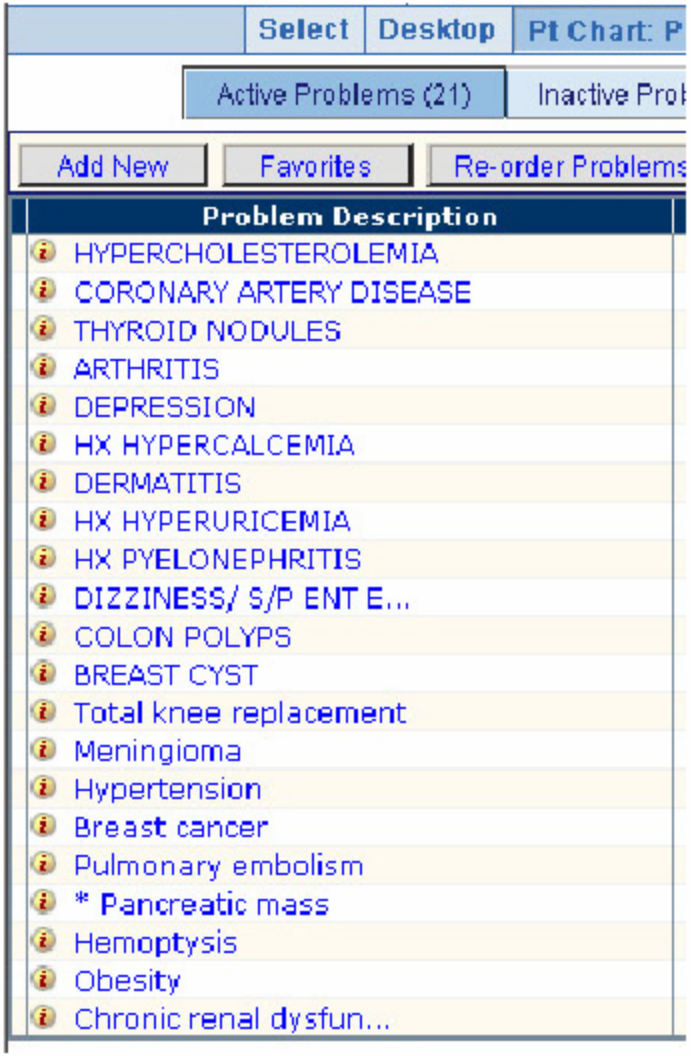
# Healthcare Data: Genetic Test Results

```
<?xml version="1.0" encoding="UTF-8"?>
<geneticTestOrder xmlns="http://www.partners.org/genetics"
            xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
            xsi:schemaLocation="http://www.partners.org/genetics geneticTestOrder_1_0.xsd">
   <order>
      <indicationCode code="DA-95200" codeSystemName="SNOMED" text="Sensorineural hearing
loss"/>
      <indicationClassCode code="Constitutive" />
      <testCategoryCode code="Diagnostic" />
   </order>

   <fulfillment>
      <fulfillmentRecord referenceSystemId="PowerPath" recordId="BL-05-N00748" />
      <testReference referenceSystemId="HPCGG GVAD" testId="35" testVersionId="3" />
      <effectiveTime>20051025</effectiveTime>
      <overallResult>Positive</overallResult>
      <variants count="2">
         <sequenceVariant>
            <dnaChange level="Intragenic" type="Deletion">
               <name>35delG</name>
            </dnaChange>
            <aminoAcidChange type="Frame Shift"/>
            <variantReference referenceSystemId="HPCGG GVAD" variantId="45873" />
            <genomicLocation>
               <chromosome>13</chromosome>
               <chromosomeRegion>13q12</chromosomeRegion>
               <gene>GJB2</gene>
               <geneRegion>Exon 1</geneRegion>
            </genomicLocation>
            <interpretationCode code="Pathogenic" />
            <allelicStateCode code="Homozygous" />
            <significanceCode code="Non-incidental" />
         </sequenceVariant>
</variants>
   </fulfillment>
</geneticTestOrder>
```

Mostly structured items

Opportunity: Link “properties” and values to standardized namespaces and contexts.

# Healthcare Data: Problem List




Structured and in some cases “coded” data

Opportunity: Link to standardized ontologies such as Snomed
Create complex definitions of concepts

# Healthcare Data: Medication List

Active Meds (21) | Inactive Meds (31) | Active Non-Meds (1) | Inactive Non-Meds (0) | Discharge (15) | All | Practice | My

Enter new medication... | Add New | Favorites | Renew | Discontinue | Verified | Pharmacy Info

Patient's Payor: Select Payor...

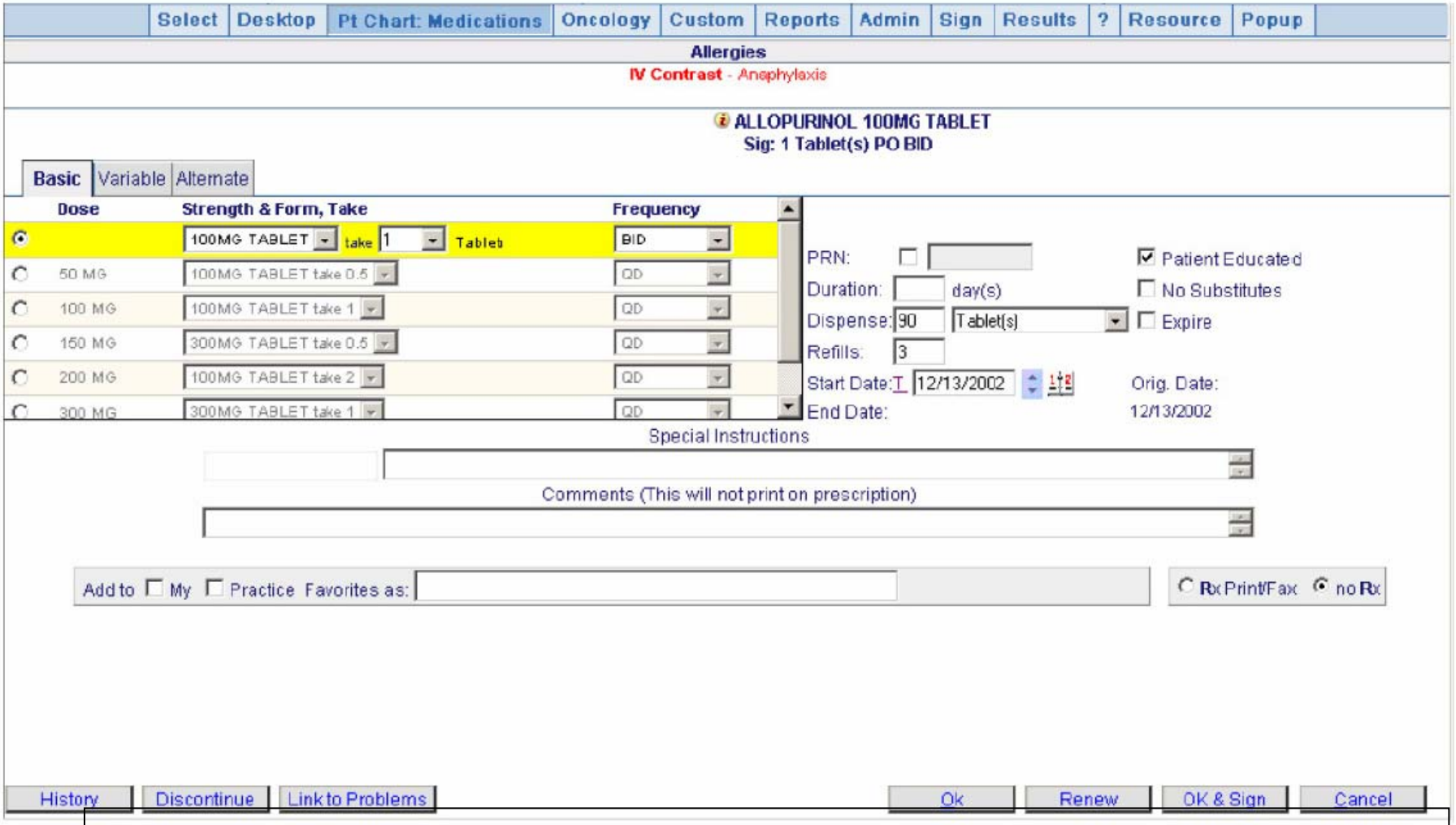
**Allergies: IV Contrast** - Anaphylaxis

| Co-pay | Medication | Rx | Sig | Special Instructions | Dispense | Rfl | Start Date | End Date | Orig. Date |
|---|---|---|---|---|---|---|---|---|---|
| | Allopurinol | Rx | 100MG TABLET take 1 Tablet(s) PO BID | | 90 TABL... | 3 | 12/13/02 | | 12/13/02 |
| | Arimidex | Rx | 1 MG (1MG TABLET take 1) PO QD | | 90 Tabl... | 3 | 03/20/02 | | 03/20/02 |
| | Aspirin | | 81 MG (81MG TABLET take 1) PO QD | | Tabl... | | 01/23/06 | | 01/23/06 |
| | Calcitriol | Rx | 0.75 MCG (0.25MCG CAPSULE take 3) PO QD | x 90 days | 90 Caps... | 3 | 09/28/05 | 12/26/05 | 09/28/05 |
| | * Calcitrol | | PO | | | | 04/21/05 | | 04/21/05 |
| | Cozaar | Rx | 100 MG (100MG TABLET take 1) PO QD | x 90 days | 90 Tabl... | 3 | 03/16/06 | 06/14/06 | 09/21/04 |
| | Ecasa | Rx | 81 MG PO QD | | 60 | 3 | 12/28/01 | | 09/02/98 |
| | Kayexalate | Rx | 15 GM (15G/60ML ORAL SUSP ML) PO QD | | 1 Mont... | 1 | 02/16/06 | | 02/16/06 |
| | Lasix | Rx | 80 MG (80MG TABLET take 1) PO BID | x 30 days | 60 Tabl... | 3 | 01/17/06 | 02/16/06 | 11/07/01 |
| | Lipitor | Rx | 80MG TABLET PO QD | x 90 days | 90 Tabl... | 3 | 02/02/04 | 05/02/04 | 02/02/04 |
| | Lisinopril | | 80 MG PO QD | | 60 | 3 | 12/28/01 | | 09/20/00 |
| Gen | Neurontin | Rx | 600 MG PO TID | | 60 | 3 | 12/13/02 | | 10/13/99 |
| | Nitroglycerin 1/150 | Rx | 1 TAB SL x3 q5 min PRN chest pain | if no relief after 3 doses call 911 | 100 | 3 | 08/02/02 | | 07/24/02 |

Structured data consisting of properties and values

Opportunity: Link to standardized drug classification ontologies and definitions of normality and abnormality

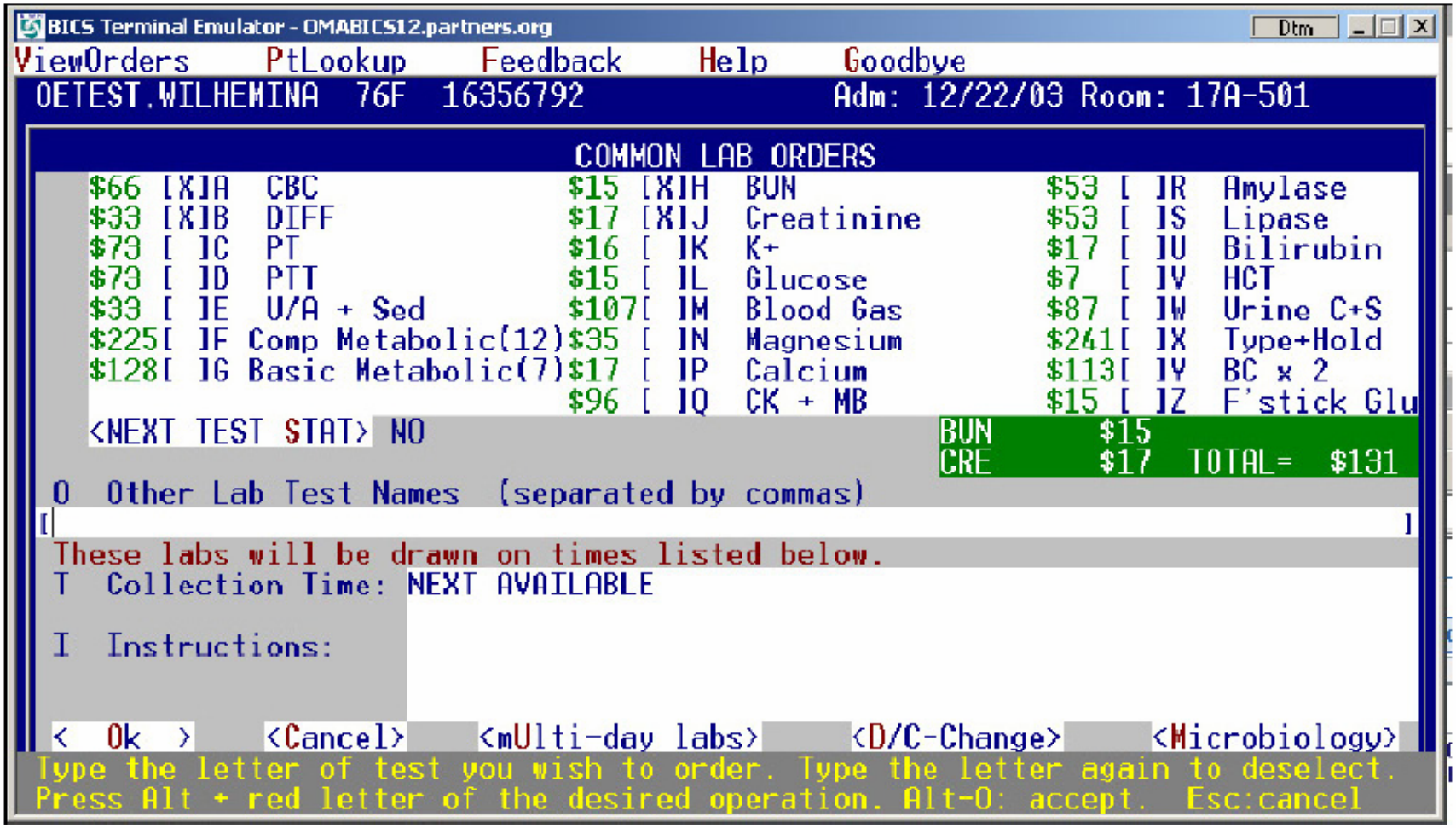
# Healthcare Data: Medication Orders




Structured and Composite Data containing multiple data items (properties, values)

Opportunity: Link to standardized information models and ontologies for interoperability and decision support

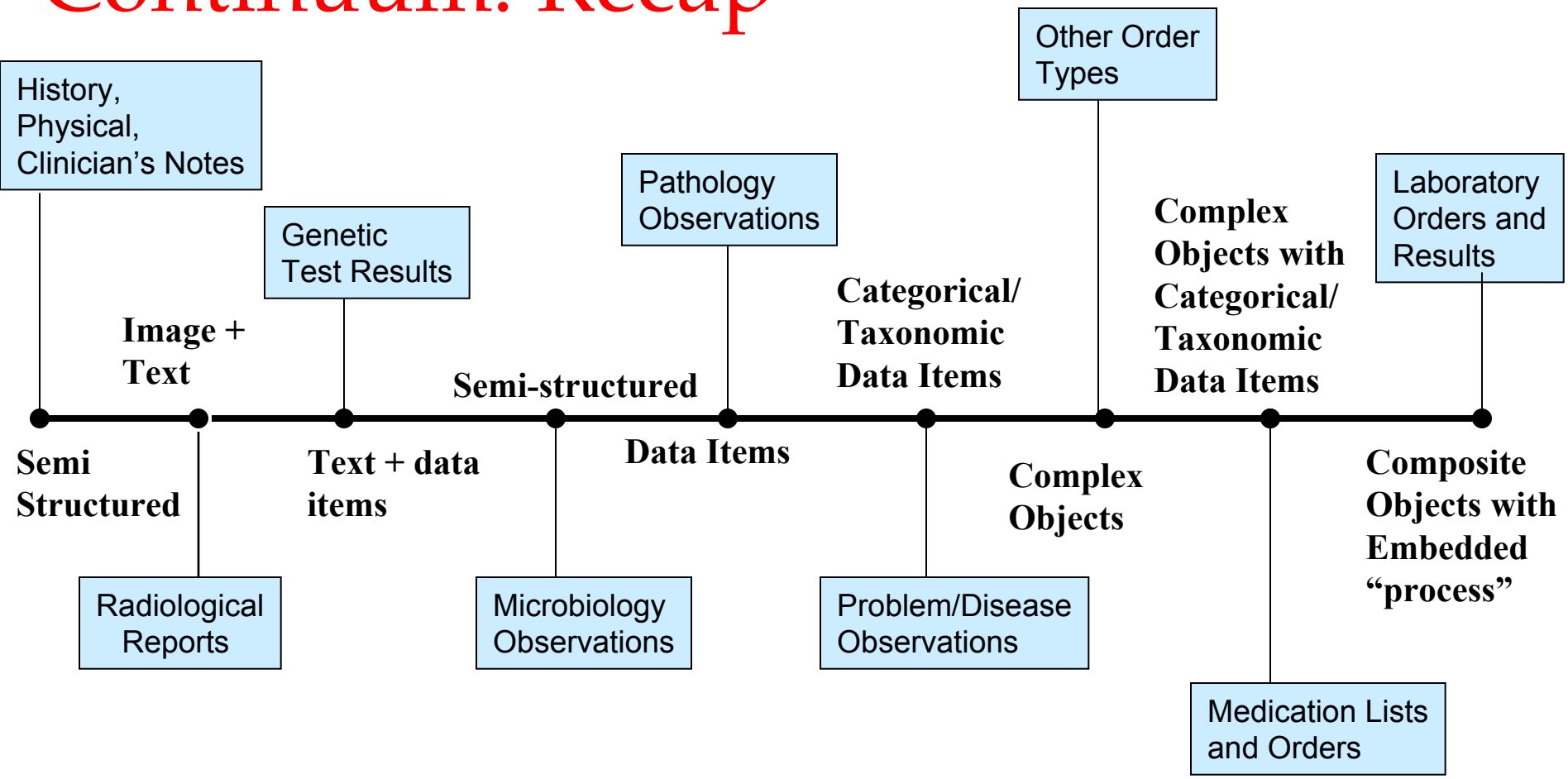
# Healthcare Data: Lab Orders




Structured and Composite Data containing process information
- Lab panel contains individual data items and panels.
- “Process” related information .. Perform a particular lab before another

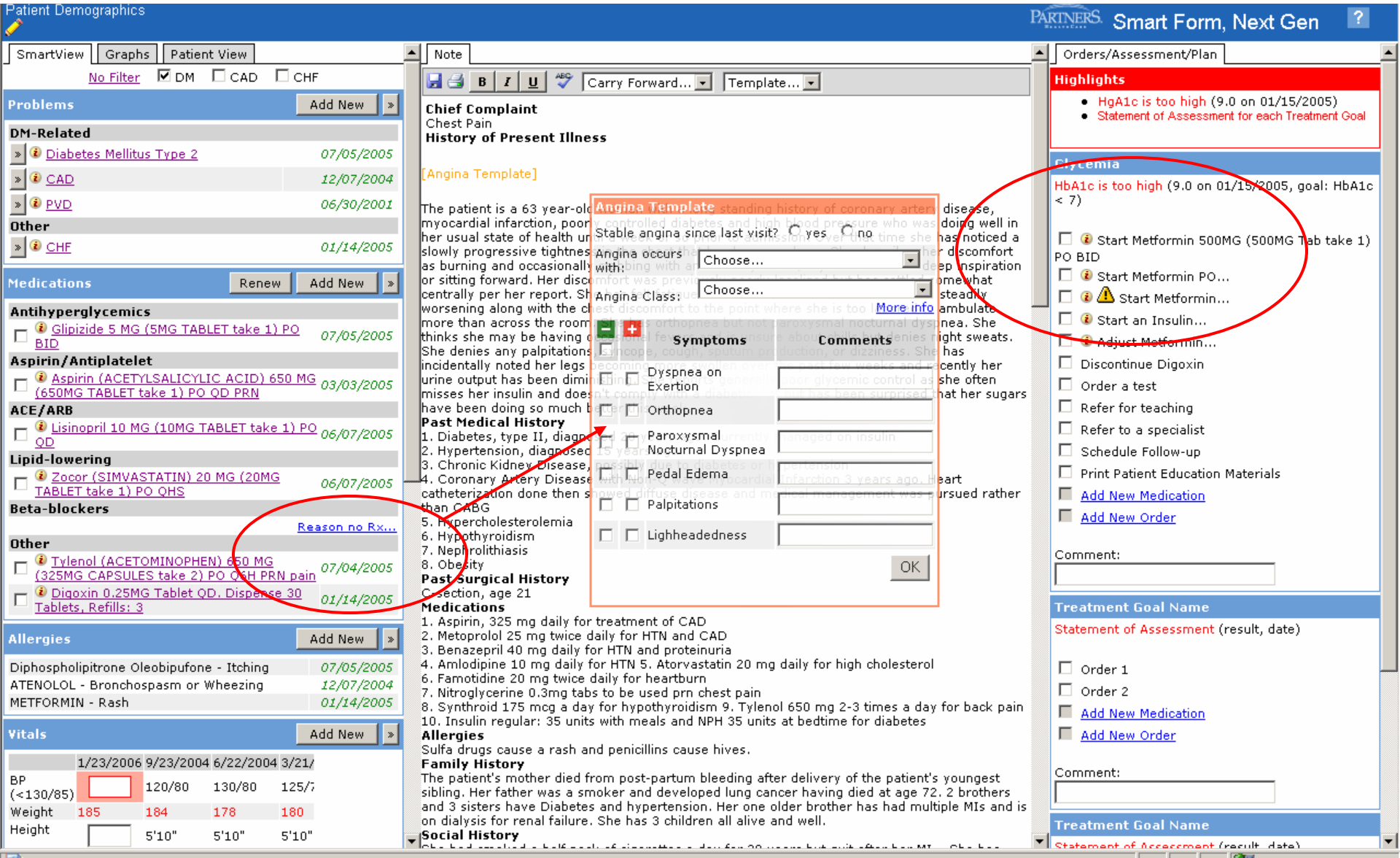
Opportunity: Link to standardized ontologies and information models
Link to descriptions of guidelines and processes

# The Healthcare Data Semantics Continuum: Recap



# Putting it all together!

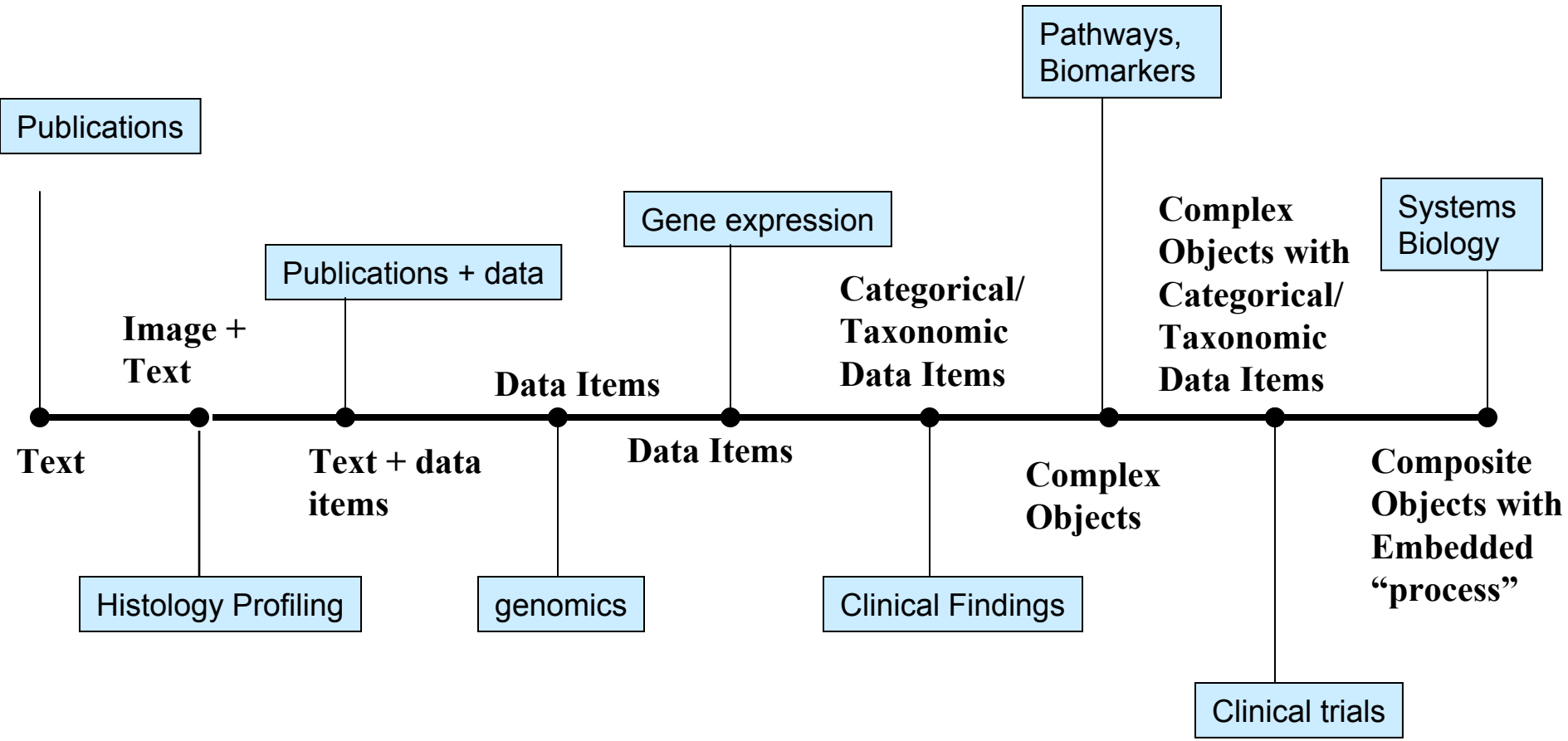
## Guided Data Interpretation  Guided Observation Capture  Guided Ordering



# Opportunities for Semantics in HealthCare

- Enhanced interoperability via:
  - Semantic Tagging
  - Grounding of concepts in Standardized Vocabularies
  - Complex Definitions
- Semantics-based Observation Capture
- Semantics-based Clinical Decision Suppport
  - Guided Data Interpretation
  - Guided Ordering
- Semantics-based Knowledge Management

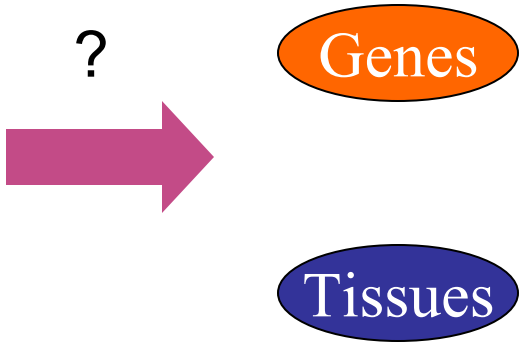
# Data Semantics in the Life Sciences



# Pharma Data: Losing Connectedness in Tables

*Fast Uptake and ease of use,*
*but loose binding to entities and terms*

| | D | E | F | G | H |
|---|---|---|---|---|---|
| 3 | | | | | |
| 4 | Sample_Tissue_ | Sample_General_Pat | CASP2 | TNFRS | BAD |
| 5 | | | | | |
| 6 | BREAST | MALIGNANT | 0.272629684 | 0.13815558 | 0.172021004 |
| 7 | BREAST | NORMAL | 0.127580378 | 0.04861223 | 0.049566081 |
| 8 | COLON | MALIGNANT | -0.044756676 | -0.0857321 | -0.11424752 |
| 9 | COLON | NORMAL | -0.152073618 | -0.2025134 | 0.054543655 |
| 10 | KIDNEY | MALIGNANT | -0.067732844 | 0.130794 | 0.096568566 |
| 11 | KIDNEY | NORMAL | -0.063332286 | -0.1209417 | -0.024562741 |
| 12 | LIVER | MALIGNANT | -0.31962625 | -0.3550275 | -0.41515775 |

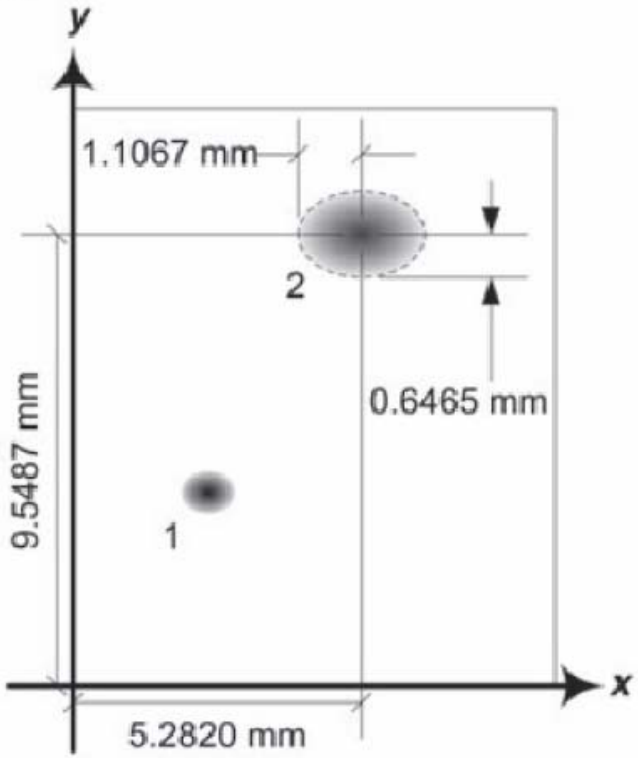



- Querying Databases is not sufficient
- Data needs to include the Context of Local Scientists
- Concepts and Vocabulary need to be associated

  *Information ⇔ Knowledge*

# Pharma Data

a




b

```
<spot>
   <spot_num>2</spot_num>
   <coord_x>5.2820</coord_x>
   <coord_y>9.5487</coord_y>
   <dia_x>1.1067</dia_x>
   <dia_y>0.6465</dia_y>
</spot>
```

c

```
<spot>
   <spot_label>2</spot_label>
   <spot_location>
      <spot_position x="5.2820"
                     y="9.5487"/>
      <spot_area width="1.1067"
                 height="0.6465"
                 type="ellipse"/>
   </spot_location>
</spot>
```

Annotated Gel Markup Language

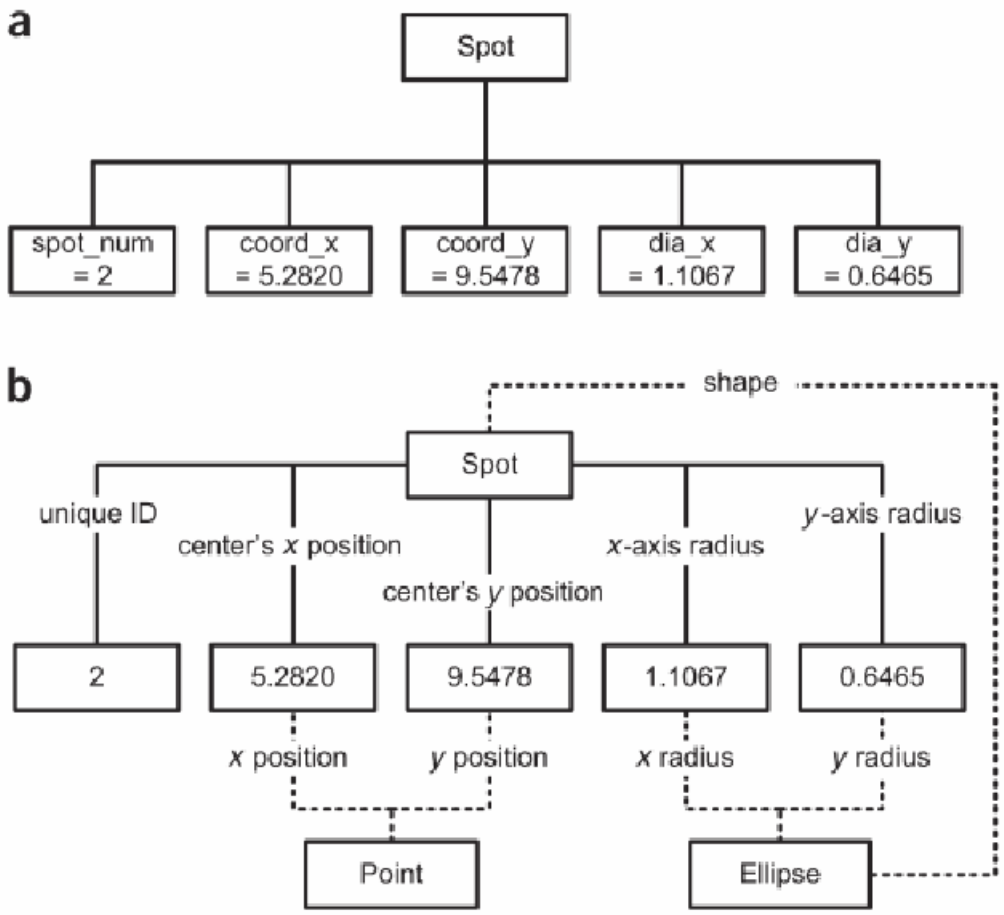
(AGML)

Human Proteome Markup Language

(HUP-ML)

(Wang, Gorlitsky & Almedia, Nature, Sep. 2005)

# Pharma Data: Lack of Semantics

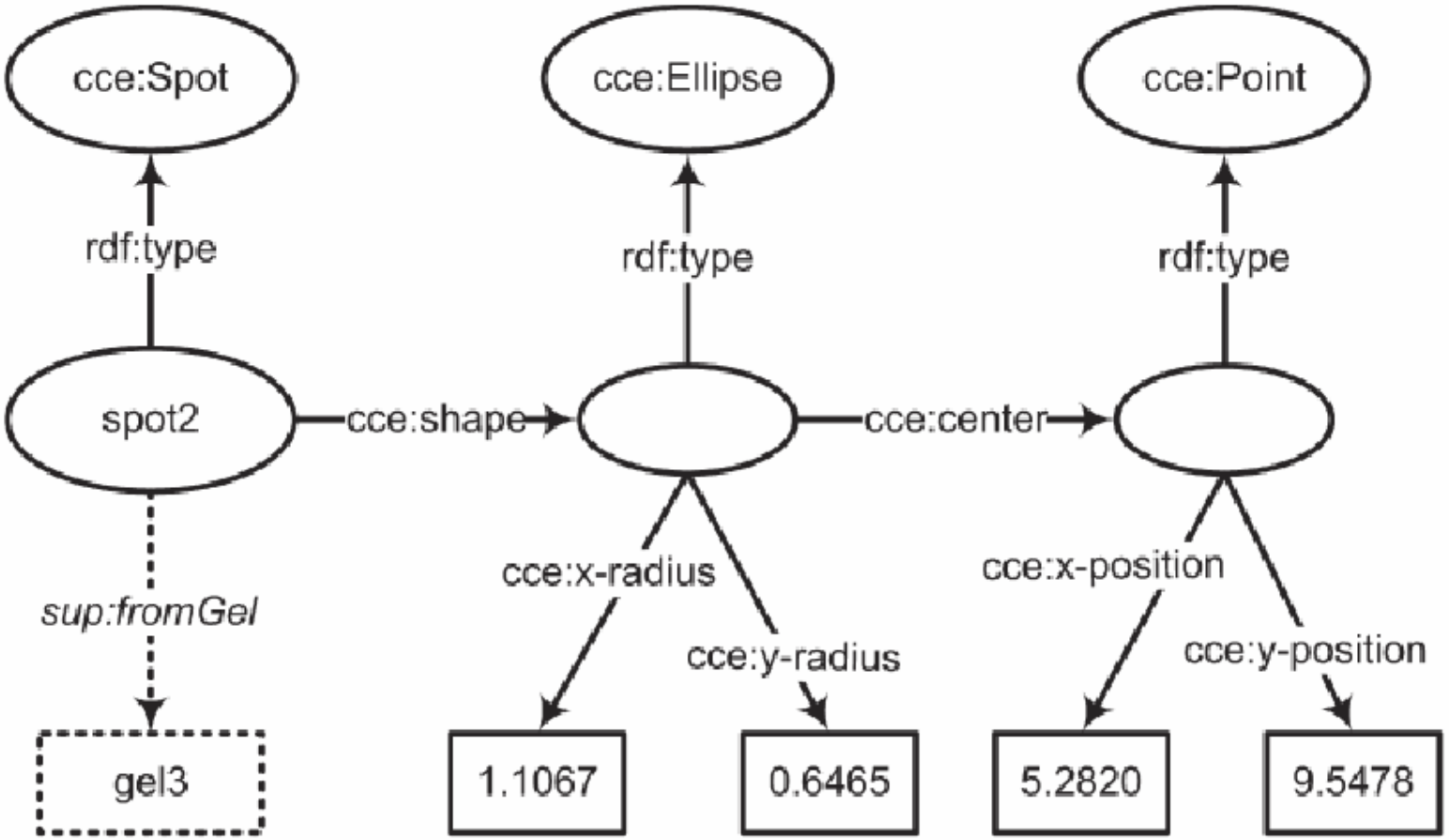



(Wang, Gorlitsky & Almedia, Nature, Sep. 2005)

Missing description of semantic *relationships* between nested holders – required to invoke appropriate algorithms (shown as dotted lines in diagram b).

This is essentially a communication problem between the information and the *application* of information.

# Pharma Data: Opportunities for Semantics



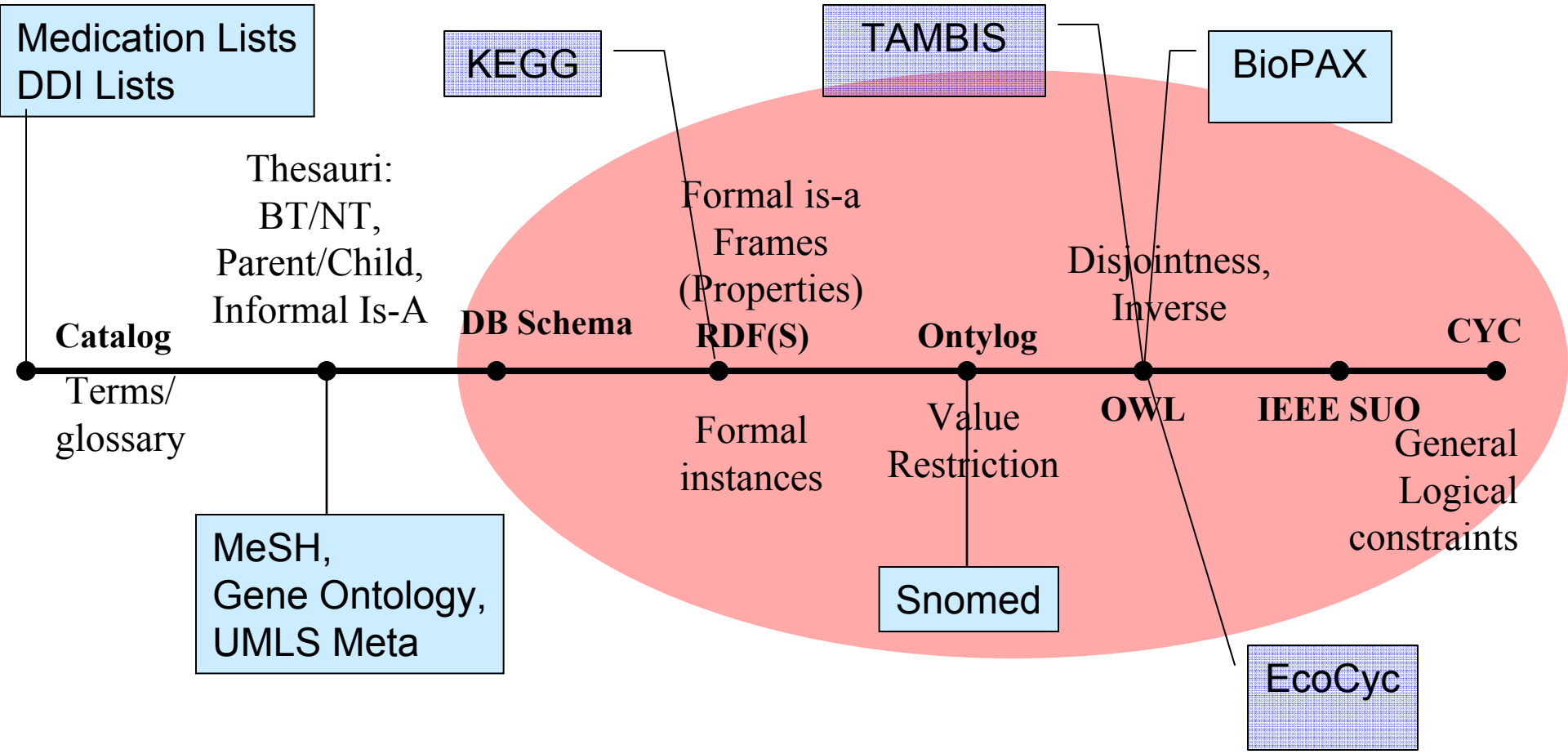

As a graph, the RDF model is oblivious to both syntax and semantics, but can be serialized into XML or N3 (NTriples).

(Wang, Gorlitsky & Almedia, Nature, Sep. 2005)

# Predictiveness

- Knowledge of Target Mechanisms
- Knowledge of Toxicity
- Knowledge of Patient-Drug Profiles

# The Knowledge Semantics Continuum

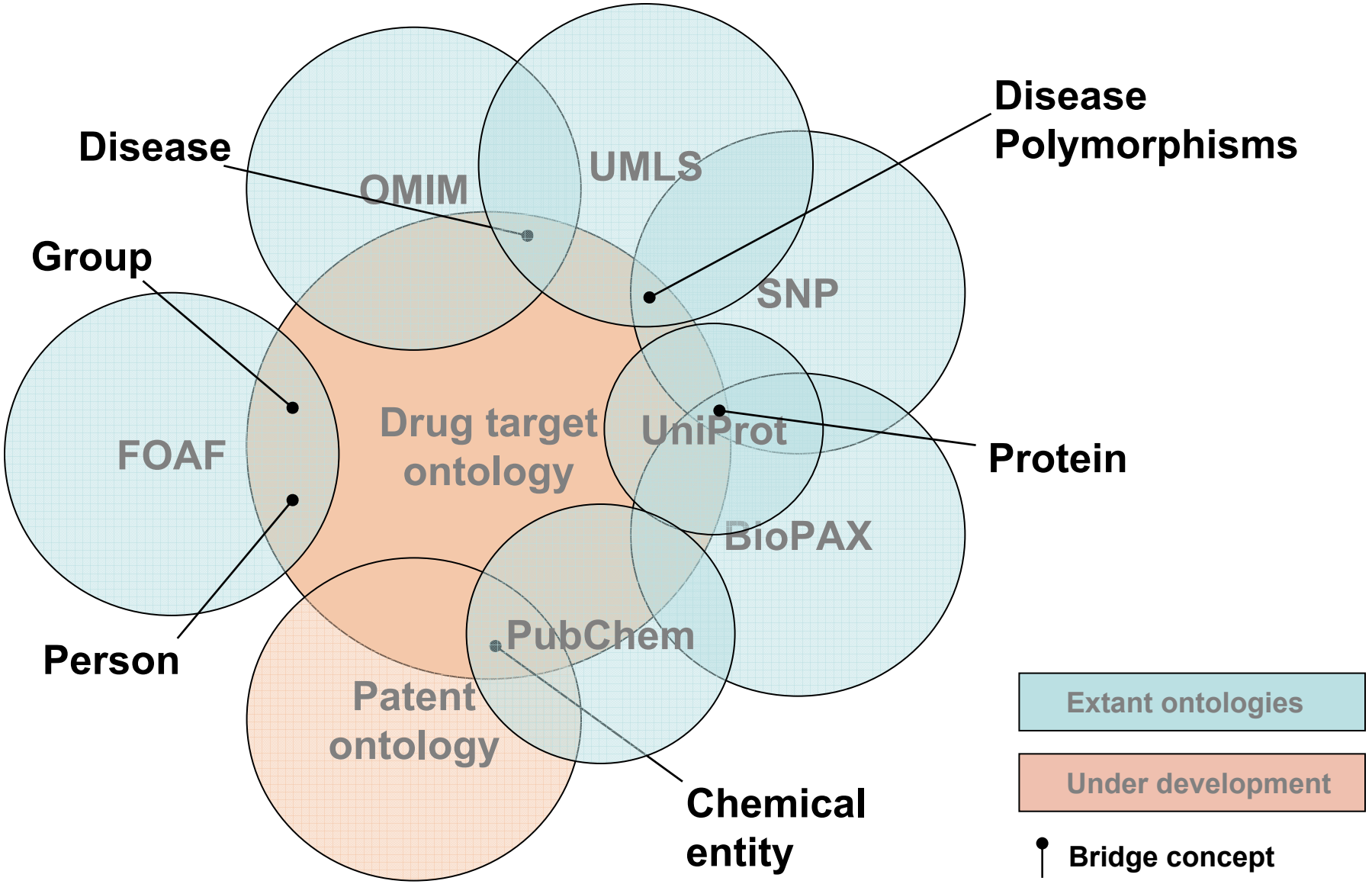



Simple Taxonomies

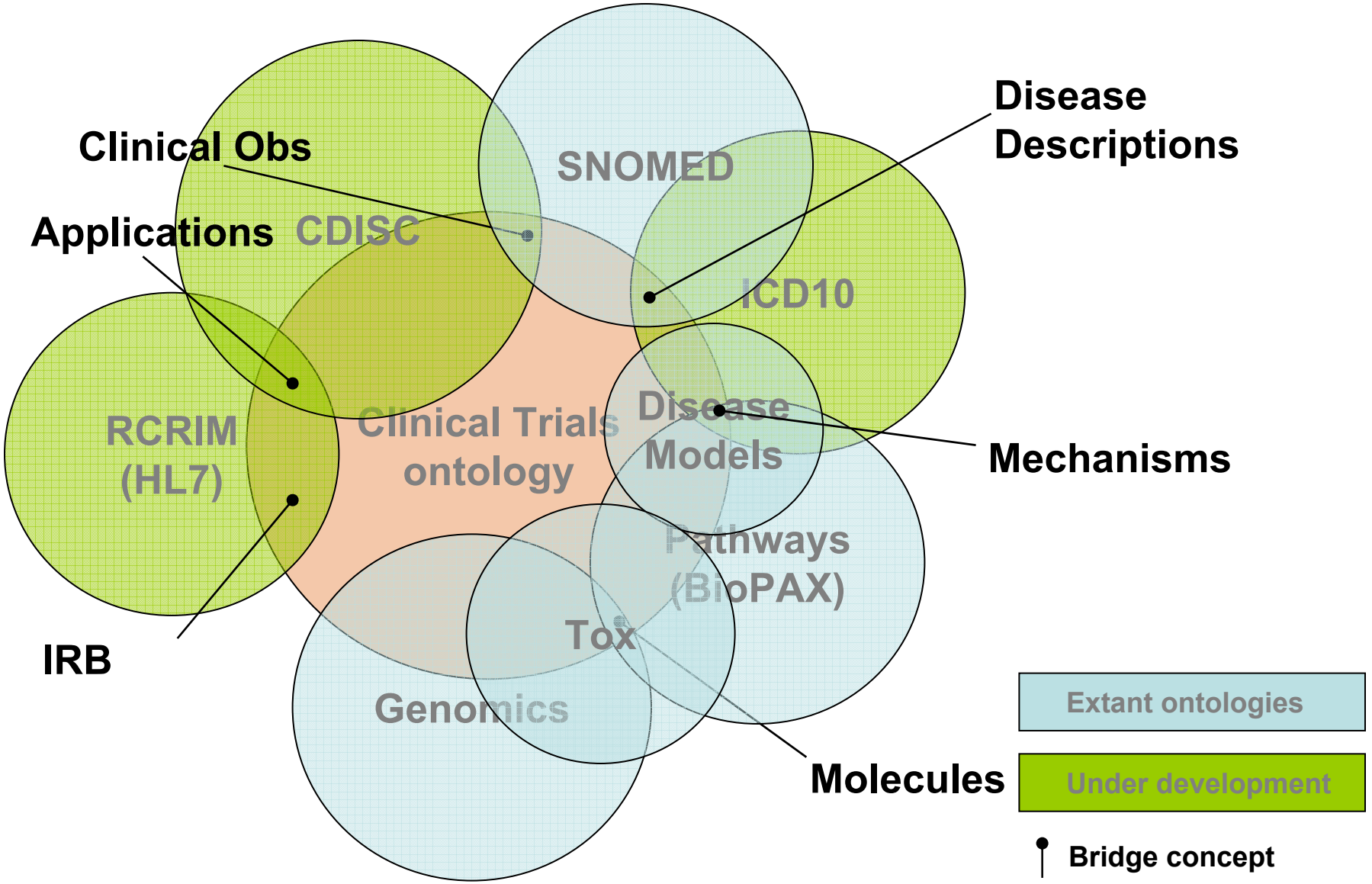
Expressive Ontologies

Ontology Dimensions based on McGuinness and Finin

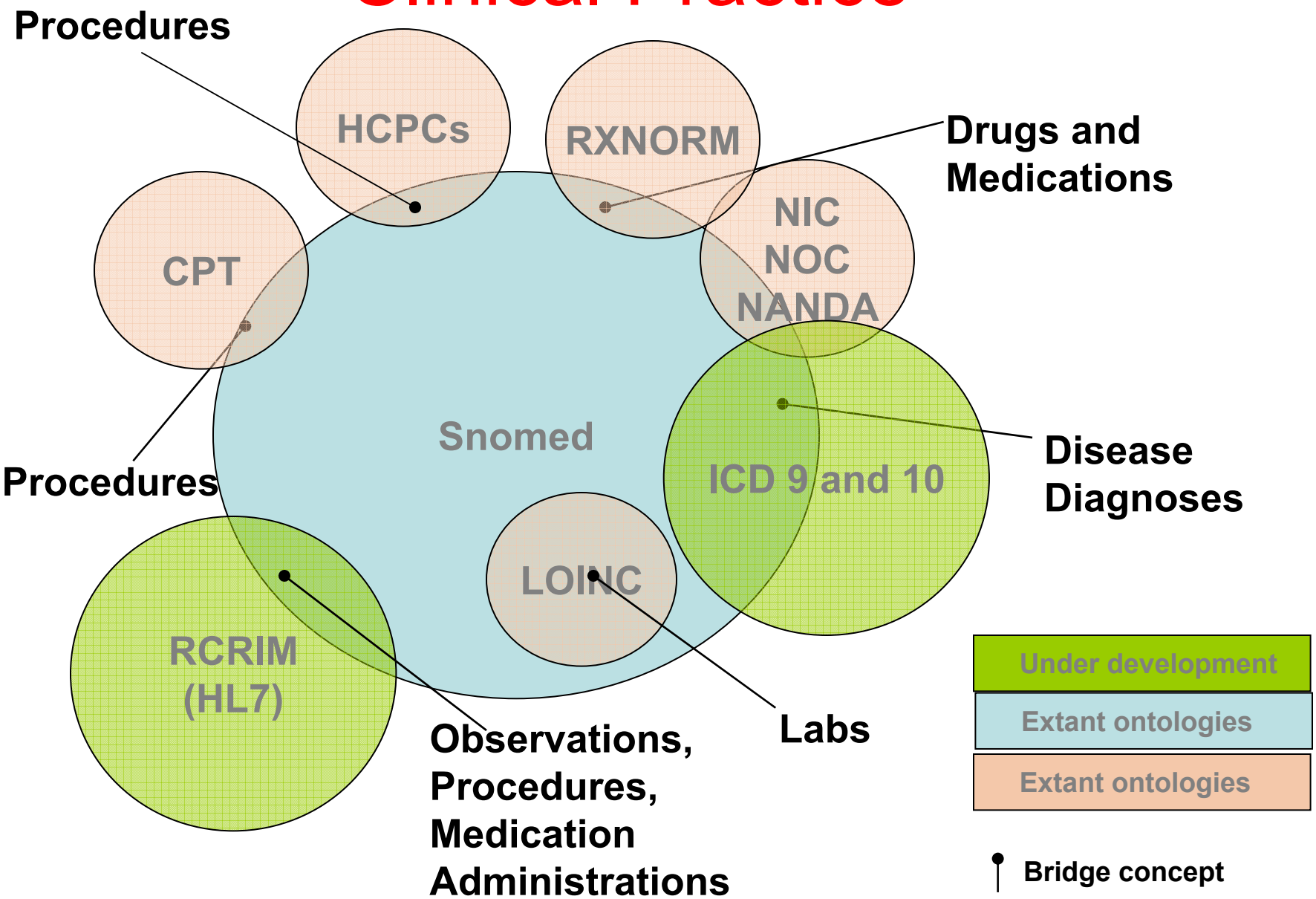
# Knowledge Brokering: Life Sciences



# Knowledge Brokering: Clinical Research



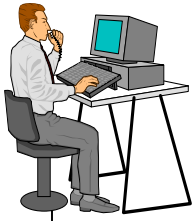
# Knowledge Brokering: Clinical Practice



# Opportunities for Semantics: Health Care

Data: 3000 Ambulatory Notes for Ortho Practice

NLP techniques + mining



Elicited or Inferred
Clinician Preference

Knowledge: Back Pain associated with:
- X History of Present Illness
- X Review of Systems
- X Physical Exam findings
- X Assessment possibilities
- X Diagnostic Test Possibilities (e.g., MRI)
- X Initial Therapy Possibilities

Rule/Policy: If Pain is > 6 weeks
And focal neuro findings,
May/Should Perform MRI

MRI is ordered only if clinical and admin/policy conditions are met!

# Opportunities for Semantics: Biomedical/Clinical Research

Hypothesis Exploration based on Semantic Reasoning

Fact: CML is caused by tyrosine kinase secreted by fused ABL-BCR gene
Fact: Gleevec inhibits tyrosine kinase
Inference: Gleevec may reverse CML

Learning Clinical Guidelines based on Semantic Reasoning + Data Mining

Fact: Confusion correlates with increased risk of Falls in age>65
Fact: Sedatives/Hypnotics increase risk of confusion even in appropriate doses for elderly
Rule/Knowledge: If patient>65 on sedatives/hypnotics, institute falls precautions protocol

# Opportunities for Semantics: Clinical Practice

- Clear definitions of Decision Support Categories
- IF patient has Diabetes and Renal Disease
  AND no contraindication to ACEi or ARB
  THEN prescribe ACEi or ARB
- Define "Contraindication to ACEi or ARB"
  - Allergy to ACEi or ARB
  - Cough symptom on adverse reaction list
  - Hyperkalemia on problem list or high K test result
  - Pregnancy (Needs further definition)
    - Could lead to complex and nested definitions
    - Post-coordinated approaches
  - Patient refuses or failed the drug
  - New Molecular diagnostic test

# Outline

- The Bench ↔ Bedside Vision
- Role of Data, Knowledge and Semantics in the HCLS Ecosystem
- Functional Requirements ☑
  - Metadata-based Semantic Annotation
  - *Recombinant Data:* Information Aggregation and Integration
  - Ontology-driven Decision Support
  - Knowledge Update and Maintenance
- Conclusions

# Functional Requirements

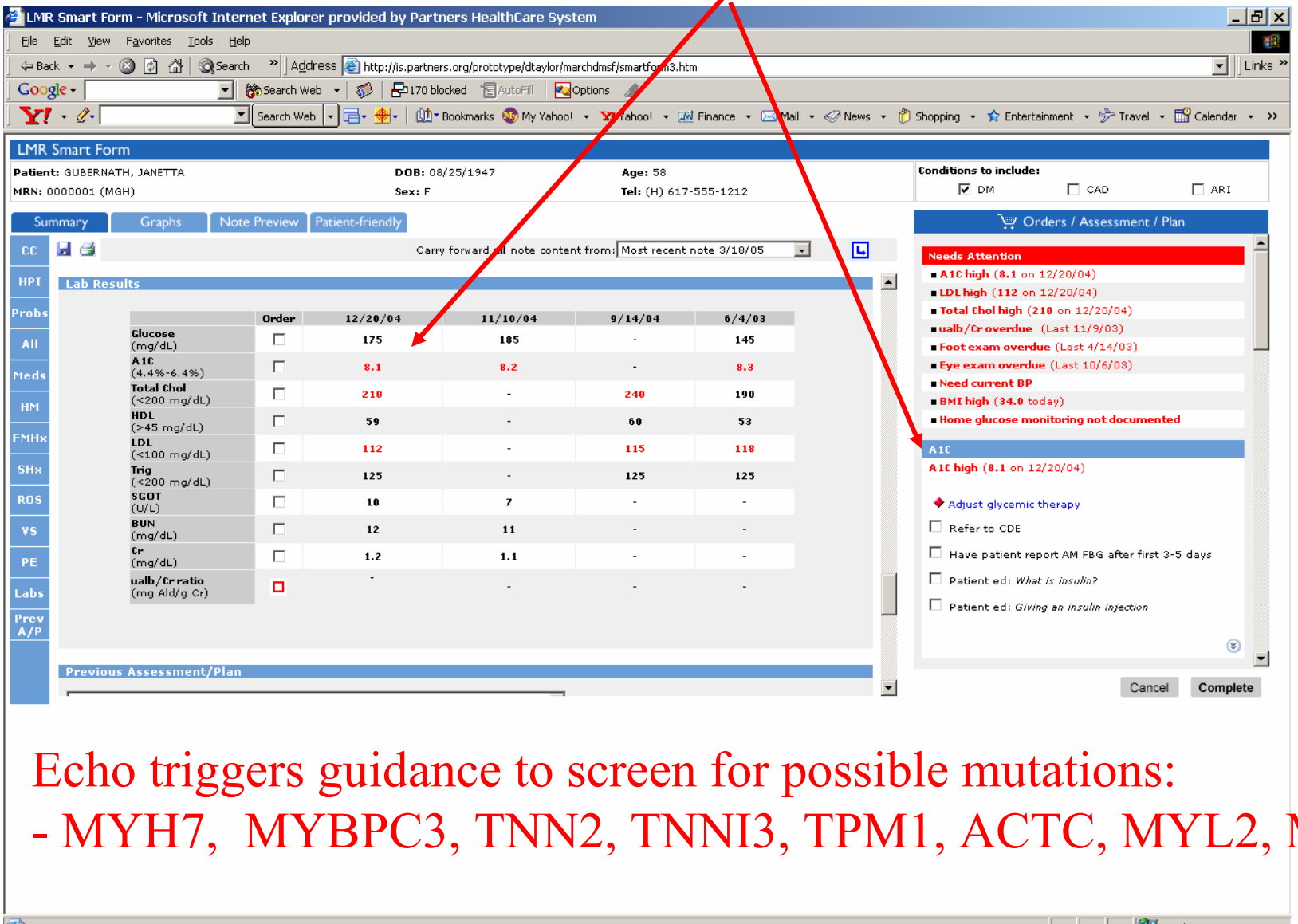
- Use Cases ☑
- Metadata-based Semantic Annotation
- *Recombinant Data:* Information Integration and Aggregation
  - Discovery Decision Support
- Ontology-driven Decision Support
- Knowledge Update and Maintenance

# Use Case: Personalized Medicine

Dr. Genomus Meets Basketball Player who fainted at Practice

- Clinical exam reveals abnormal heart sounds → **Structured Physical Exam**
- Family History: Father with sudden death at 40, → **Structured Family History**
- 2 younger brothers apparently normal
- Ultrasound ordered based on clinical exam reveals cardiomyopathy → **Imaging Study Reports with Metadata Annotations**

# Use Case: Actionable Decision Support

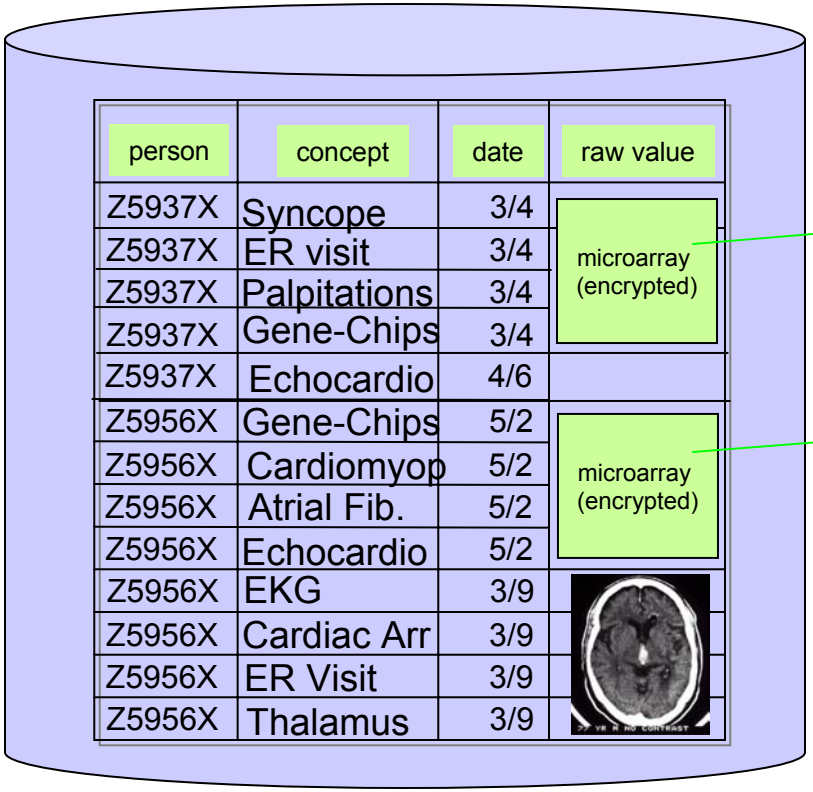



Echo triggers guidance to screen for possible mutations:

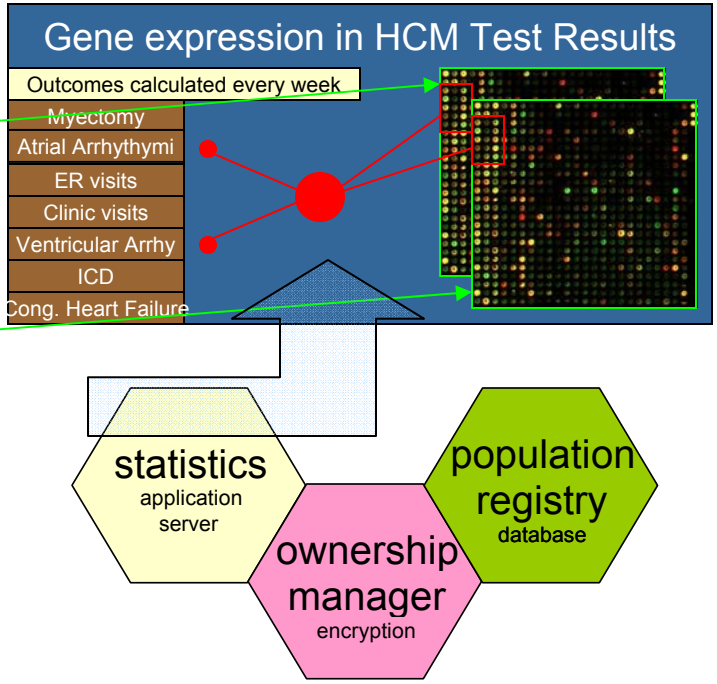
- MYH7, MYBPC3, TNN2, TNNI3, TPM1, ACTC, MYL2, MYL3

# Use Case:
# Connecting Genotypic and Phenotypic Data

## Connecting Dx, Rx, Outcomes and Prognosis Data to Genotypic Data for Cardiomyopathy



| person | concept | date | raw value |
|---|---|---|---|
| Z5937X | Syncope | 3/4 | microarray (encrypted) |
| Z5937X | ER visit | 3/4 | |
| Z5937X | Palpitations | 3/4 | |
| Z5937X | Gene-Chips | 3/4 | |
| Z5937X | Echocardio | 4/6 | |
| Z5956X | Gene-Chips | 5/2 | microarray (encrypted) |
| Z5956X | Cardiomyop | 5/2 | |
| Z5956X | Atrial Fib. | 5/2 | |
| Z5956X | Echocardio | 5/2 | |
| Z5956X | EKG | 3/9 | |
| Z5956X | Cardiac Arr | 3/9 | |
| Z5956X | ER Visit | 3/9 | |
| Z5956X | Thalamus | 3/9 | |



# Use Case: Drug Discovery

**ApoA1 …**

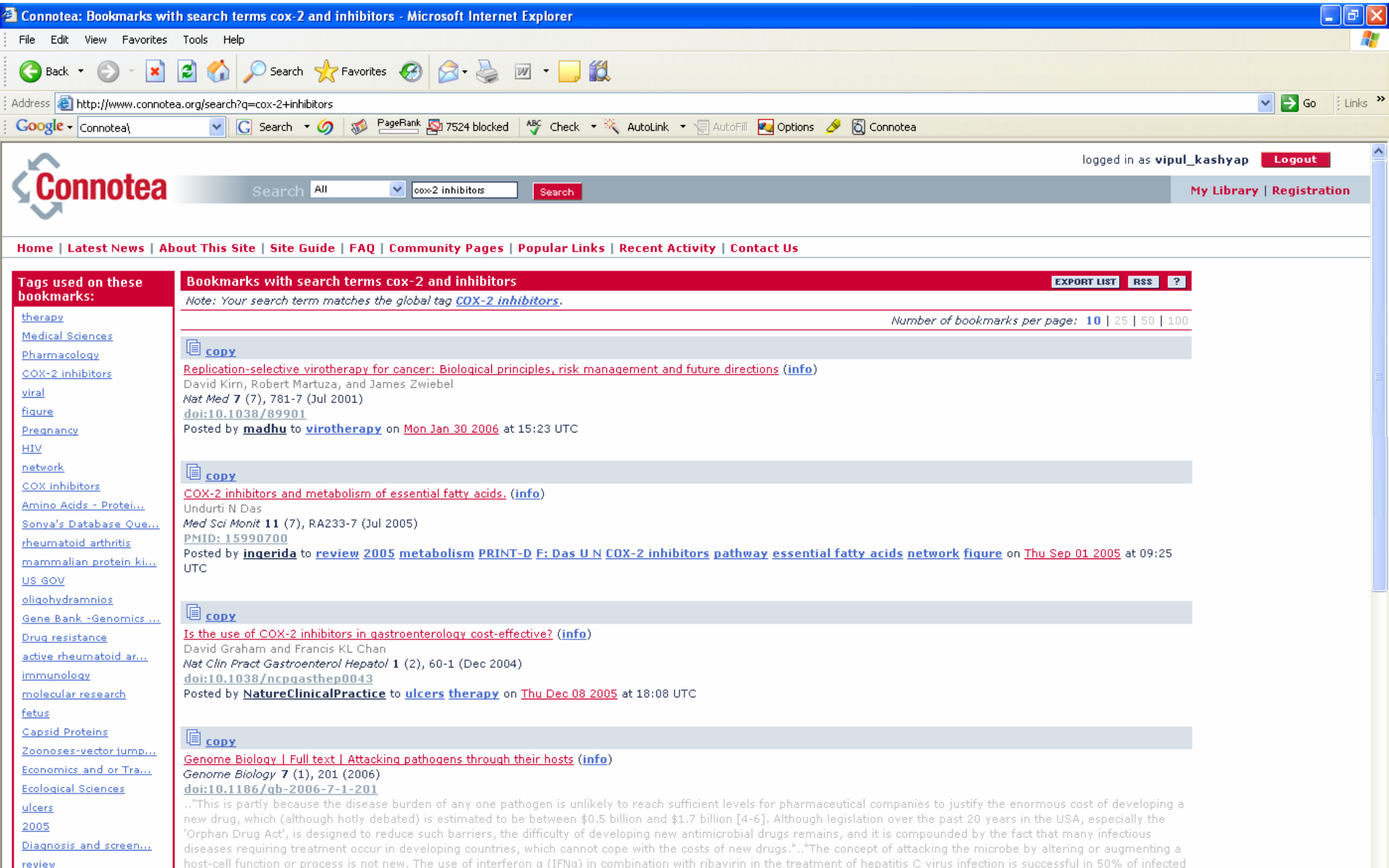
- **… is produced by the Liver**
- **… is expressed less in Atherosclerotic Liver**
- **… is correlated with DKK1**
- **… is cited regarding Tangier's disease**
- **… has Tx Reg elements like HNFR1**

# Functional Requirements

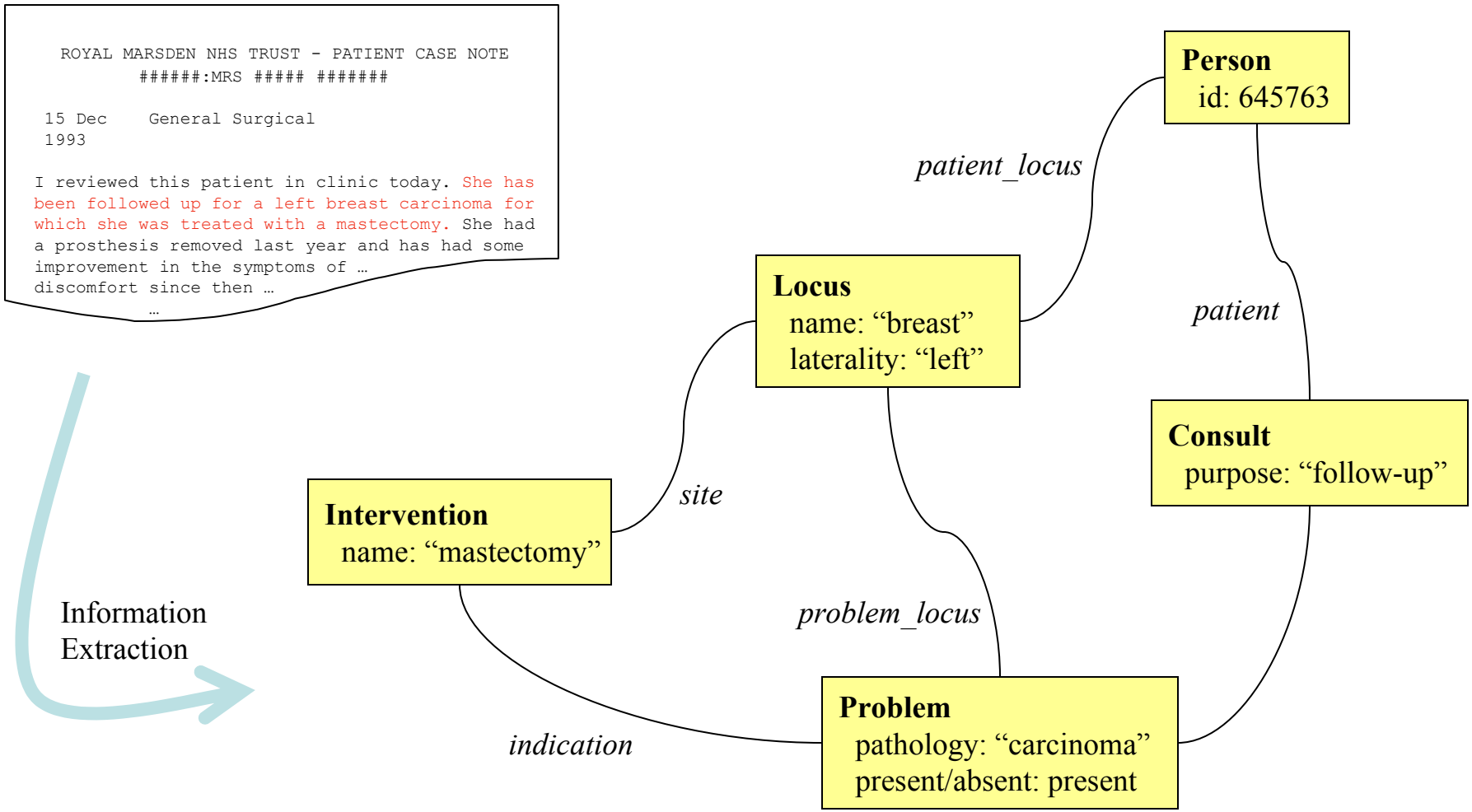
- Use Cases
- Metadata-based Semantic Annotation ☑
- *Recombinant Data:* Information Integration and Aggregation
  - Discovery Decision Support
- Ontology-driven Decision Support
- Knowledge Update and Maintenance

*The first step of any biomedical activity (research, practice, knowledge gathering) should be on the computer!*

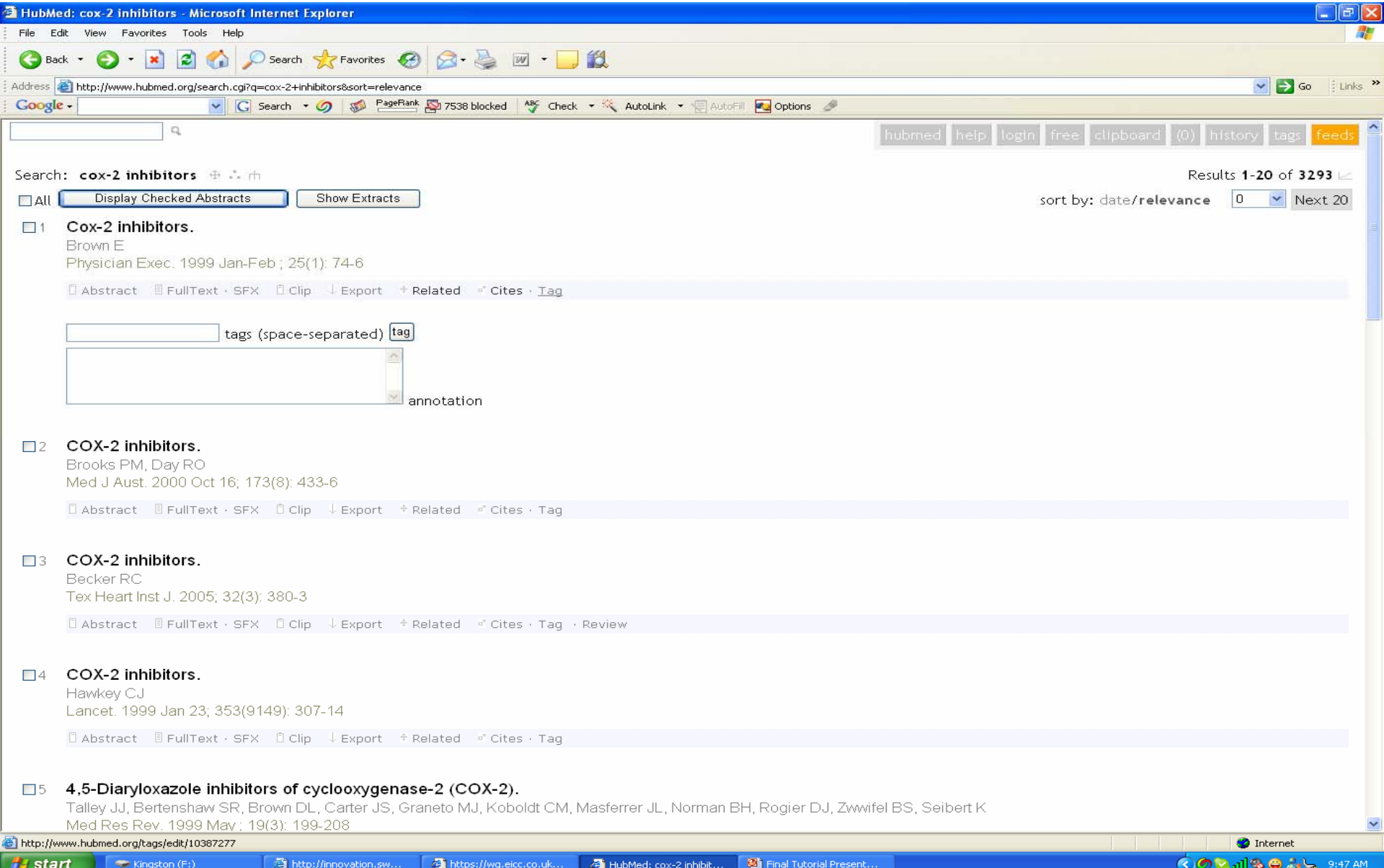
# Metadata-based Semantic Annotations: Connotea



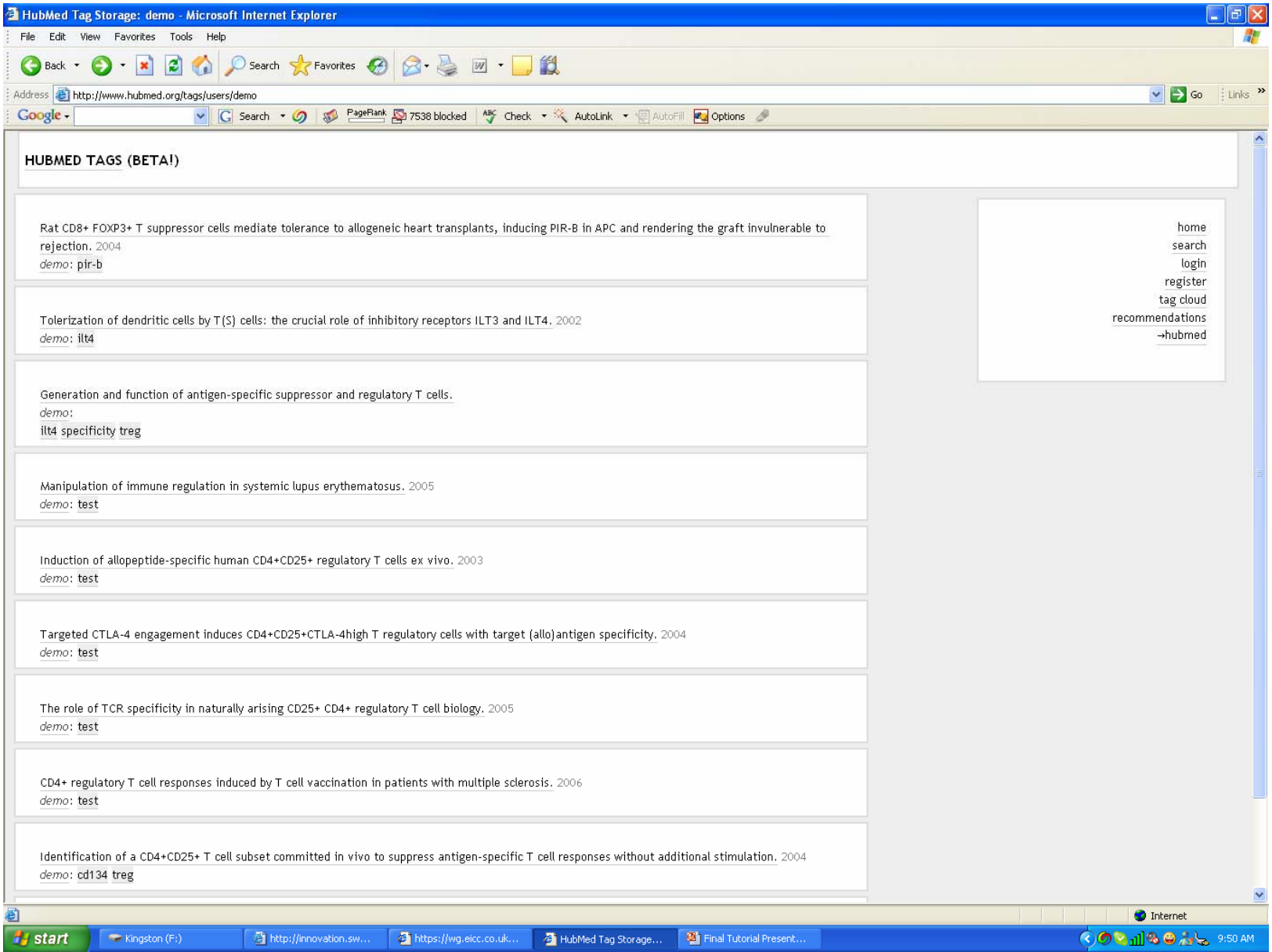
# Metadata-based Semantic Annotations: Clinical E-Science Framework



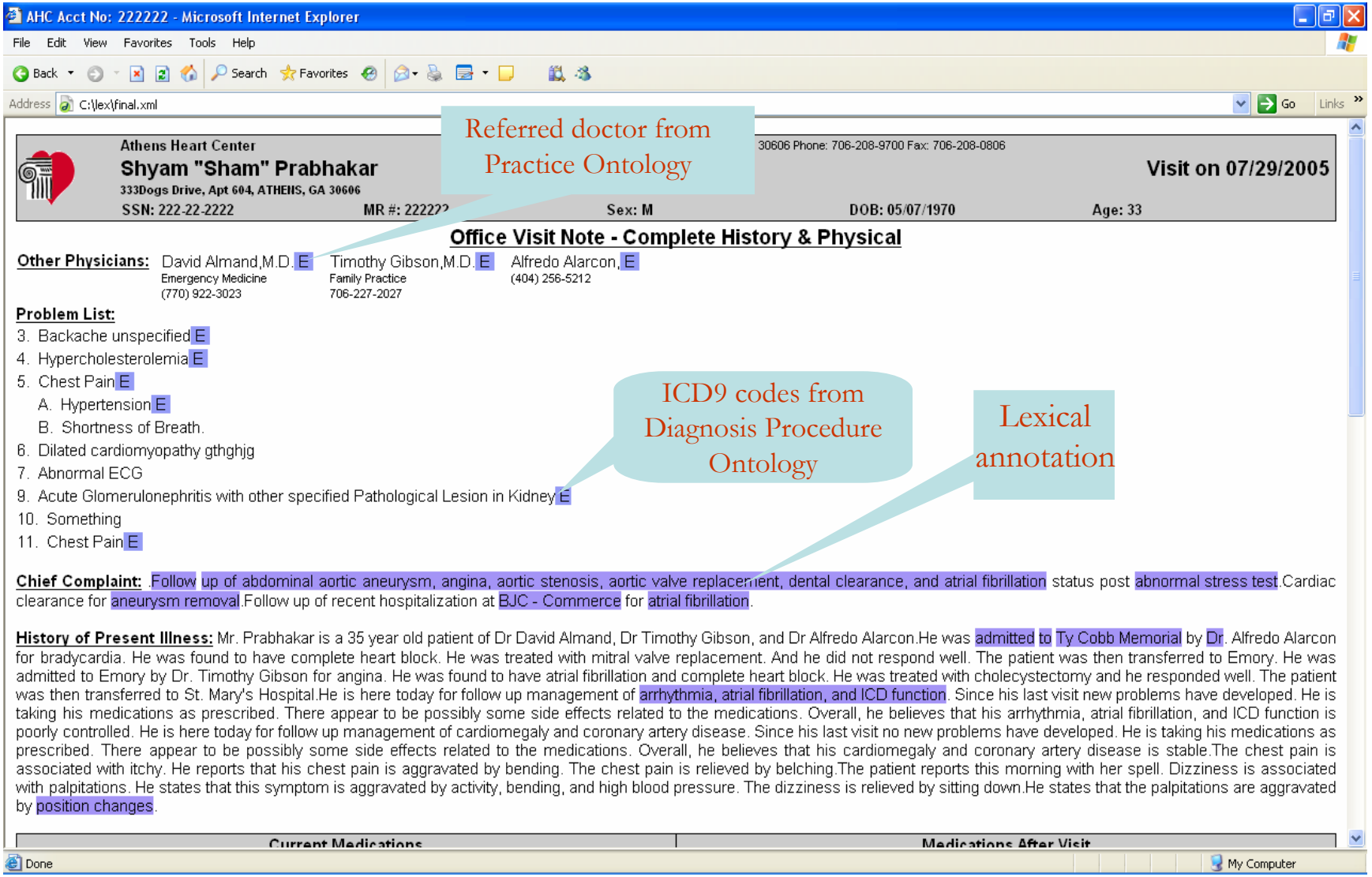
# Metadata-based Semantic Annotations (HubMed)



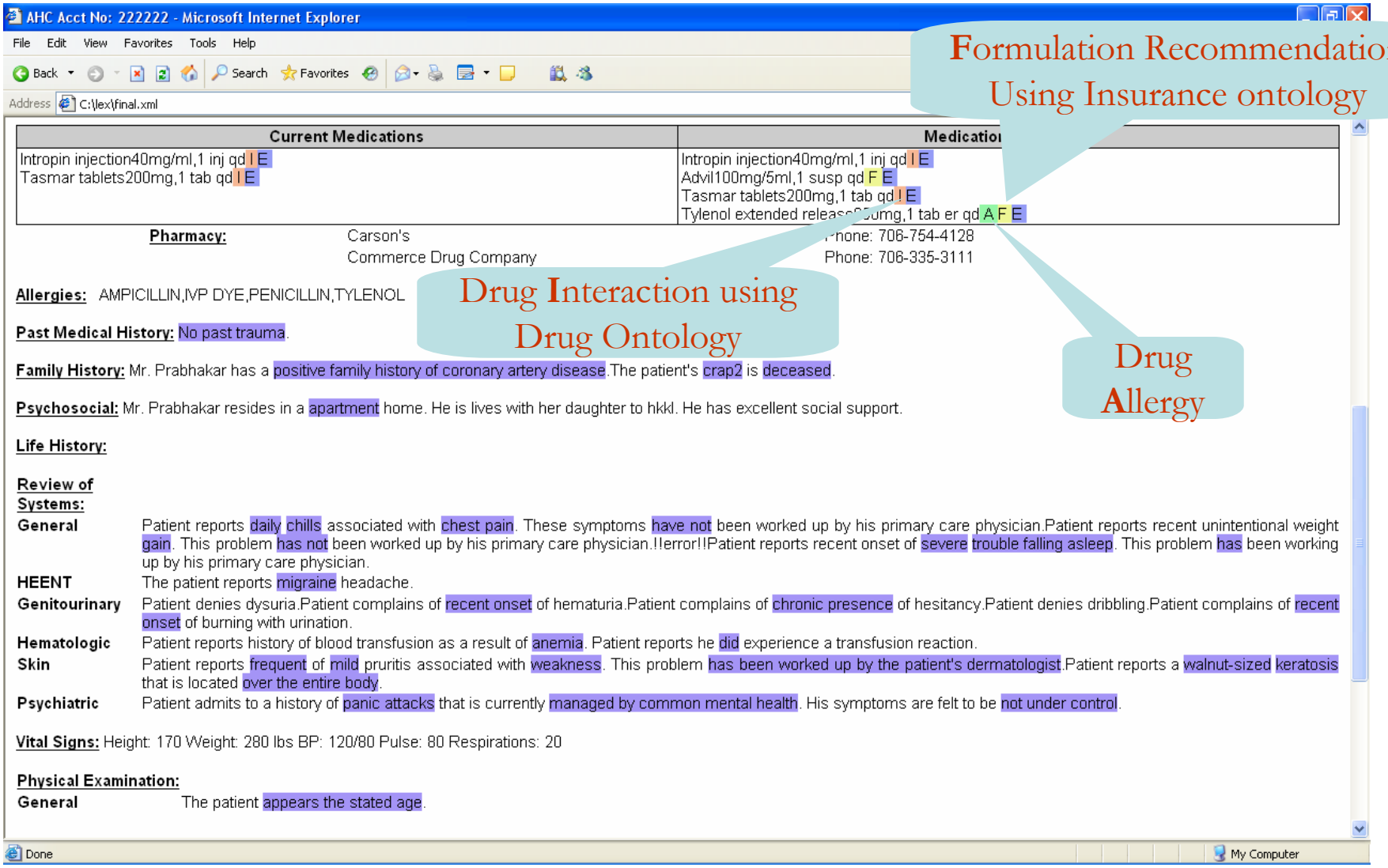
# Metadata-based Semantic Annotations: HubMed



# Metadata-based Semantic Annotations: Active Semantic EMR



# Metadata-based Semantic Annotations: Active Semantic EMR




| Current Medications | Medicatio |
|---|---|
| Intropin injection40mg/ml,1 inj qd I E<br>Tasmar tablets200mg,1 tab qd I E | Intropin injection40mg/ml,1 inj qd I E<br>Advil100mg/5ml,1 susp qd F E<br>Tasmar tablets200mg,1 tab qd I E<br>Tylenol extended release[illegible]mg,1 tab er qd A F E |

**Pharmacy:** Carson's — Phone: 706-754-4128
Commerce Drug Company — Phone: 706-335-3111

**Allergies:** AMPICILLIN,IVP DYE,PENICILLIN,TYLENOL

**Past Medical History:** No past trauma.

**Family History:** Mr. Prabhakar has a positive family history of coronary artery disease.The patient's crap2 is deceased.

**Psychosocial:** Mr. Prabhakar resides in a apartment home. He is lives with her daughter to hkkl. He has excellent social support.

**Life History:**

**Review of Systems:**

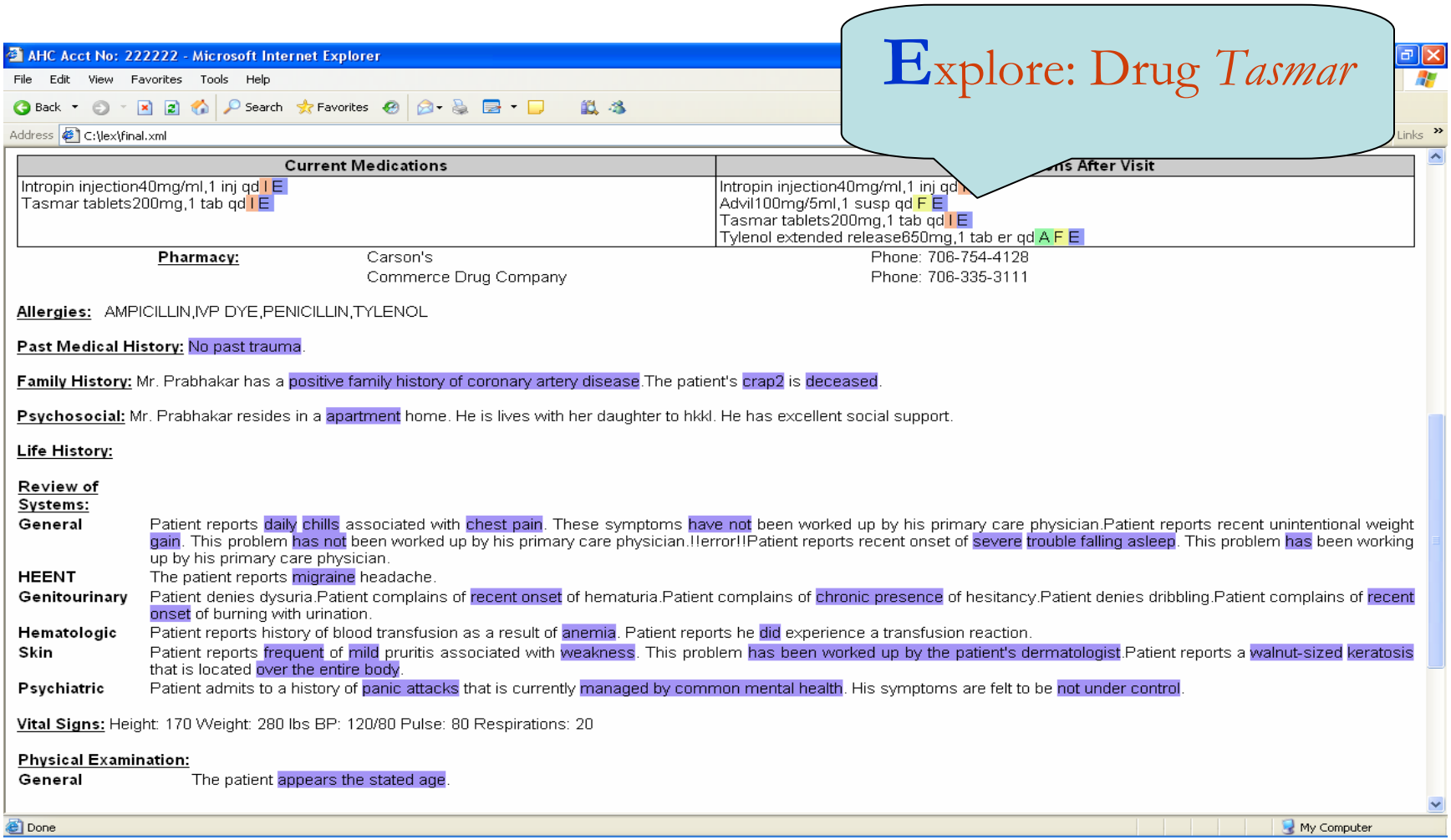
| | |
|---|---|
| **General** | Patient reports daily chills associated with chest pain. These symptoms have not been worked up by his primary care physician.Patient reports recent unintentional weight gain. This problem has not been worked up by his primary care physician.!!error!!Patient reports recent onset of severe trouble falling asleep. This problem has been working up by his primary care physician. |
| **HEENT** | The patient reports migraine headache. |
| **Genitourinary** | Patient denies dysuria.Patient complains of recent onset of hematuria.Patient complains of chronic presence of hesitancy.Patient denies dribbling.Patient complains of recent onset of burning with urination. |
| **Hematologic** | Patient reports history of blood transfusion as a result of anemia. Patient reports he did experience a transfusion reaction. |
| **Skin** | Patient reports frequent of mild pruritis associated with weakness. This problem has been worked up by the patient's dermatologist.Patient reports a walnut-sized keratosis that is located over the entire body. |
| **Psychiatric** | Patient admits to a history of panic attacks that is currently managed by common mental health. His symptoms are felt to be not under control. |

**Vital Signs:** Height: 170 Weight: 280 lbs BP: 120/80 Pulse: 80 Respirations: 20

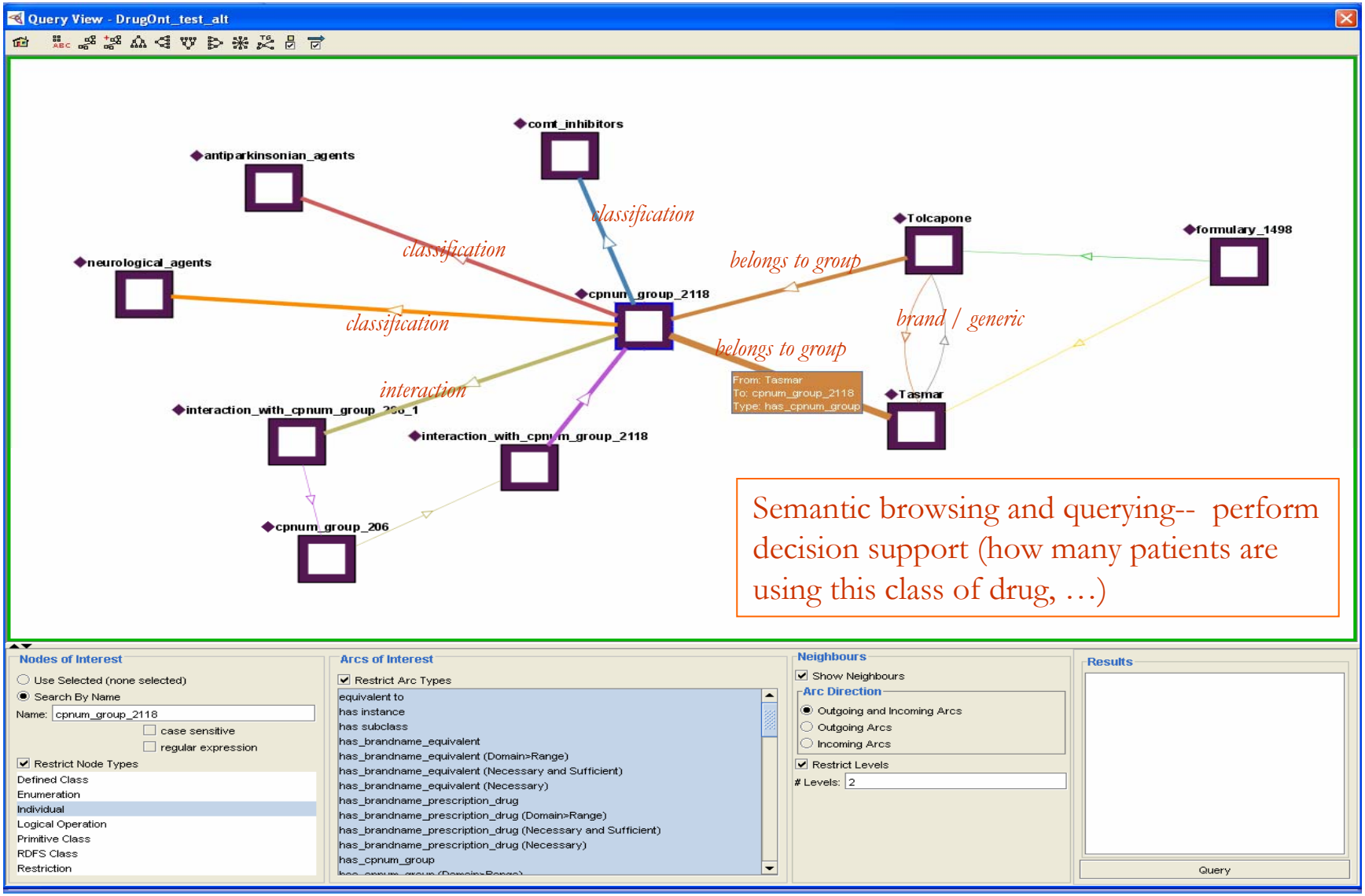
**Physical Examination:**

**General** The patient appears the stated age.

# Metadata-based Semantic Annotations: Active Semantic EMR



# Metadata-based Semantic Annotations: Active Semantic EMR



# Functional Requirements

- Use Cases
- Metadata-based Semantic Annotation
- *Recombinant Data:* Information Integration and Aggregation ☑
  - Discovery Decision Support
- Ontology-driven Decision Support
- Knowledge Update and Maintenance

# Information Integration: Ontology

***OWL ontologies that blend knowledge from the Clinical and Genomic Domains***

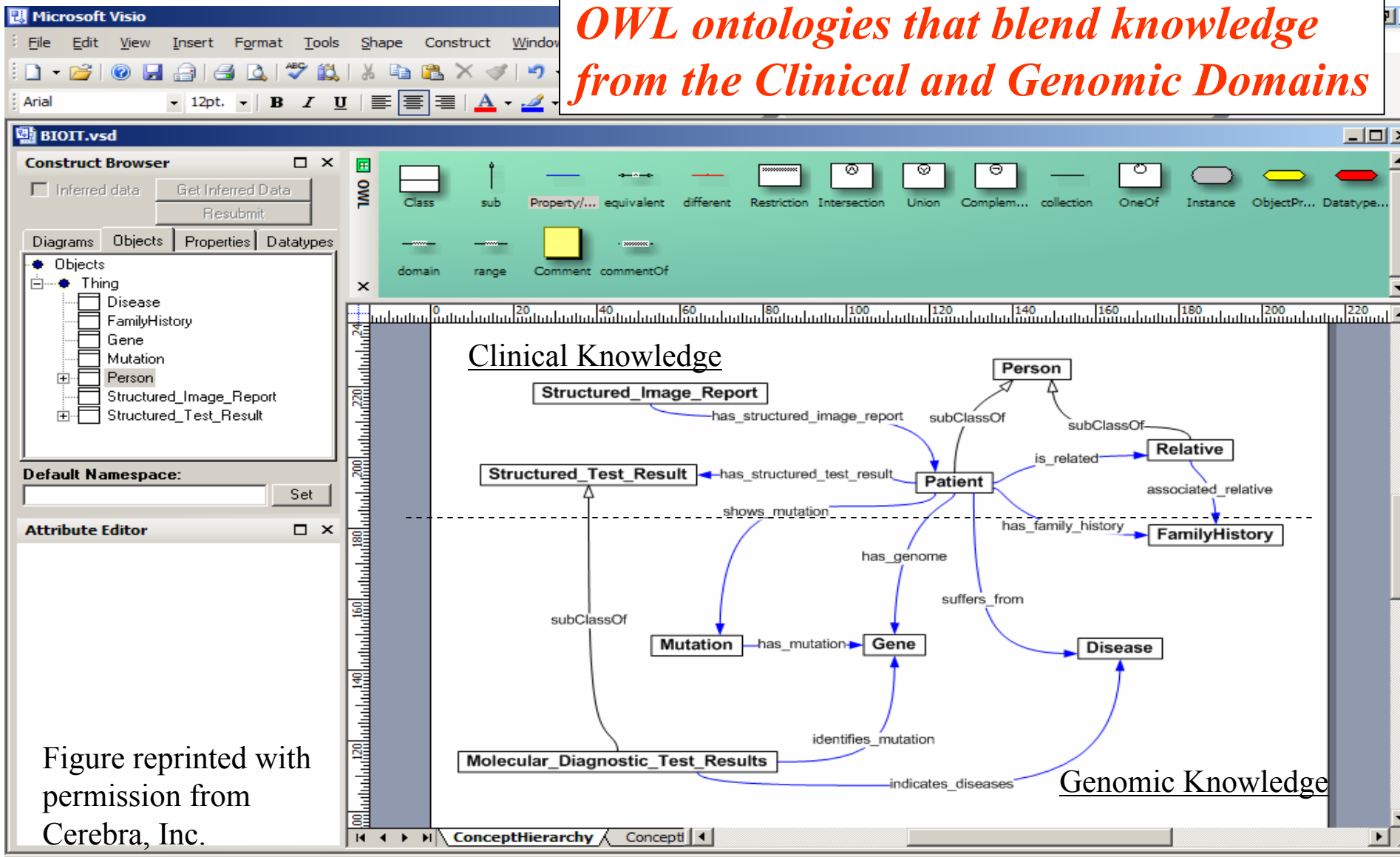
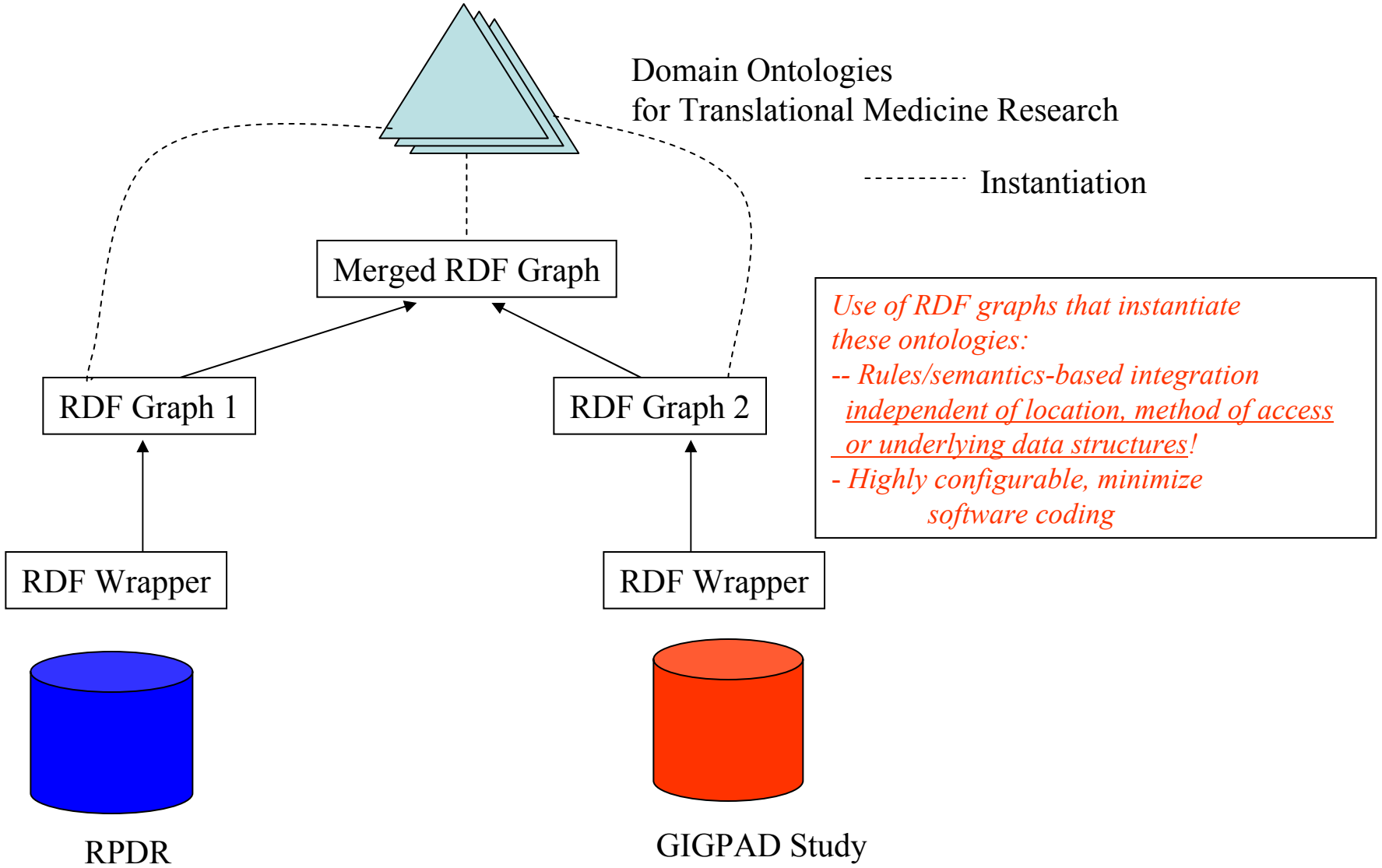


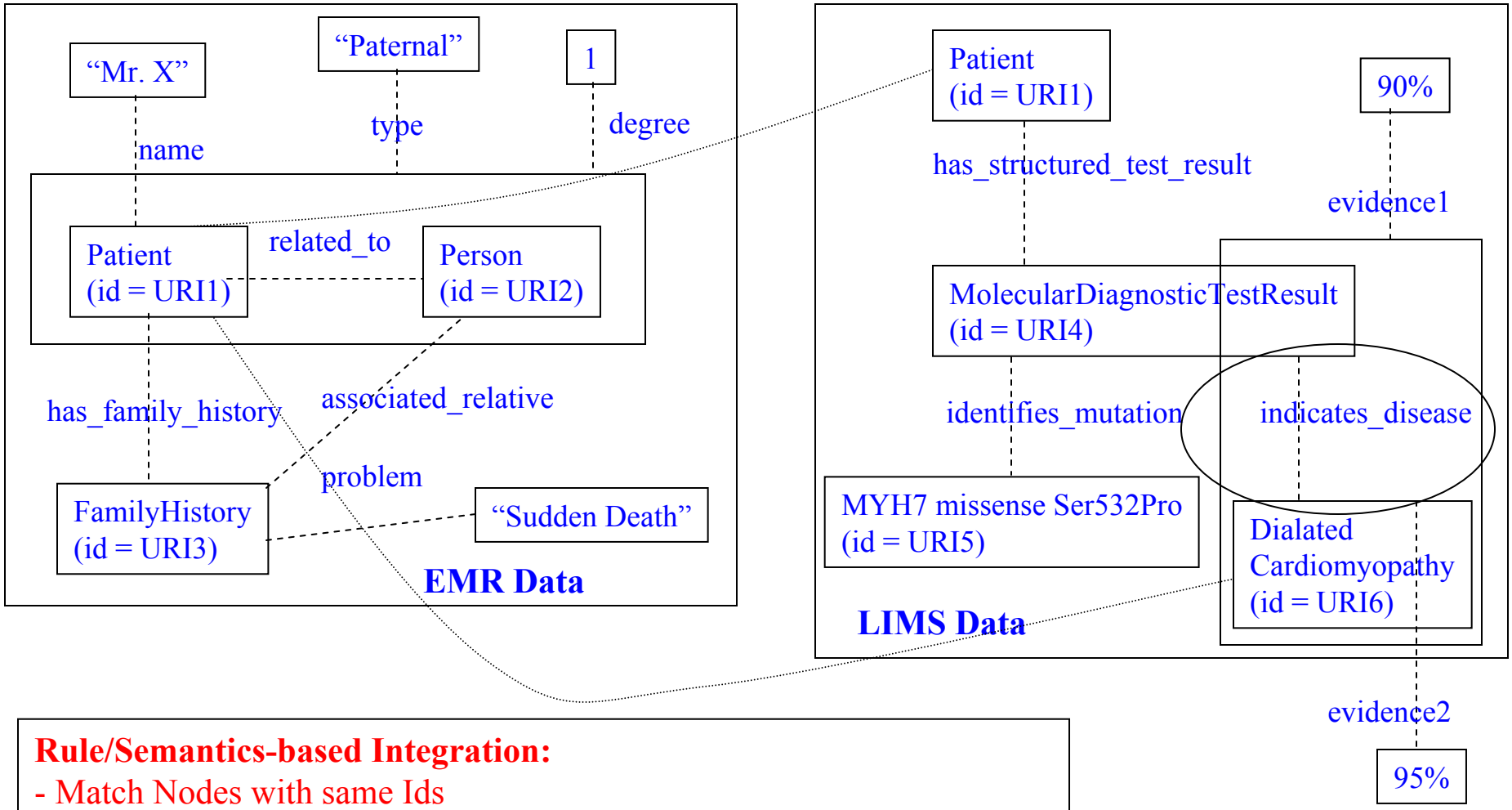

Figure reprinted with permission from Cerebra, Inc.

# Information Integration: Architecture




*Use of RDF graphs that instantiate these ontologies:*
*-- Rules/semantics-based integration independent of location, method of access or underlying data structures!*
*- Highly configurable, minimize software coding*

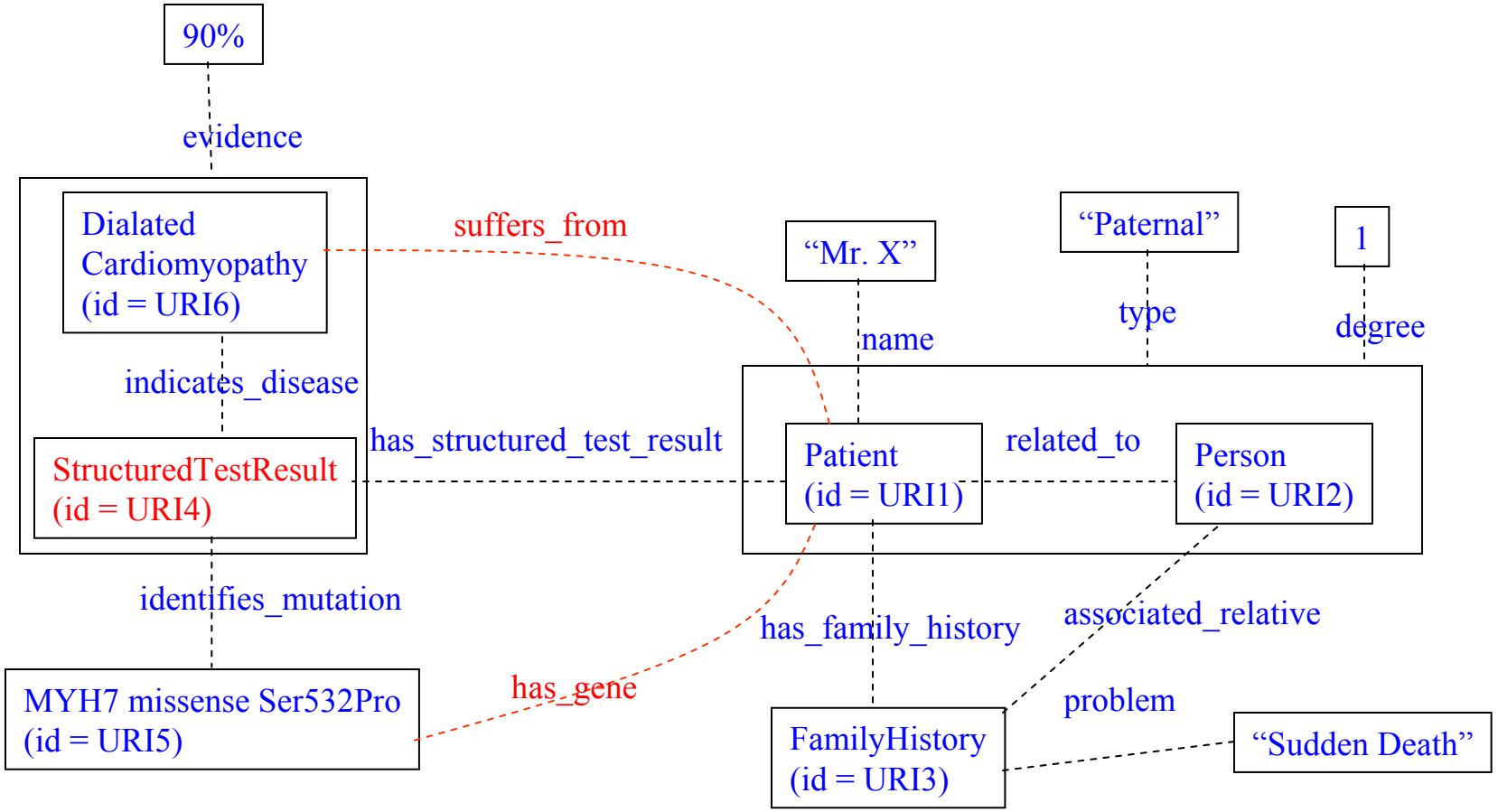
# Bridging Clinical and Genomic Information




**Rule/Semantics-based Integration:**

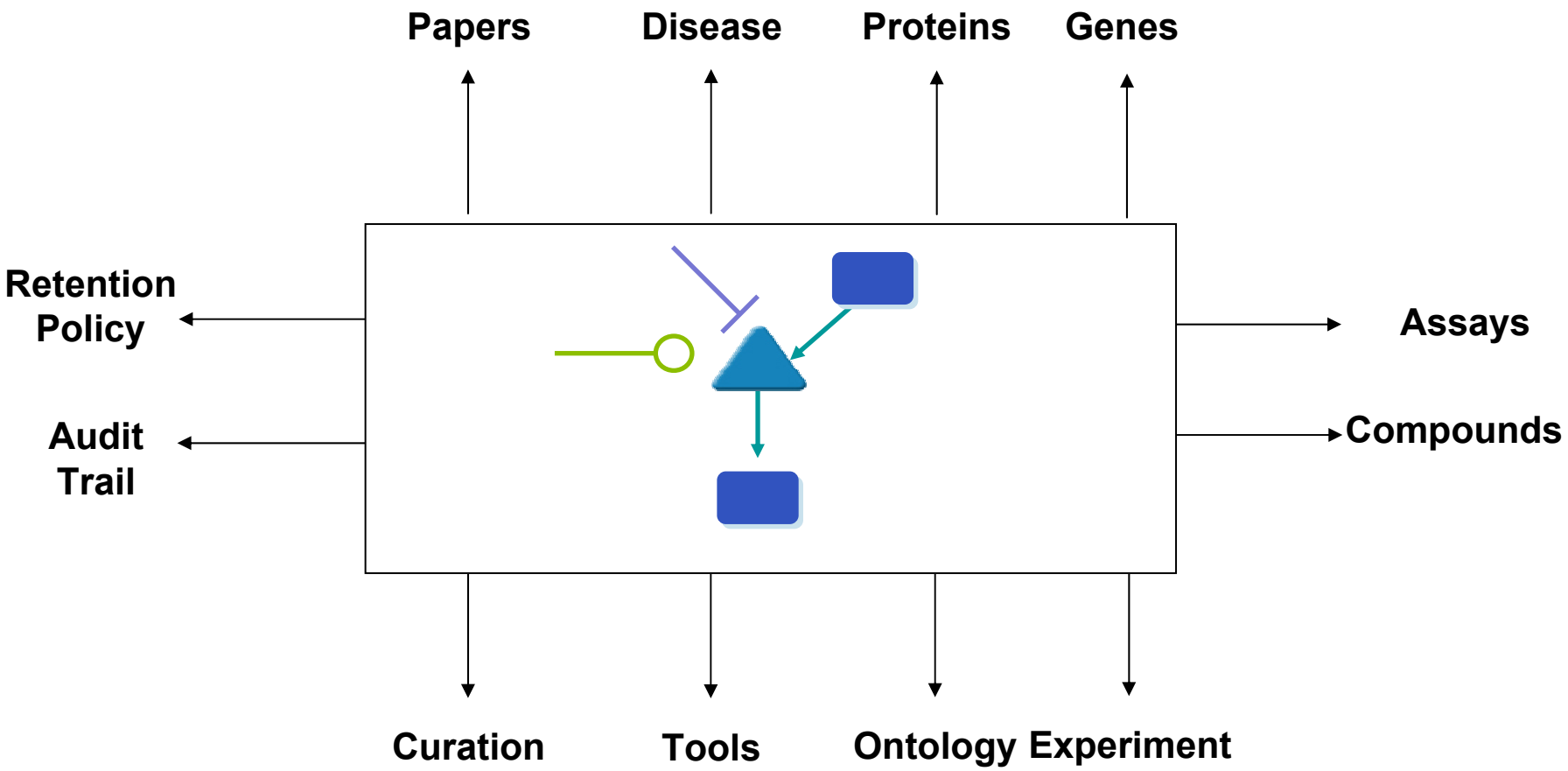
- Match Nodes with same Ids
- Create new links: IF a patient's structured test result indicates a disease
  THEN add a "suffers from link" to that disease

# Bridging Clinical and Genomic Information

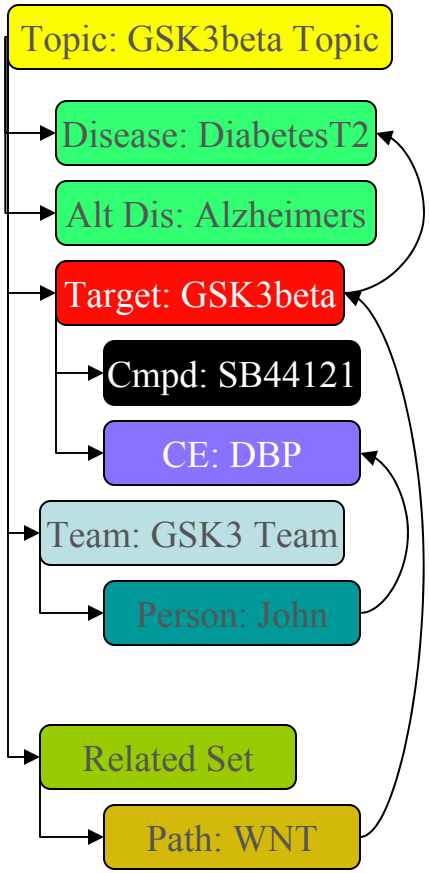


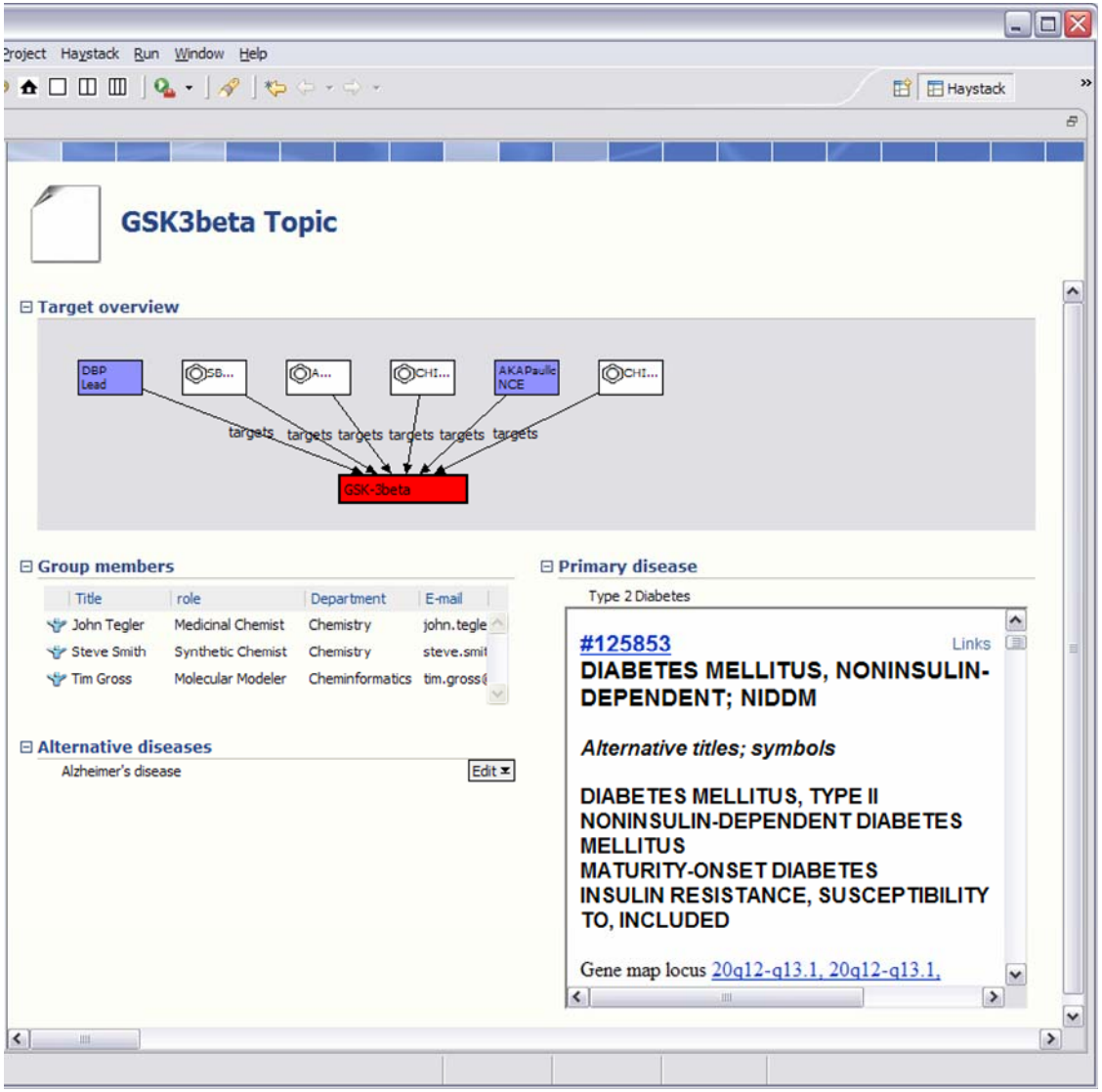

***RDF Graphs provide a semantics-rich substrate for decision support. Can be exploited by SWRL Rules***

# Information Integration: Biology Requirements



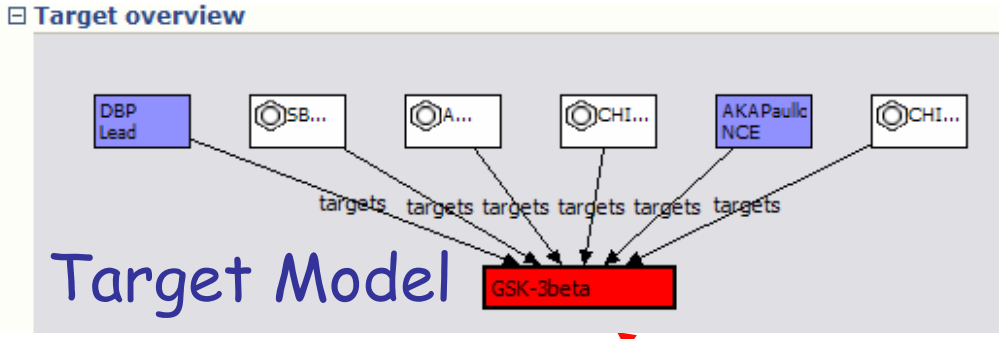
# Information Integration: Drug Discovery

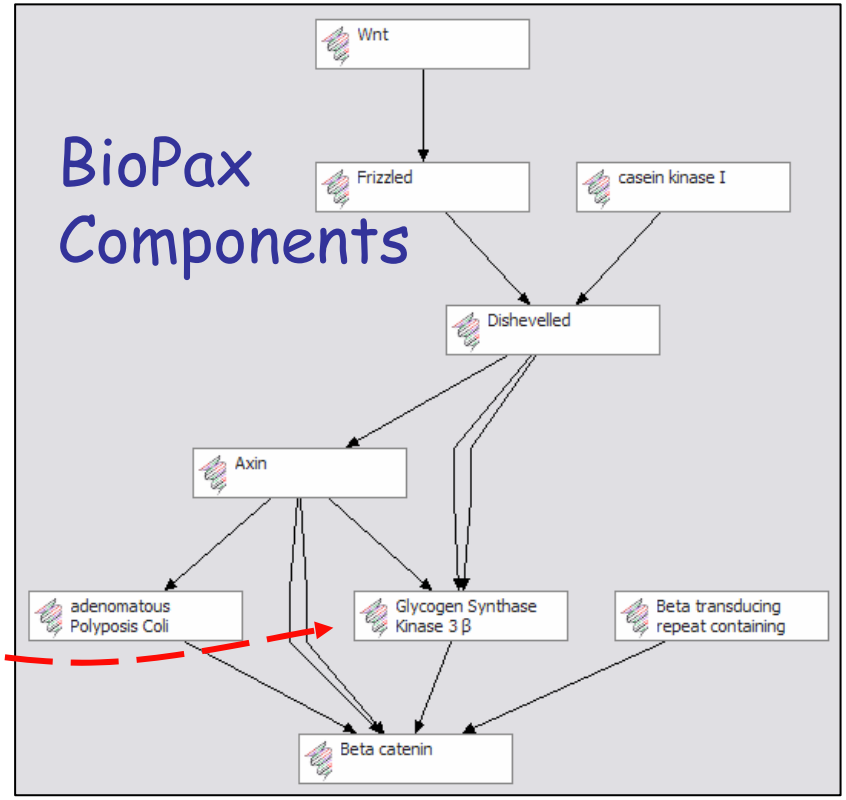


# Bridging Chemistry and Molecular Biology

**Semantic Lenses: Different Views of the same data**



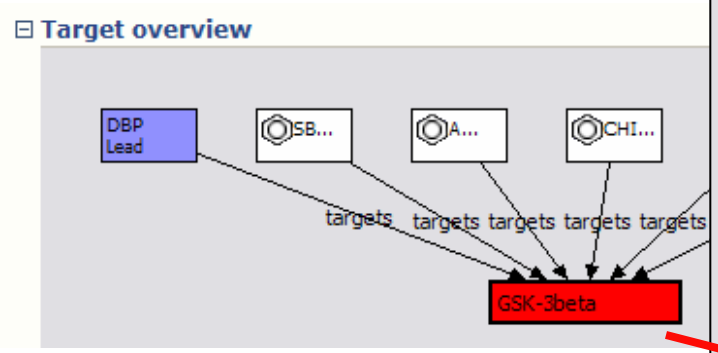



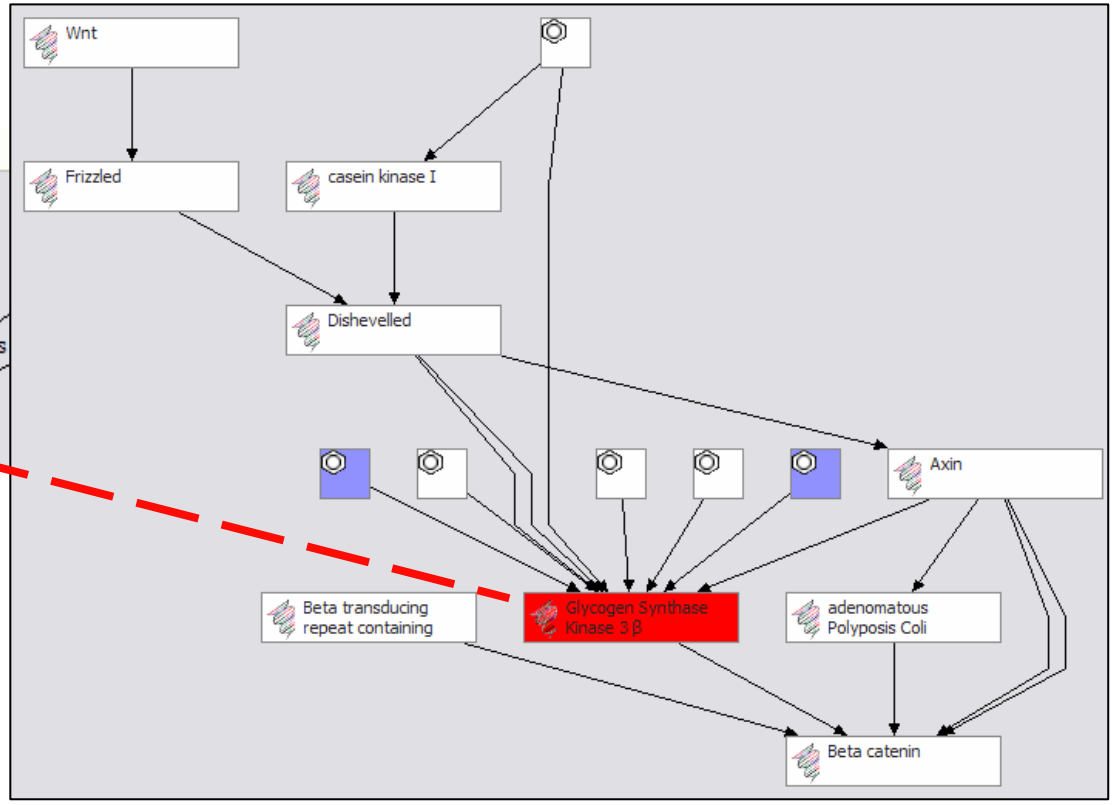

urn:lsid:uniprot.org:uniprot:P49841

**Apply Correspondence Rule:**
if ?target.xref.lsid == ?bpx:prot.xref.lsid
then ?target.correspondsTo.?bpx:prot

# Bridging Chemistry and Molecular Biology

- Lenses can aggregate, accentuate, or even analyze new result sets
- Behind the lens, the data can be persistently stored as RDF-OWL




- Correspondence does not need to mean "same descriptive object", but may mean objects with identical references

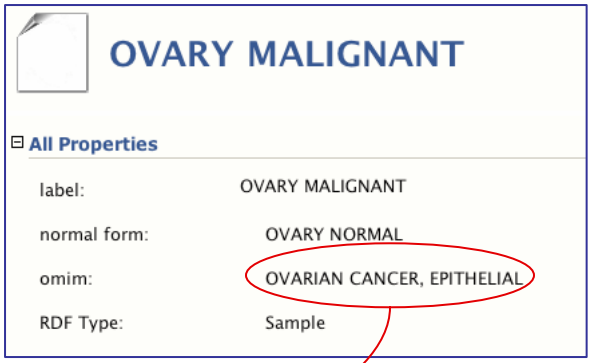
# Case Study: Drug Safety
# '*Safety Lenses*'

- **Lenses can 'focus data in specific ways**
  - Hepatoxicity, genotoxicity, hERG, metabolites
- **Can be "wrapped" around statistical tools**
- ***Aggregate* other papers and findings (*knowledge)* in context with a particular project**
- ***Align* animal studies with clinical results**
- **Support special "Alert-channels" by regulators for each different toxicity issue**
- **Integrate JIT information on newly published mechanisms of actions**

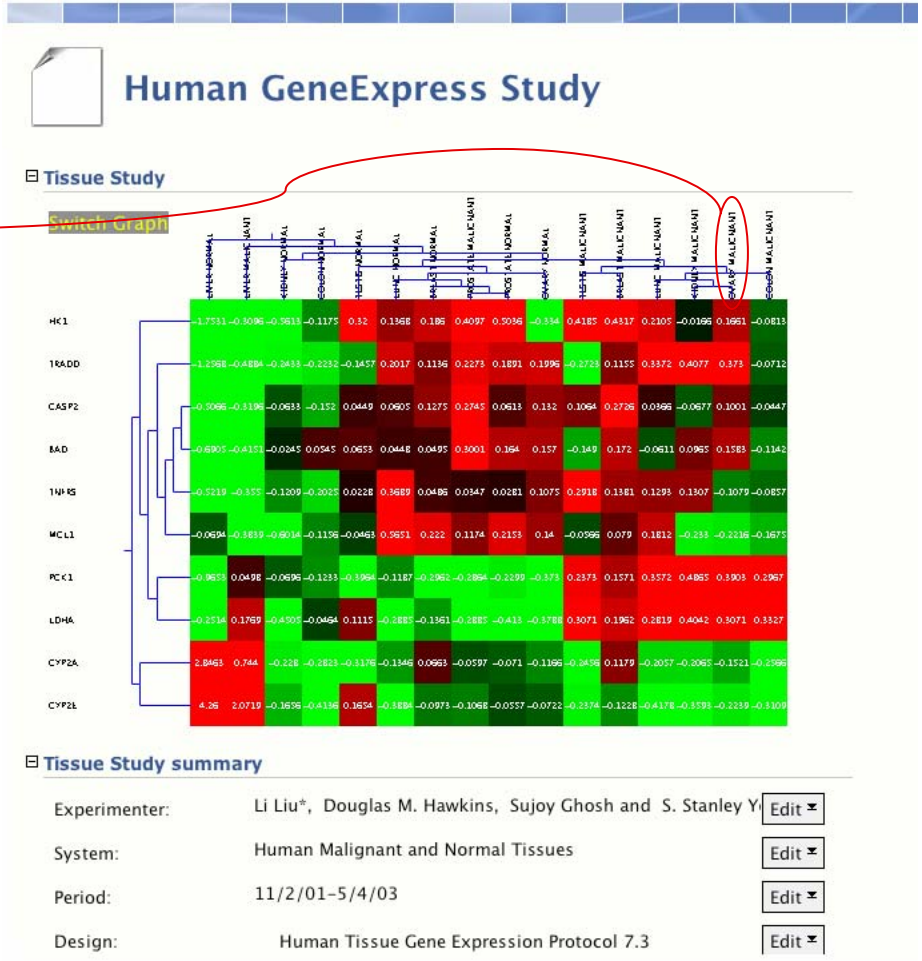
# GeneLogic *GeneExpress* Data

- **Additional relations and aspects can be defined additionally**

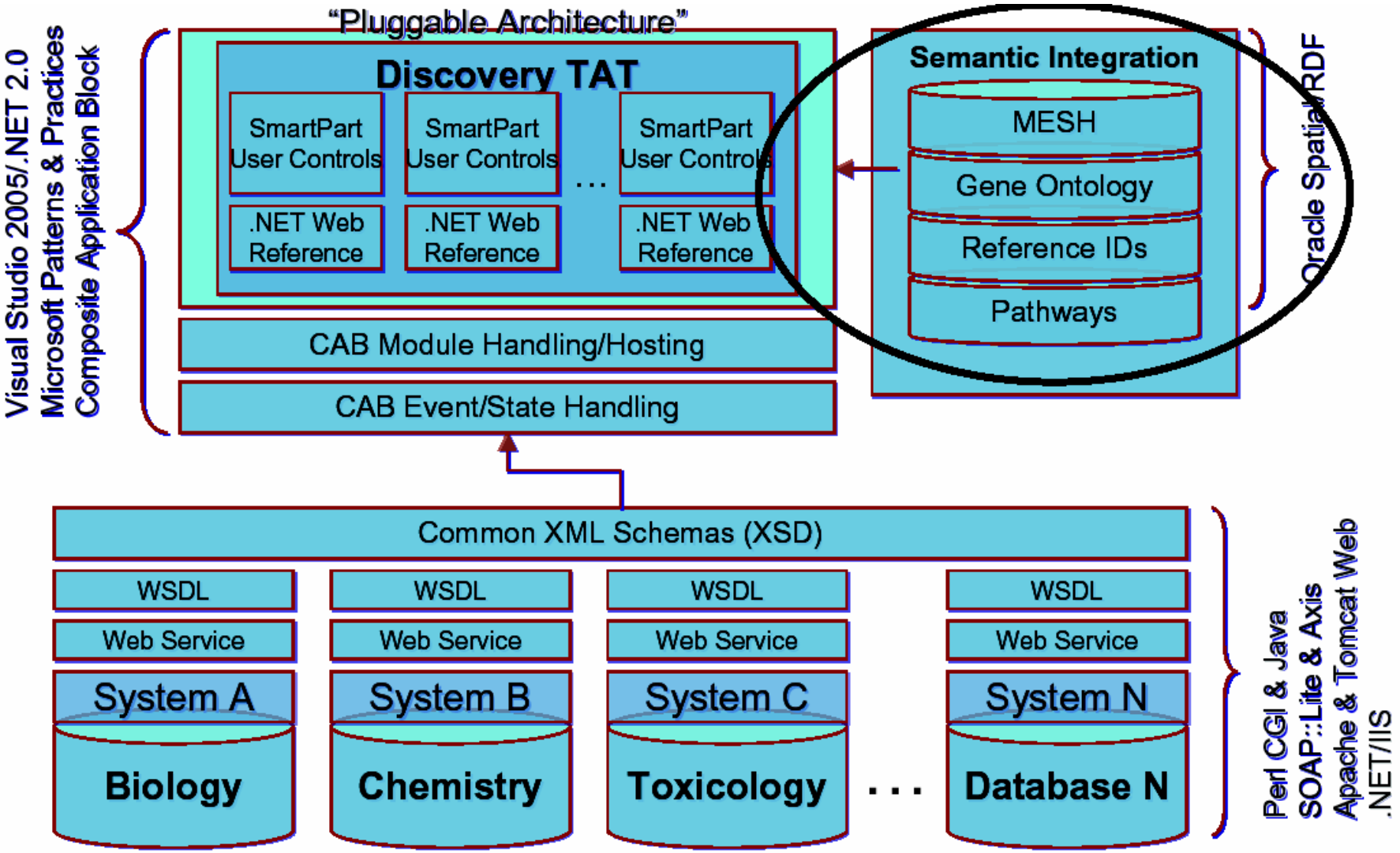
Diseased Tissue




Links to OMIM (RDF)



# Drug Discovery Architecture



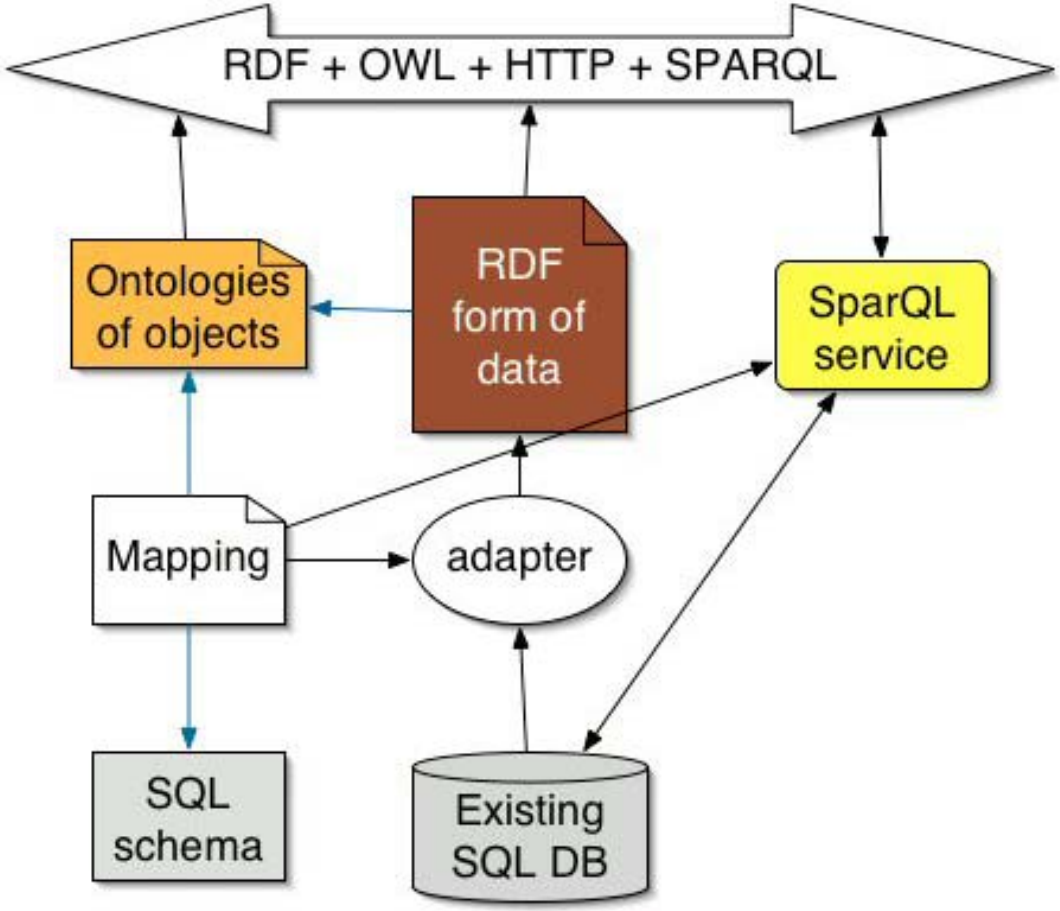
# Advantages of Semantics

- RDF: Graph based data model
  - More expressive than the tree based XML Schema Model
- RDF: Reification
  - Same piece of information can be given different values of belief by different clinical genomic researchers
- Potential for “Schema-less” Data Integration
  - Hypothesis driven approach to defining mapping rules
  - Can define mapping rules on the fly
- Incremental approach for Data Integration
  - Ability to introduce new data sources into the mix incrementally at low cost
- Use of Ontology to disallow meaningless mapping rules?
  - For e.g., mapping a gene to a protein…

# Information Integration: Two Approaches

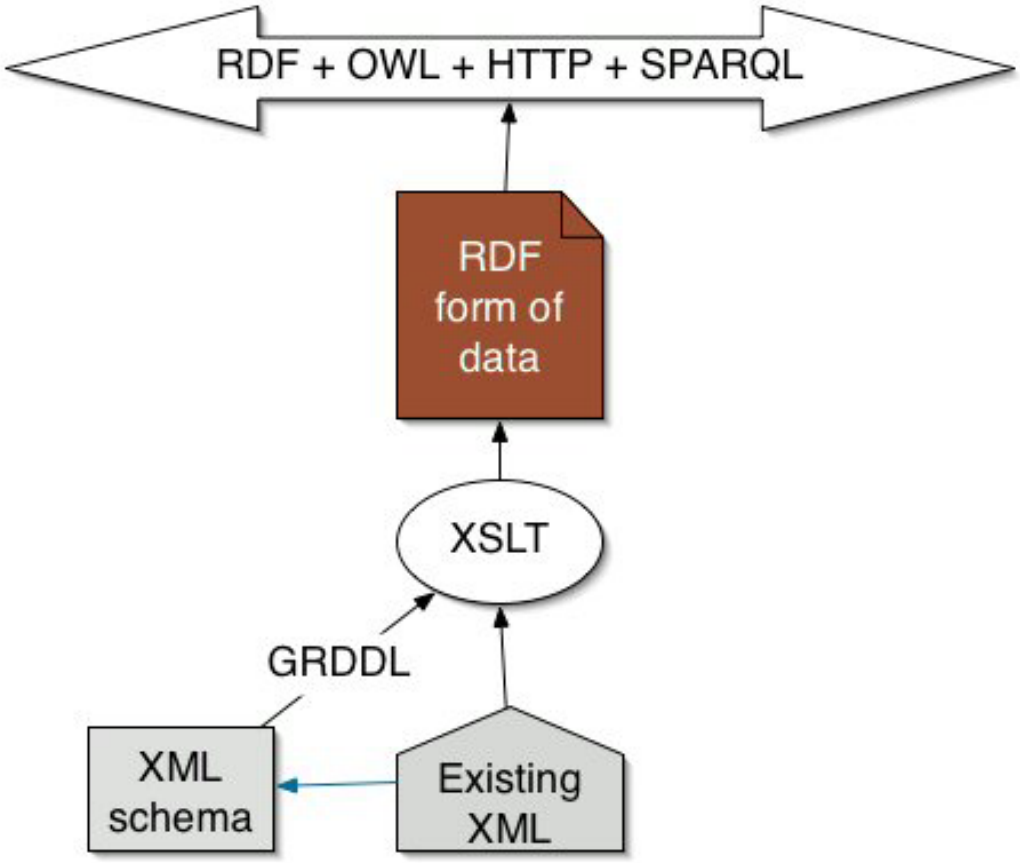
- RDF Data Warehousing
  - Data is stored in a centralized data repository
  - Example: Oracle RDF Data Store
- RDF Wrappers/Interfaces
  - The data remains in the source repository
  - Create RDF Wrappers and Interfaces to expose and RDF view over the repository
  - Example: Jena RDF Engine and D2R Mapping Tool

# Adapting RDBMS for RDF



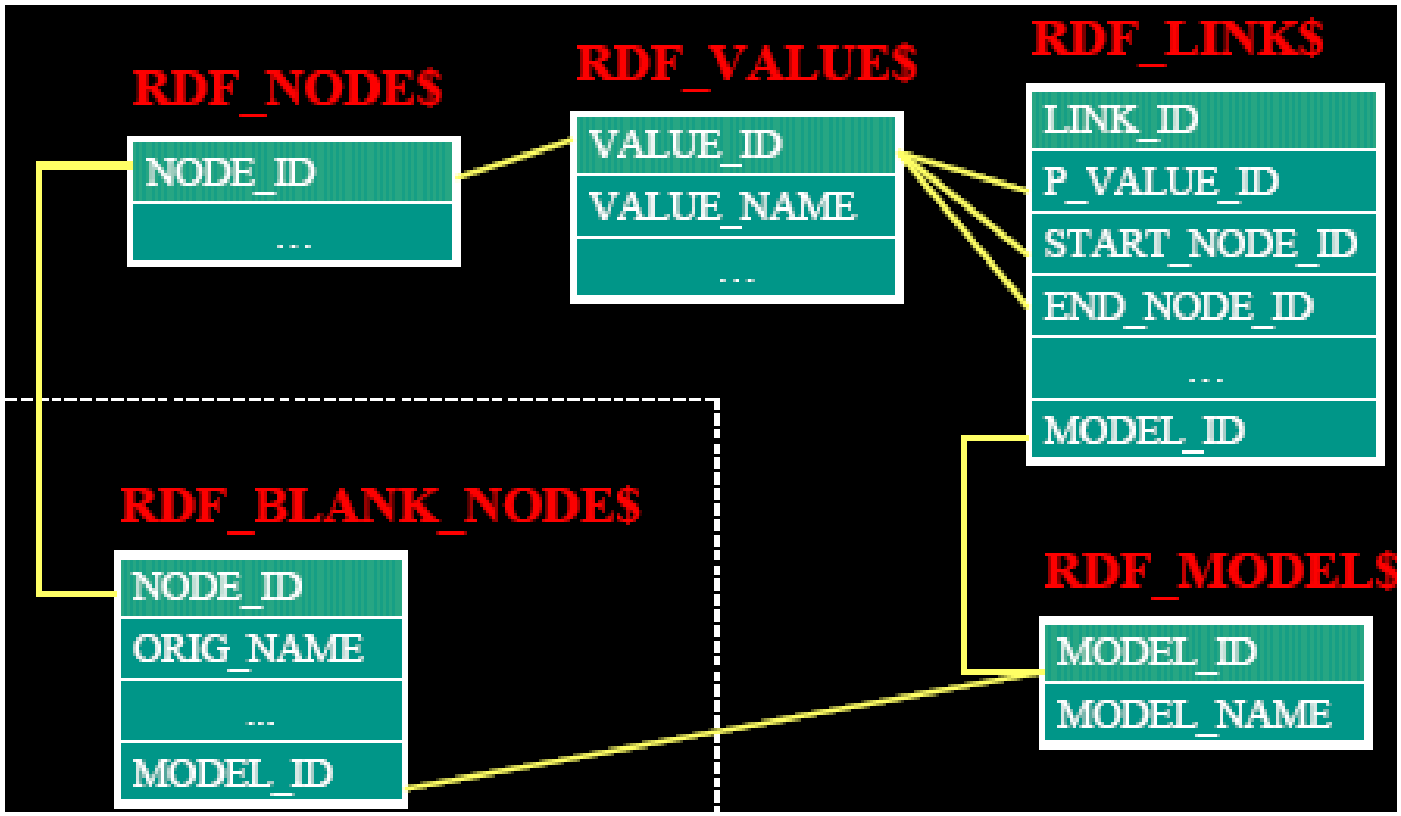

Source: Tim Berners-Lee, Bio-IT World 2005

# Adapting XML Schema to RDF




Source: Tim Berners-Lee, Bio-IT World 2005

# Oracle RDF Data Store: Schema



# Oracle RDF Data Store: Hypothetical RDB to RDF Mappings

**Employee Table**

| EmpID | Name | SiteID | Role |
|---|---|---|---|
| 110 | S Hagan | 1 | Development |
| 120 | B Shimp | 2 | Marketing |
| 130 | K Bock | 3 | Sales |

| SQL Component | URI relative to database |
|---|---|
| Table EMPLOYEE | EMPLOYEE/schema#EMPLOYEE |
| Column EMPLOYEE. EMPID | EMPLOYEE/schema#empid |
| Row with EMPID=110 | EMPLOYEE/rowBy/empid/110 |
| NAME cell in that row | EMPLOYEE/rowBy/empid/110#name |

# Oracle RDF Data Store: SPARQL-like Query Capability

- A table function allows a graph query to be embedded in a SQL query
- Searches for an arbitrary pattern against the RDF data
- Includes inferencing, based on RDF, RDFS, and user-defined rules
- Automatically resolve multiple representations of the same point in value space, e.g. 1 vs. 1.00

# RDF Querying Problem

- Given
  - RDF graphs: the data set to be searched
  - Graph Pattern: containing a set of variables
- Find
  - Matching Subgraphs
- Return
  - Sets of variable bindings: where each set corresponds to a Matching Subgraph

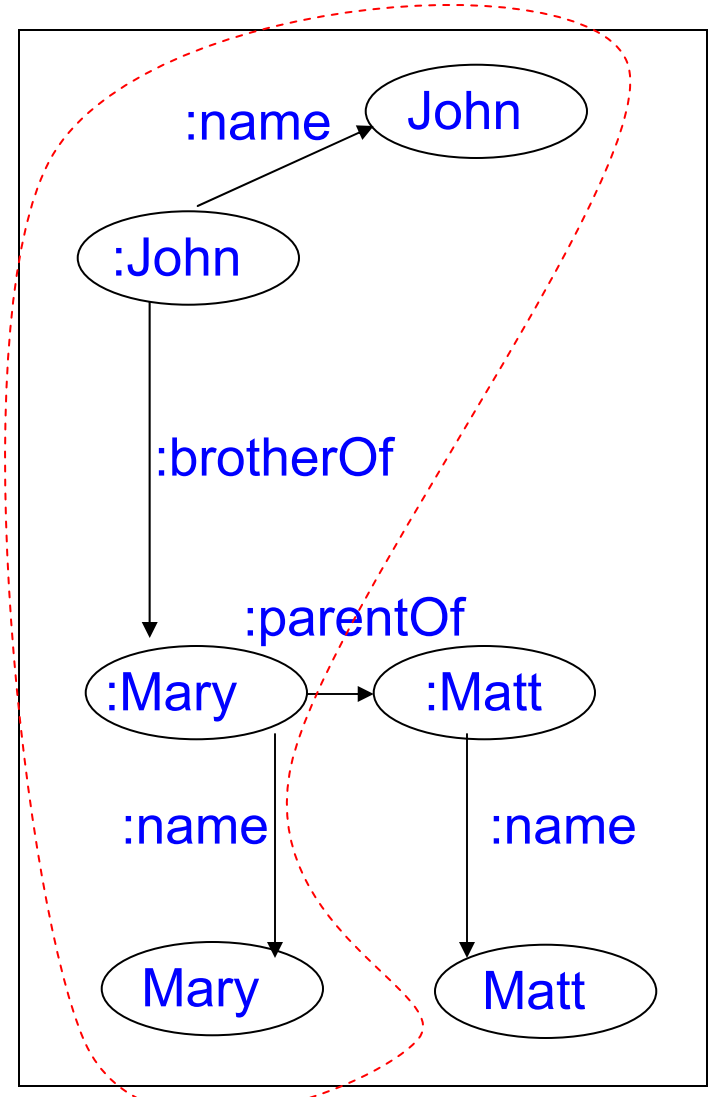
# RDF Query Example

**Family Data:** (:John :brotherOf :Mary)
(:Mary :parentOf :Matt)
(:John :name "John")
(:Mary :name "Mary")
(:Matt :name "Matt")

**Graph Pattern:** (names of Mary's brothers)
(?x :brotherOf ?y)
(?y :name "Mary")
(?x :name ?n)

**Variable Bindings:**
x = :John, y = :Mary, n = "John"

**Matching Subgraph:**
(:John :brotherOf :Mary)
(:Mary :name "Mary")
(:John :name "John")




Matching Subgraph

# RDF Querying Issues

- Support specification of graph pattern-based SQL query
- Occurrence of same variables in multiple triples of graph pattern: Processing requires self-join
  - e.g. **(?x :brotherOf ?y)**
    **(?y :name "Mary")**
    **(?x :name ?n)**
- Query processing (e.g for filter conditions, ORDER BY) requires datatype-specific comparison semantics

**Schema Triple: (:age rdfs:range xsd:int)**
**Graph Pattern: (?x :age ?a)**
**Filter Condition: a > 60**
**ORDER BY: a DESCENDING**

# RDF Querying Issues: Inference

- Query processing may involve Inferencing

- Example:

**Data**: **(:Jim :brotherOf :John) (:John :fatherOf :Mary)**
**Graph Pattern:(?x :uncleOf ?y)**
**Result: Empty**

**Rule:**
**(?x :brotherOf ?y) (?y :fatherOf ?z)**
**➔ (?x :uncleOf ?z)**
**Inferred data: (:Jim :uncleOf :Mary)**
**Result: x = :Jim, y = :Mary**

# RDF Querying Approach

- General Approach
  - Create a new (declarative, SQL-like) query language
  - e.g.: RQL, SeRQL, TRIPLE, N3, Versa, SPARQL, RDQL, RDFQL, SquishQL, RSQL, etc.

- SQL-based Approach
  - Introduces a *SQL Table Function RDF_MATCH* that uses SPARQL-like graph pattern to express RDF queries

- Benefits of SQL-based Approach
  - Leverages all the powerful constructs in SQL (e.g., SELECT / FROM / WHERE, ORDER BY, GROUP BY, aggregates, Join) to process graph query results
  - RDF queries can easily be combined with conventional queries on database tables thereby avoiding staging

# Embedding RDF Query in SQL

- **SELECT …**
  **FROM …,**
  **TABLE (**

  RDF Query
  (expressed as RDF_MATCH
  Table Function invocation)

  **) t, …**
  **WHERE …;**

- Use of RDF_MATCH Table Function allows embedding a graph query in a SQL query

# RDF_MATCH Table Function

- Input parameters

```
RDF_MATCH (
    Pattern,        ← graph pattern
    Models,         ← Data (set of RDF graphs)
    RuleBases,      ← Rules (0 or more rulebases)
    Aliases         ← list of prefixes for namespaces
    )
```

- Returns a set of columns containing variable bindings
  - Variable matching URI returned as single VARCHAR2 column with the same name (e.g. x for ?x)
  - Variable matching literal returned as a pair of VARCHAR2 columns with a name (e.g. x for ?x) and the type (x$type for ?x)

# RDF_MATCH Example

- Example: student reviewers less than 25 years old

```
SELECT t.r reviewer,   t.c conf,   t.a age
FROM TABLE (
   RDF_MATCH (
                        '(?r rdf:type :Student)
                         (?r :reviewerOf ?c)
                         (?r :age ?a)',
      RDFModels('reviewers'),
      NULL,
      RDFAliases(…))
) t
WHERE  t.a < 25;
```

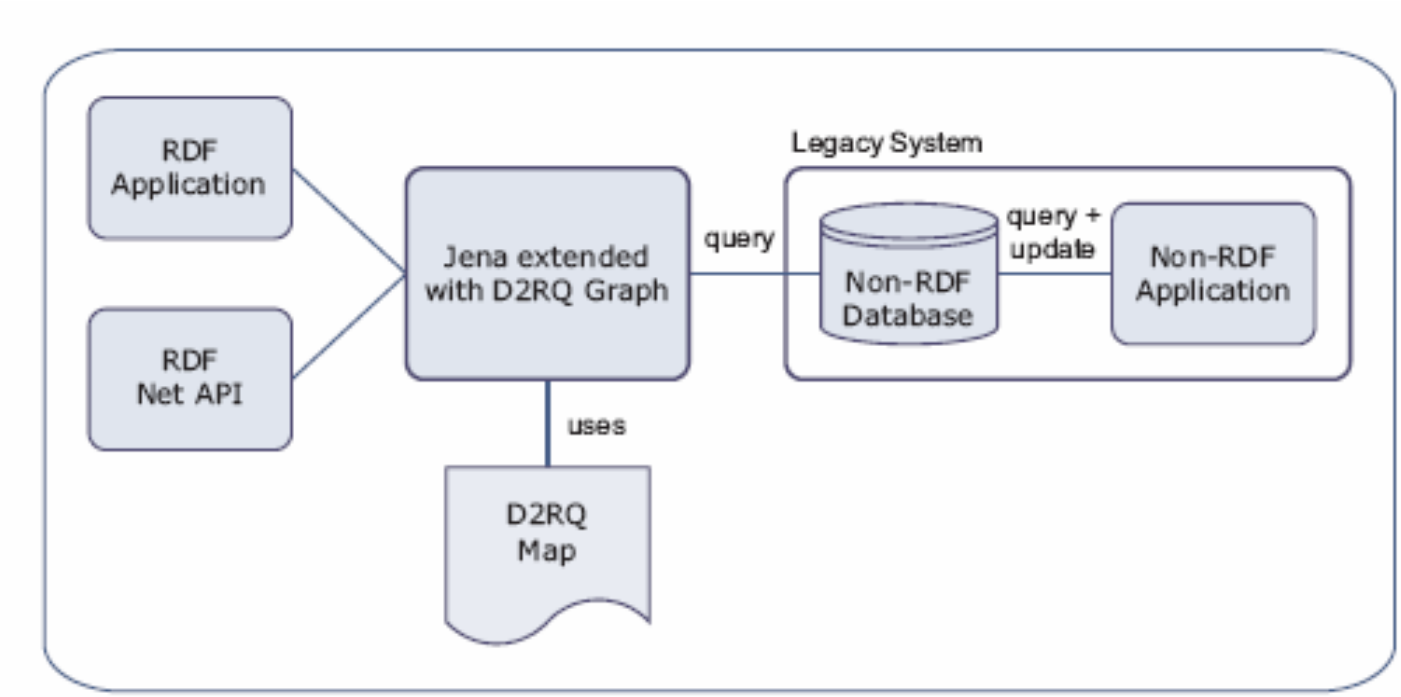
# Uniprot Sample Queries using Oracle RDF Data Store

## UniProt Sample Queries

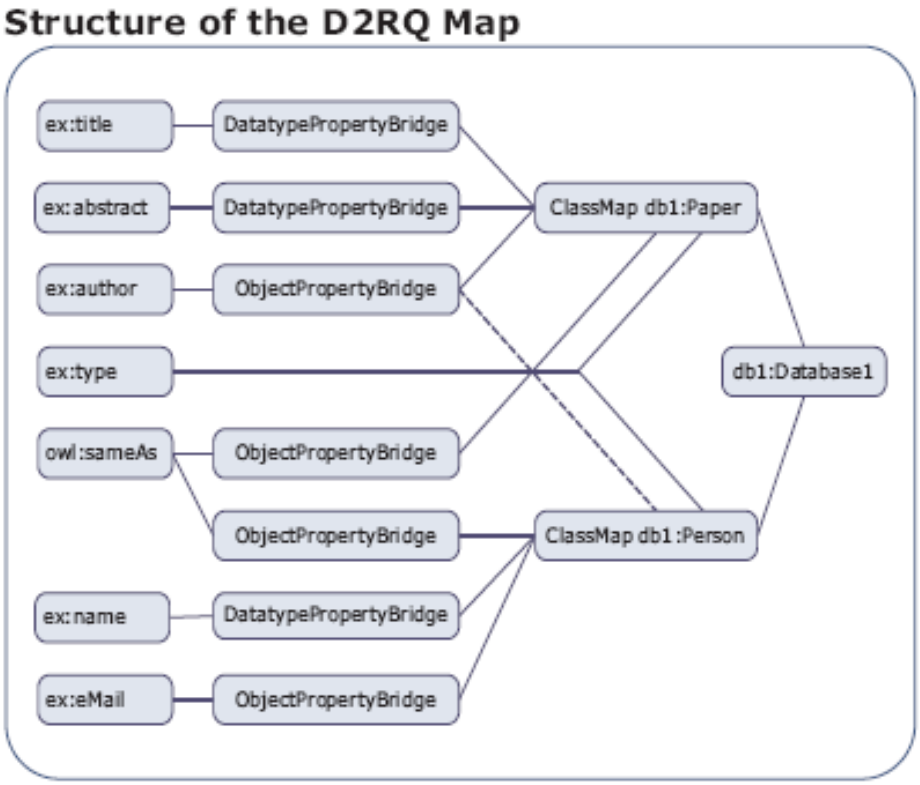
| Description | Pattern | Projection | Result limit |
|---|---|---|---|
| Q1: Display the ranges of transmembrane regions | 6 triples<br>5 vars | 3 vars | 15000 rows |
| Q2: List proteins with publications by authors with matching names | 5 triples<br>5 vars<br>1 LIKE pred. | 3 vars | 10 rows |
| Q3: Count the number of times a publication by a specific author is cited | 3 triples<br>2 vars | 0 vars | 32 rows |
| Q4: List resources that are related to proteins annotated with a specific keyword | 3 triples<br>2 vars | 1 var | 3000 rows |
| Q5: List genes associated with human diseases | 7 triples<br>5 vars | 3 vars | 750 rows |
| Q6: List recently modified entries | 2 triples<br>2 vars<br>1 range pred. | 2 vars | 8000 rows |

(Chong et al, VLDB Conference, Sep. 2005 – from Erik Jain's work?)

# RDF Applications: Jena



# Mapping RDBMS to RDF: D2RQ



# RDF Applications: Jena

## RDQL Query

```
SELECT ?x
WHERE (<http://www.papers.org/3465>,
       ex:author, ?x)
```

## SQL Query

```
SELECT Persons.Email
FROM PersonPaper, Persons
  WHERE PersonPaper.PersonID =
        Persons.PersonID
  AND PersonPaper.PaperID = 3465;
```

## Databaes Tables

Persons

| PersonID | Name | Email |
|---|---|---|
| 1 | Andy Seaborne | andy.seaborne@hp.com |
| 2 | Christian Bizer | chris@bizer.de |

Papers

| PaperID | Title |
|---|---|
| 3465 | D2RQ-Treating Non RDF Databases as Virtual RDF Graphs |
| 5728 | The Impact of Semantic Web Technologies on Job Recr. |

PersonPaper

| PaperID | PersonID |
|---|---|
| 3465 | 2 |
| 3465 | 1 |
| 5728 | 2 |

# Advantage: “Schema-free” data integration

- Low cost approach for data integration
- No need for maintenance of costly schema mappings
- Ability to “merge” RDF graphs based on simple declarative rules that specify:
  - Equality of URIs
  - Connecting nodes of same type
  - Connecting two nodes associated by a “path”
- Disadvantage: Potential for specifying spurious non-sensical rules

# “Schema-free” Integration Example

- Match nodes with the same URIs
  - Can be represented using OWL same-as
- If a patient’s structured test result indicates a disease, then the patient suffers from the disease
  - has_structured_test_result.indicates_disease = suffers_from
  - Needs Rules for representation: Role composition not supported by OWL.

# Rule-based approaches

- Rule ML
- Semantic Web Rules Language (SWRL)
- Production Rules Systems
  - ILOG
  - Blaze
- Open Source Rule Engines
  - JESS (Forward chaining, production rules)
  - XSB (Backward chaining, prolog implementation)

# Rule ML

```
<imp>
        <_head>
                <atom>
                        <rel>suffers_from</rel>
                        <var>patient</var>
                        <ind>”Hypertrophic Cardiomyopathy”</var>
                </atom>
        </_head>
        <_body>
                <and>
                        <atom>
                                <rel>has_structured_result</rel>
                                <var>patient</var>
                                <var>test_result</var>
                        </atom>
                        <atom>
                                <rel>indicates</rel>
                                <var>test_result</var>
                                <var>”Hypertrophic Cardiomyopathy”</var>
                        </atom>
                </and>
        </_body>
</imp>
```

# SWRL

```
Implies(Antecedent(Patient(I-variable(x)),
                   TestResult(I-variable(y)),
                   has_structured_result(I-variable(x), I-variable(y)),
                   indicates(I-variable(y), “Hypertrophic Cardiomyopathy”))
        Consequent(suffers_from(I-variable(x), “Hypertrophic Cardiomypathy”))
```

# Production Systems: ILOG

**Class Patient: Person**
method get_name(): string;
method has_genetic_test_result(): StructuredTestResult;
method has_mutation(): string;
method suffers_from(): Disease;
method set_suffers_from(Disease): void;

**Class StructuredTestResult**
method get_patient(): Patient;
method indicates_disease(): Disease;
method identifies_mutation(): set of string;
method evidence_of_mutation(string): real

```
the_result = the_patient.has_genetic_test_result();

IF the_patient.has_genetic_test_resutl().indicates_disease()
                                    = “Hypertrophic Cardiomyopathy”
THEN
   the_patient.set_suffers_from(“Hypertrophic Cardiomyopathy”)
```

# Some thoughts on Rules

- Ease of use: SWRL is comparatively easier to use
- Expressivity: SWRL expressivity is less than RuleML
- Ontological Underpinnings: SWRL enables incorporation of OWL classes and constraints.
- Re-uses Rule ML and OWL standards, e.g., tags, XML, etc.
- Production Systems such as ILOG and Blaze have their own internal XML-based representation format.
  - SWRL could be a potential interchange language
  - Issues currently being investigated in the W3C RIF working group

# Reification: Annotation of existing data

- Level of accuracy of test result.
  - Sensitivity and Specificity of lab result
  - Level of confidence in genotyping or gene sequencing
- Probabilistic relationships
  - Likelihood that a particular test result or condition is indicative of a disease or other medical condition
- Level of trust in a resource
  - Results from a lab may be trusted more than result from another
  - Results from well known health sites (NLM) may be trusted more than others
- Belief attribution
  - Scientific hypotheses may be attributed to appropriate researchers

# Functional Requirements

- Use Cases
- Metadata-based Semantic Annotation
- *Recombinant Data:* Information Integration and Aggregation
  - Discovery Decision Support
- Ontology-driven Decision Support ☑
- Knowledge Update and Maintenance

# Clinical and Genomic Decision Support

IF the patient's LDL test result is greater than 120

AND the patient has a contraindication to Fibric Acid

THEN

Prescribe Zetia Lipid Management Protocol

Contraindication to Fibric Acid: Clinical Definition (Old)

The patient is contraindicated for Fibric Acid if he has an allergy to Fibric Acid or has elevated Liver Panel

Contraindication to Fibric Acid: Clinical+Genomic Definition (New)

The patient is contraindicated for Fibric Acid if he has an allergy to Fibric Acid or has elevated Liver Panel or has a genetic mutation Missense: XYZ3:Ser@$#Pro

Please note: Hypothetical – assume a genetic variant is a biomarker for patients contraindicated to Fibric Acid.

# Clinical and Genomic Decision Support: A Rules-based Implementation

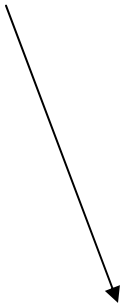
## Business Object Model Design

```
Class Patient: Person
method get_name(): string;
method has_genetic_test_result(): StructuredTestResult;
method has_liver_panel_result(): LiverPanelResult;
method has_ldl_result(): real;
method has_contraindication(): set of string;
method has_mutation(): string;
method has_therapy(): set of string;
method set_therapy(string): void;
method has_allergy(): set of string;
Method get_category(): set of string;

Class StructuredTestResult
method get_patient(): Patient;
method indicates_disease(): Disease;
method identifies_mutation(): set of string;
method evidence_of_mutation(string): real;

Class LiverPanelResult
method get_patient(): Patient;
method get_ALP(): real;
method get_ALT(): real;
method get_AST(): real;
method get_Total_Bilirubin(): real;
method get_Creatinine(): real;
```

# Clinical and Genomic Decision Support: A Rules-based Implementation

## Rule base Design

```
IF the_patient.has_ldl_result() > 120
AND ((the_patient.has_liver_panel_result().get_ALP() ≥ <NormalRange>
      AND the_patient.has_liver_panel_result().get_ALT() ≥ <NormalRange>
      AND the_patient.has_liver_panel_result().get_AST() ≥ <NormalRange>
      AND the_patient.has_liver_panel_result().get_Total_Bilirubin() ≥ <NormalRange>
      AND the_patient.has_liver_panel_result().get_Creatinine() ≥ <NormalRange>)
    OR "Fibric Acid Allergy" ∈ the_patient.has_allergy()
    OR "Missense: XYZ3:Ser@$#Pro" ∈ the_patient.has_mutation())
THEN
    the_patient.set_therapy("Zetia Lipid Management Protocol")
```



Definition of "Fibric Acid Contraindication"

# Clinical and Genomic Decision Support: Definitions vs Decisions

Commonly occurring design pattern:

- The definition of a “Fibric Acid Contraindication” is represented using rules.
- The decision related to therapeutic intervention is also represented using rules.

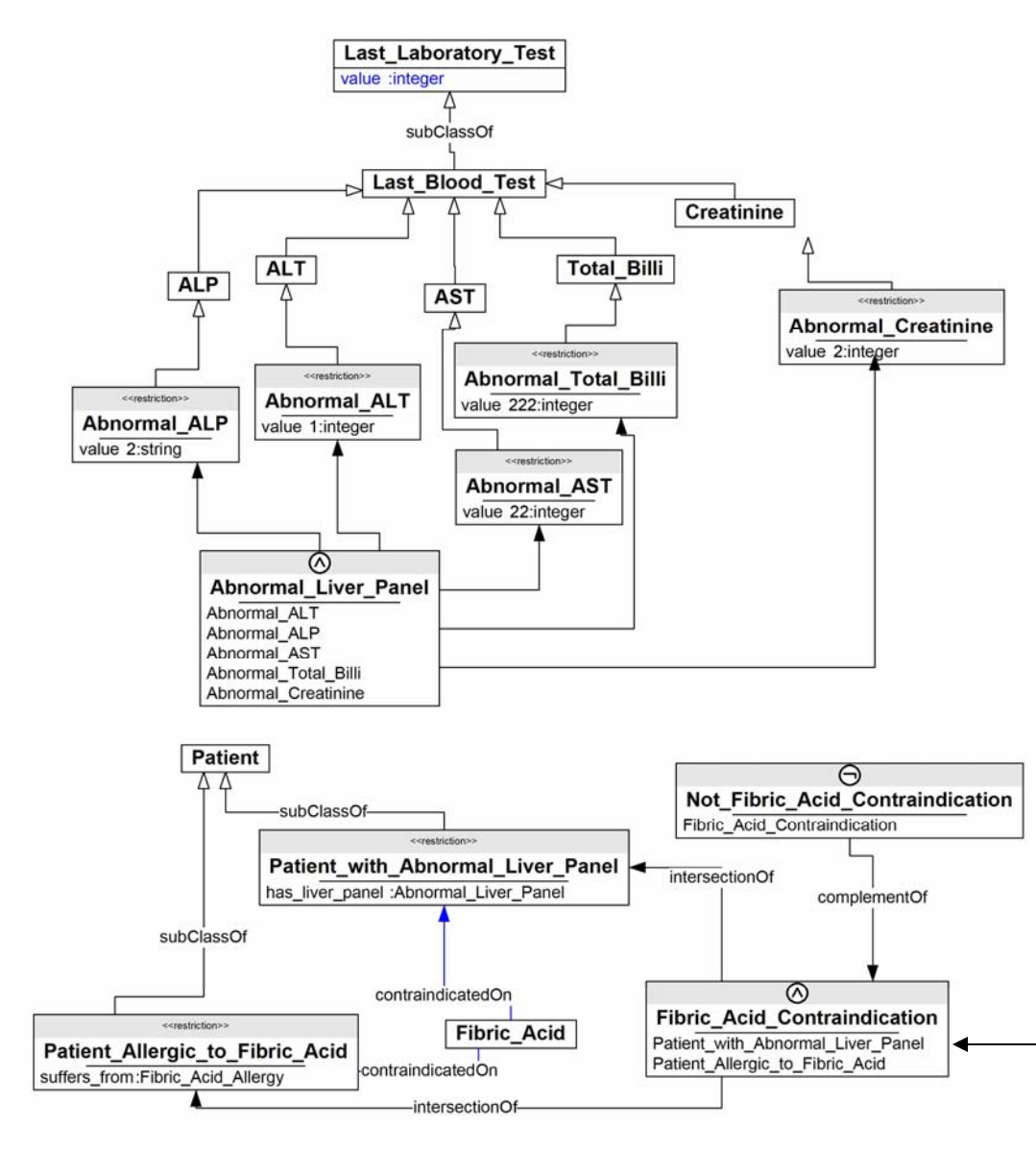
Currently, both these inferences are performed by the rules engine.

# Clinical and Genomic Decision Support
# Role of Ontology Engine

```
IF the_patient.has_ldl_result() > 120
AND the_patient.get_category() = PatientWithFibricAcidContraindication

THEN
set the_patient.has_therapy("Zetia Lipid Management Protocol")
```

implemented in an OWL-based ontology engine

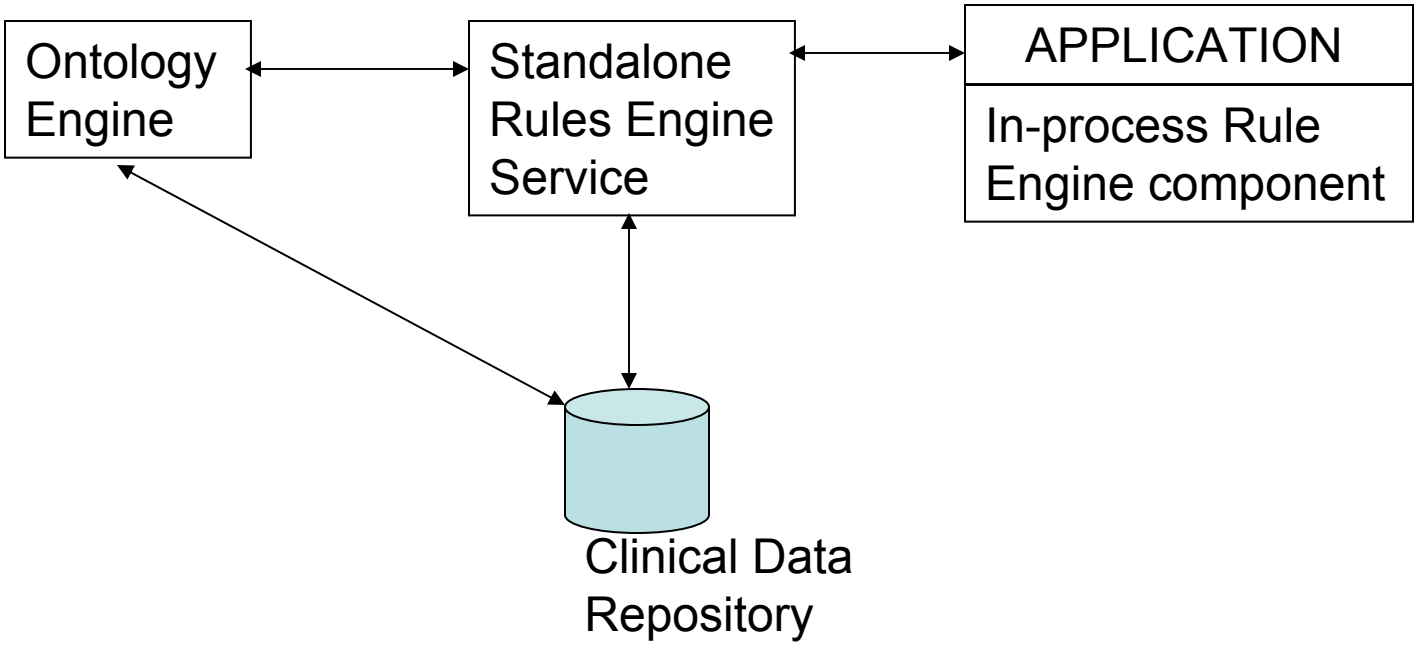
# OWL representation of Fibric Acid Contraindication




**Patient_with_Biomarker**

has_mutation: “Missense: XYZ3:Ser@$#Pro”

# Ontology Driven Clinical Decision Support: Architecture



# Clinical Decision Support: Decoupling definitions vs decisions

- Classification inferences (does patient have a fibric acid contraindication?) can be evaluated by an ontology engine.
- Reduces overhead on Rule Engine
- Opens up the possibility of plugging-in other specialized inference engines (e.g., spatio-temporal conditions)
- Makes knowledge maintenance easier
  - Each definition may be referred to in 100s of rules..

# Decision Support: Statistical vs Symbolic Approaches

- Symbolic:
  - Knowledge Driven: Needs input of Subject Matter Experts
  - Not scaleable: Knowledge Bases can get huge in case of interacting conditions
  - Example:
    - Set of Rules for “CAD”
    - Set of Rules for “Diabetes”
    - What about rules for “Diabetes” and “CAD”
  - In general for N conditions, the Knowledge base size can be of the order of $2^N$.

- Statistical:
  - Data Driven: Models can be “learned” from the data
  - More scaleable
  - Probabilistic conclusions, Thresholding required
  - Blackbox: No explanations possible!

- Hybrid: Need some combination of the two…

# OWL Reasoners

- CEL
  - Polynomial time classifier for the description logic EL+
  - EL+ is specially geared towards biomedical ontologies
- Cerebra
  - Commerical C++ reasoner, Support for OWL-API
  - Tableaux based reasoning for TBoxes and ABoxes
- Fact++
  - Free open source reasoner for DL reasoning
  - Support for Lisp API and OWL API
- KAON2
  - Free Java based DL reasoner with support for SWRL fragment
  - Support for DIG API
- MSPASS
  - A generalized theorem prover for numerous logics, also works for DLs
- Pellet
  - Free open source Java based reasoner for DLs
  - Support for OWL, DIG APIs and Jena Interface
- RacerPro
  - Commercial lisp based reasoner for DLs
  - Support for OWL APIs and DIG APIs

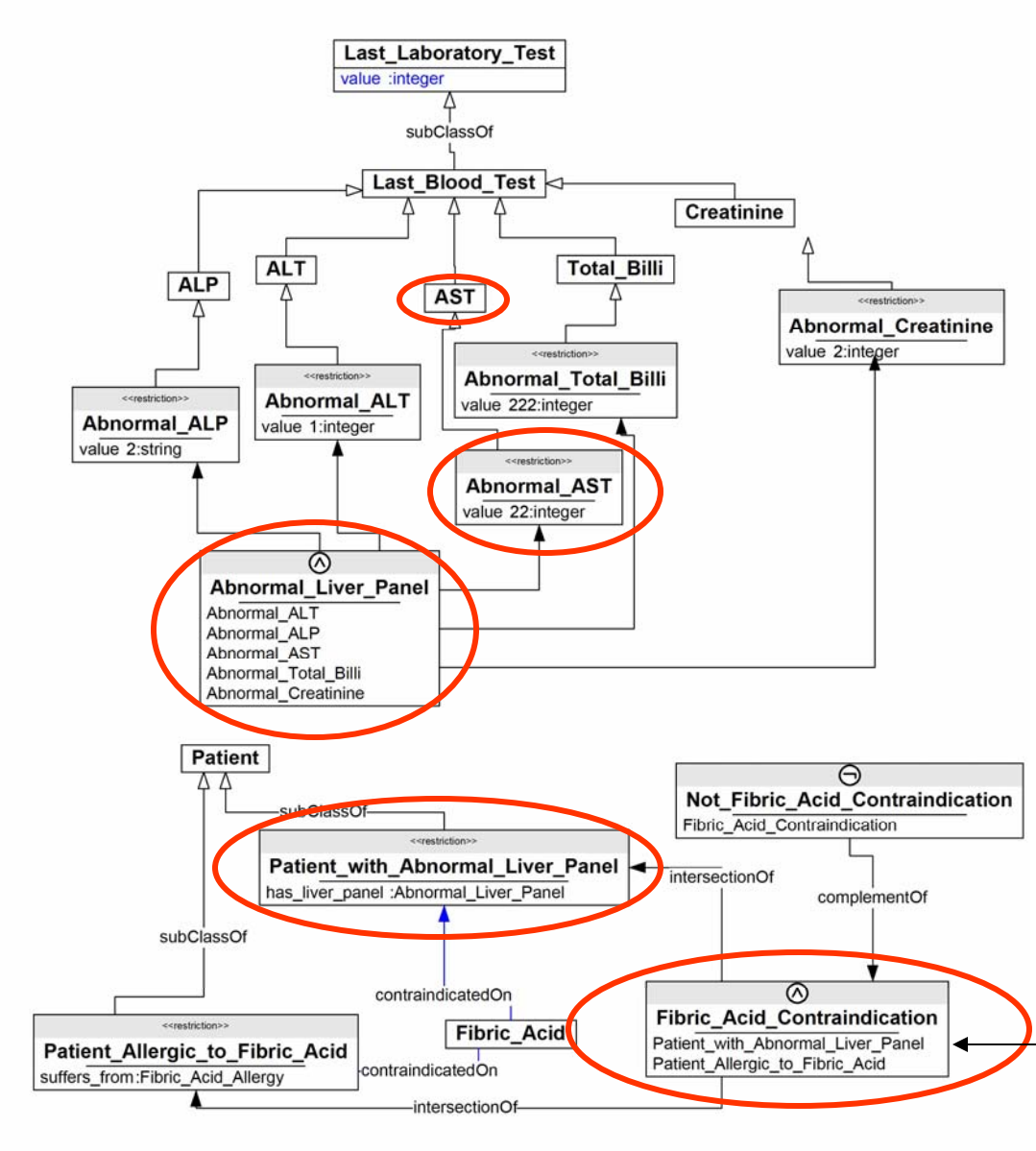
# Functional Requirements

- Use Cases
- Metadata-based Semantic Annotation
- *Recombinant Data:* Information Integration and Aggregation
  - Discovery Decision Support
- Ontology-driven Decision Support
- Knowledge Update and Maintenance ☑

# Knowledge Update and Maintenance

- There is rapid knowledge discovery and evolution in the Healthcare and Life Sciences
- Provenance is an important aspect of maintaining knowledge consistence
- There is a close interrelationship between knowledge change and provenance
  - What has changed? – Change
  - Why did it change? – Provenance
    - Did someone change it? – Provenance
    - Did its components change? – Change
  - Who changed it? – Provenance

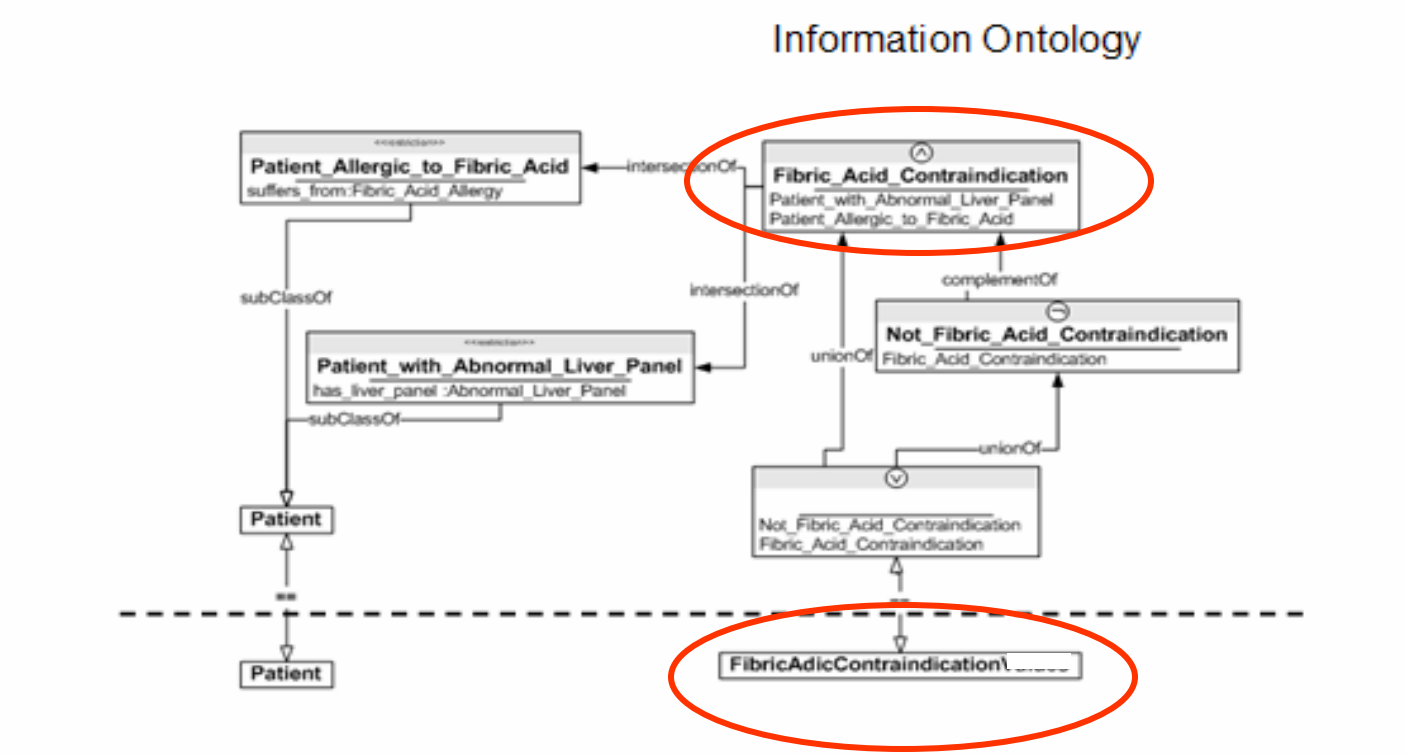
# Domain Ontology




**Patient_with_Biomarker**

has_mutation: “Missense: XYZ3:Ser@$#Pro”

# Bridge – Composition Ontology




Rule base

# Knowledge Change and Provenance

- At each stage, Knowledge Engineer gets notified of:
  - What has changed?
    - The definition of Fibric Acid Contraindication
  - Why did it change?
    - Fibric Acid Contraindication ← Patient with Abnormal Liver Panel ← Abnormal Liver Panel ← Abnormal AST ← Change in AST Values
    - Fibric Acid Contraindication ← Patient with Biomarker
  - Who was responsible for the change?
    - Knowledge Engineer who entered the changed AST values?
    - Change in a Clinical Guideline?
    - New Molecular Diagnostic Test appears in the market?

# Knowledge Update and Maintenance

- Knowledge Dependency Propagation
  - If the definition of a concept changes,
    - What other concepts does it impact?
    - What other clinical decision support rules does it impact?

- Assertion Dependency Propagation
  - If a clinical decision support rule is changed, how does this impact potential decisions made for a patient?
  - How and when should such decisions be updated?
    - What if the decision involved a drug which has already been administered?

# Implementation Options

- Relational Databases
  - Set up RDBMS triggers or stored procedures
  - The semantics of the various dependencies are hard-coded in the application code associated with RDBMS triggers or stored procedures
- Rule Engines
  - Encode the semantics of the various dependencies of into rules.
  - Better than previous option as rules can be changed easier than application code
  - However, potential dependencies may be very high and depend upon the underlying KR language
- Ontology Engines and Reasoners
  - The reasoner can identify dependencies
  - Requires modeling knowledge appropriately in the OWL-DL model

# Current State: Healthcare KM

- Market is very siloized
  - Different Vendors for Different Knowledge Types
- Order Sets and Templates
  - Next Gen, Zynx
- Vocabularies
  - HLi, IMO, Apelon
- Documentation Templates
  - IMDSoft
- Not Supported
  - Clinical  Guidelines, Clinical Decision Support Rules, etc.
- Lack of a comprehensive semantics-based platform from KM

# Semantics-based Knowledge Maintenance

- Managing change and provenance is a very difficult problem
- Semantics can play a crucial role in it:
  - A reasoner can navigate a semantic model of knowledge and propagate change
  - One can declaratively change the model at any time
  - The reasoner will compute the new changes!
- Configuration v/s coding. Could read to a huge ROI!
- Could be the potential “killer app” for the Semantic Web

# Conclusions

- Healthcare and Life Sciences is a knowledge intensive field. The ability to capture semantics of this knowledge is crucial for implementation.
- Incremental and cost-effective approaches to support “as needed” data integration need to be supported.
- Scalable and modular approaches for decision support need to be designed and implemented.
- The rate of Knowledge Updates will change drastically as Genomic knowledge explodes. Automated Semantics-based Knowledge Update and Propagation will be key in keeping the knowledge updated and current
- Personalized/Translational Medicine cannot be implemented in a scalable, efficient and extensible manner without Semantic Web technologies