

From the Bench to the Bedside: The Role of Semantics in enabling the Vision of Translational Medicine

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BIOSTEC 2008

Funchal, Madeira, Portugal

31st January, 2008

Outline

- Vision
- Healthcare and Life Sciences
 - What is Translational Medicine?
 - Ecosystem: Current and Future State
 - Clinical Information Systems: Current State and Goal Architectures
- Translation 1: Genomic Research and Clinical Practice
 - Value Proposition of Semantic Technologies
- Translation 2: Clinical Research and Clinical Practice
- Conclusions: Semantics – A Transformational Enabler

Vision

The Next Generation Healthcare Enterprise provides services across the healthcare and life sciences (HCLS) spectrum targeted towards delivering optimum wellness, therapy and care for the patient.

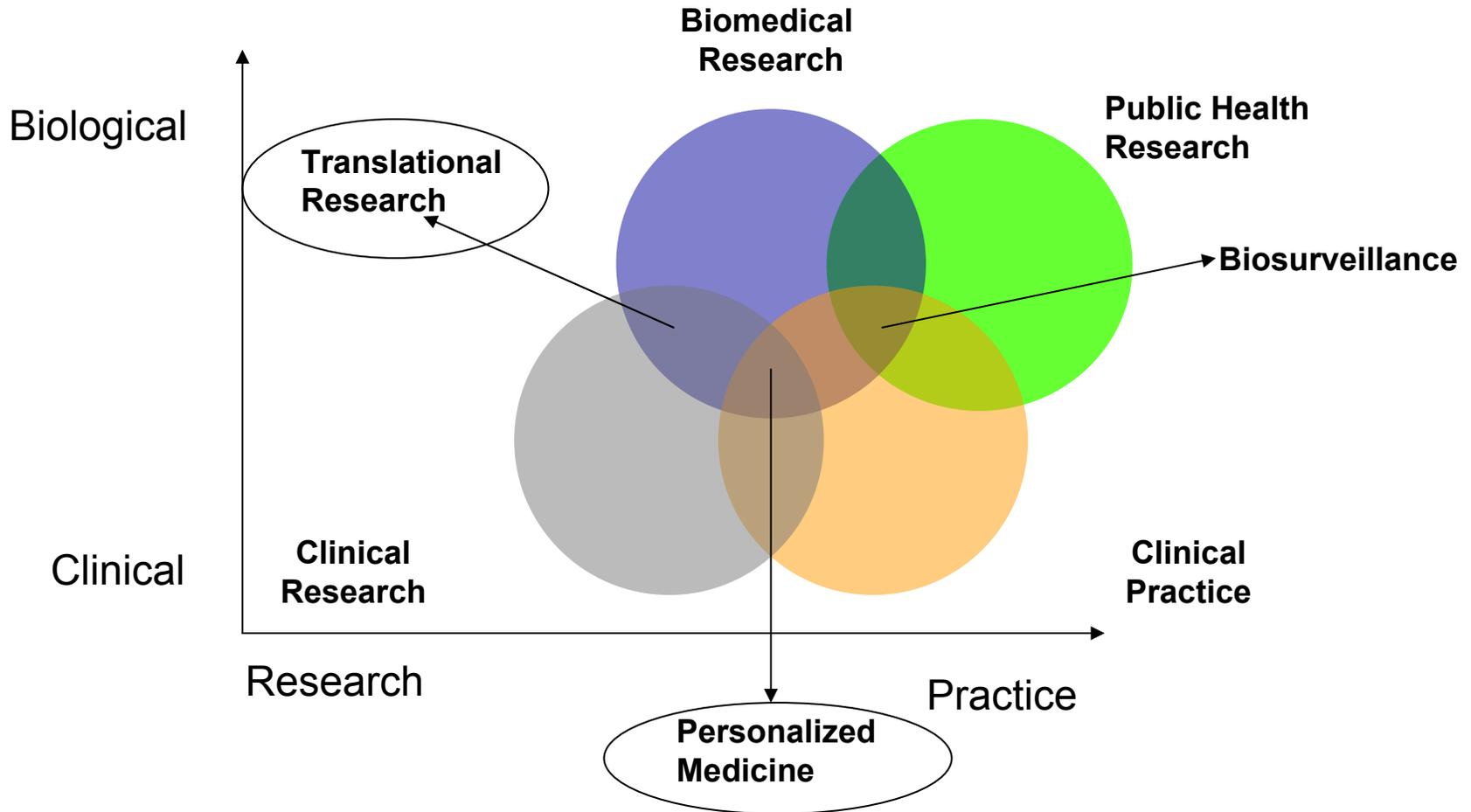
These holistic services cut across biomedical research, clinical research and practice and **create a need for** the accelerated adoption of genomic and clinical research into clinical practice.

This is the fundamental goal and promise of Translational Medicine!

What is Translational Medicine?

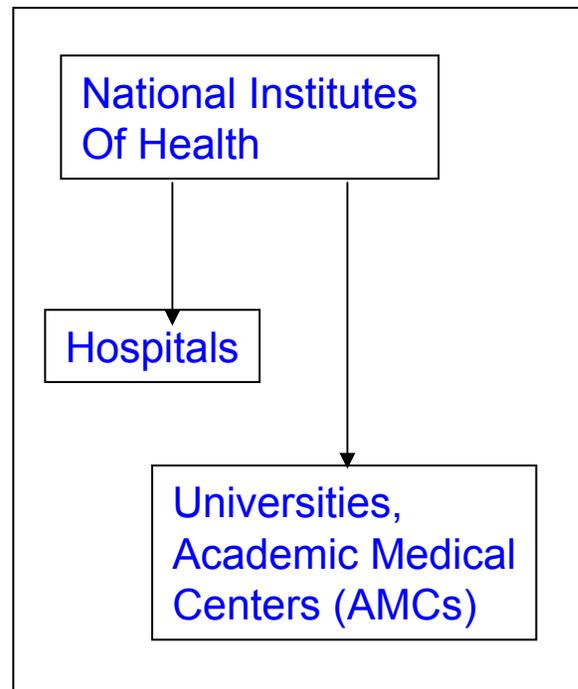
- Improve communication between basic and clinical science so that more therapeutic insights may be derived from new scientific ideas - and vice versa.
- Testing of theories emerging from preclinical experimentation are tested on disease-affected human subjects.
- Information obtained from preliminary 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>

What is Translational Medicine?

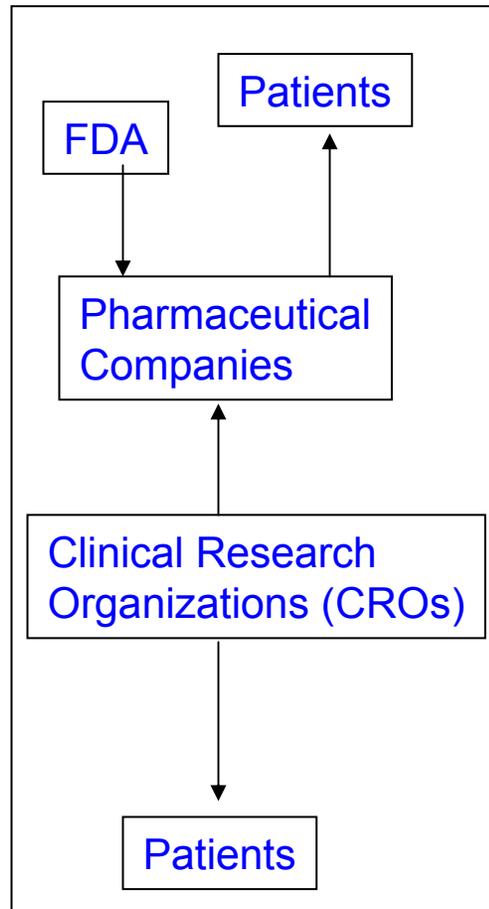


Healthcare and Life Sciences: Current State

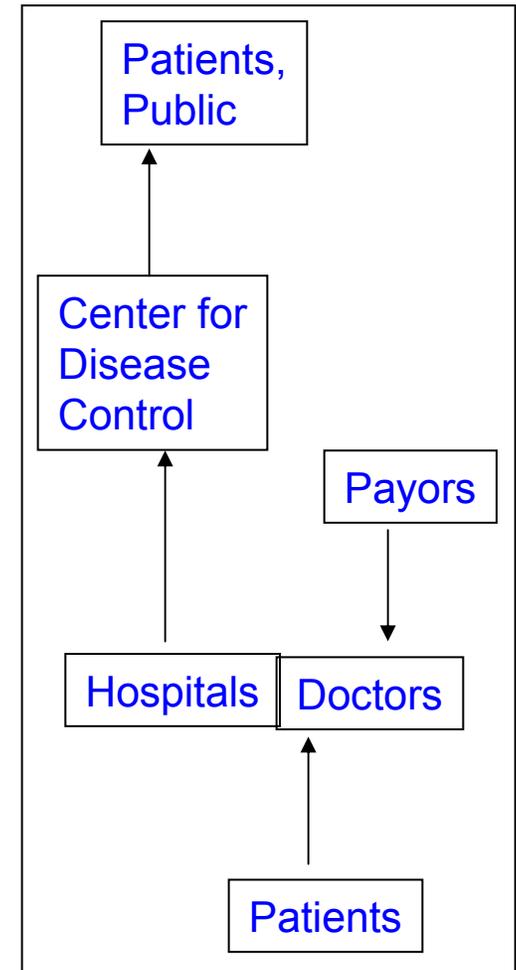
Characterized by silos with uncoordinated supply chains leading to inefficiencies in the system



Biomedical Research
Clinical Practice



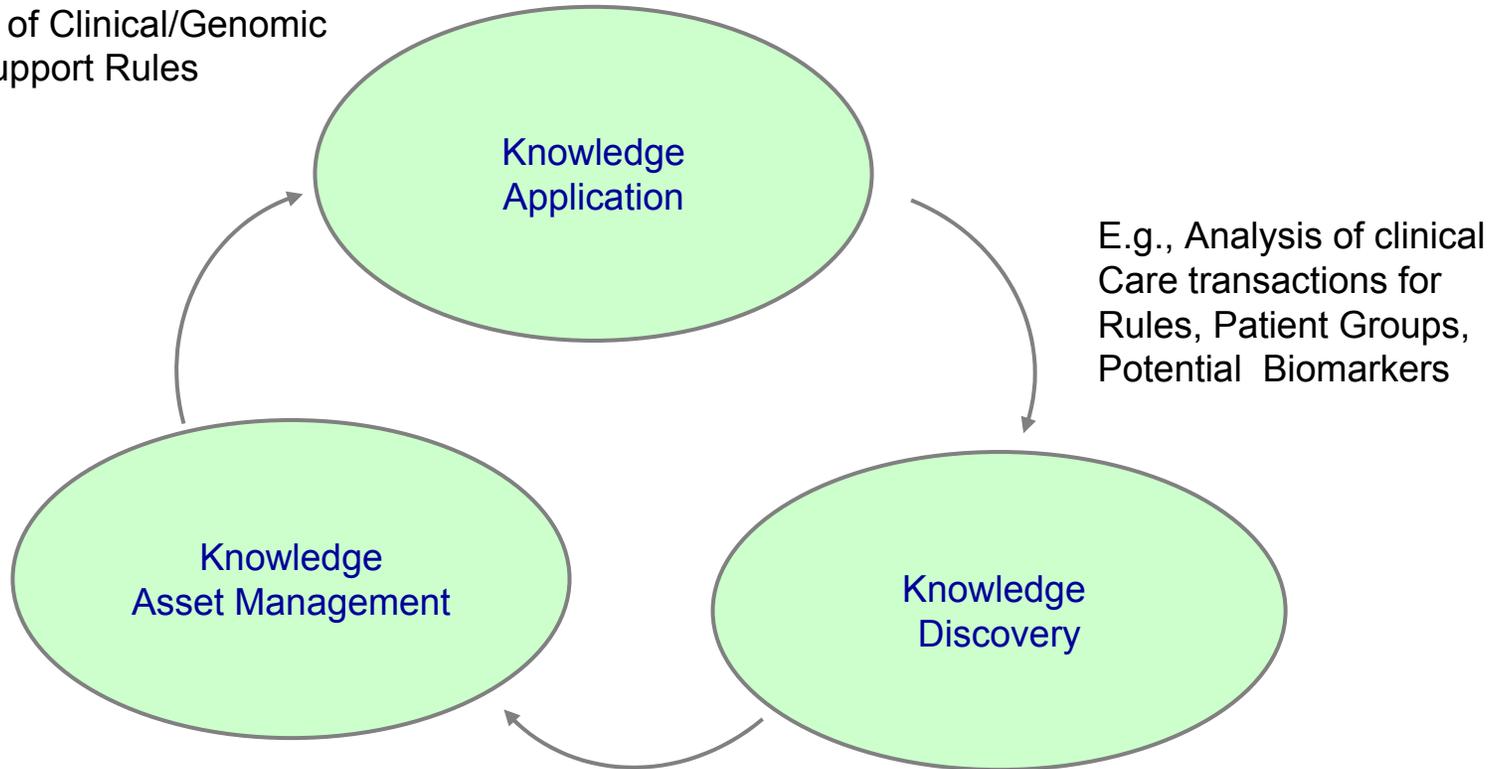
Clinical Trials/Research



Clinical Practice

Future State: A Knowledge Perspective

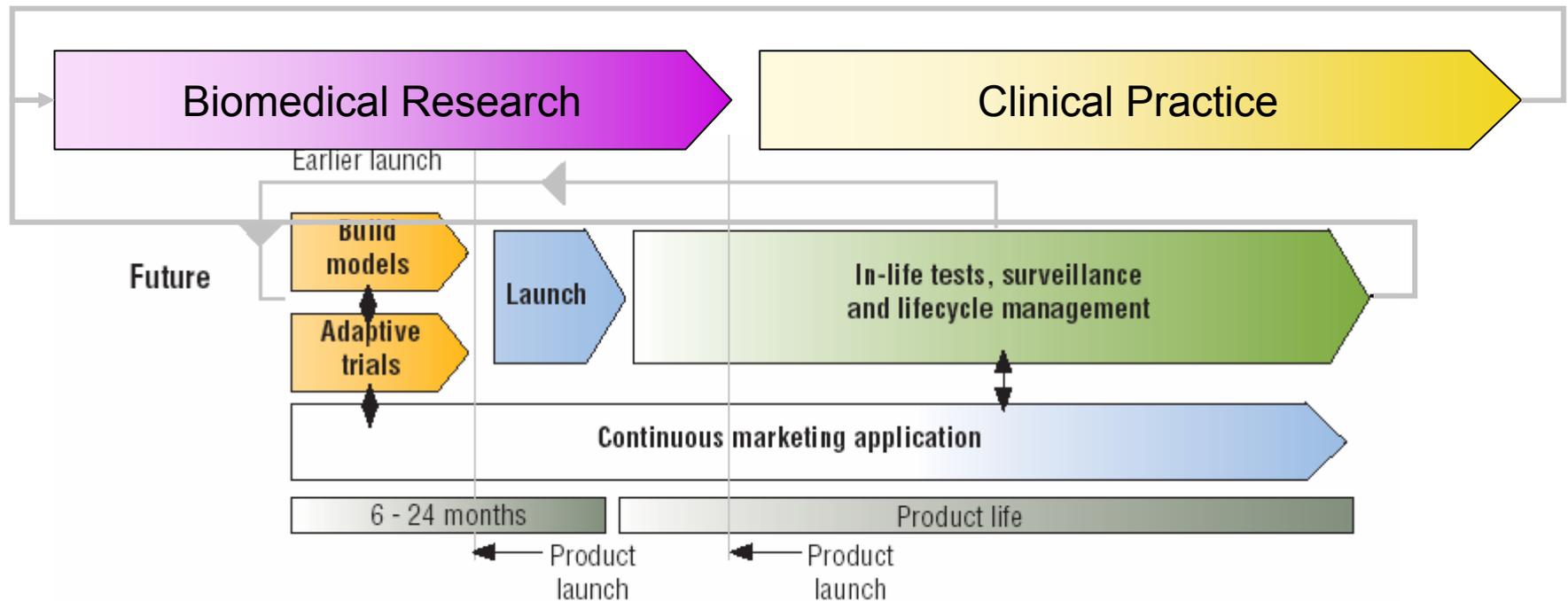
E.g., Application of Clinical/Genomic
Decision Support Rules



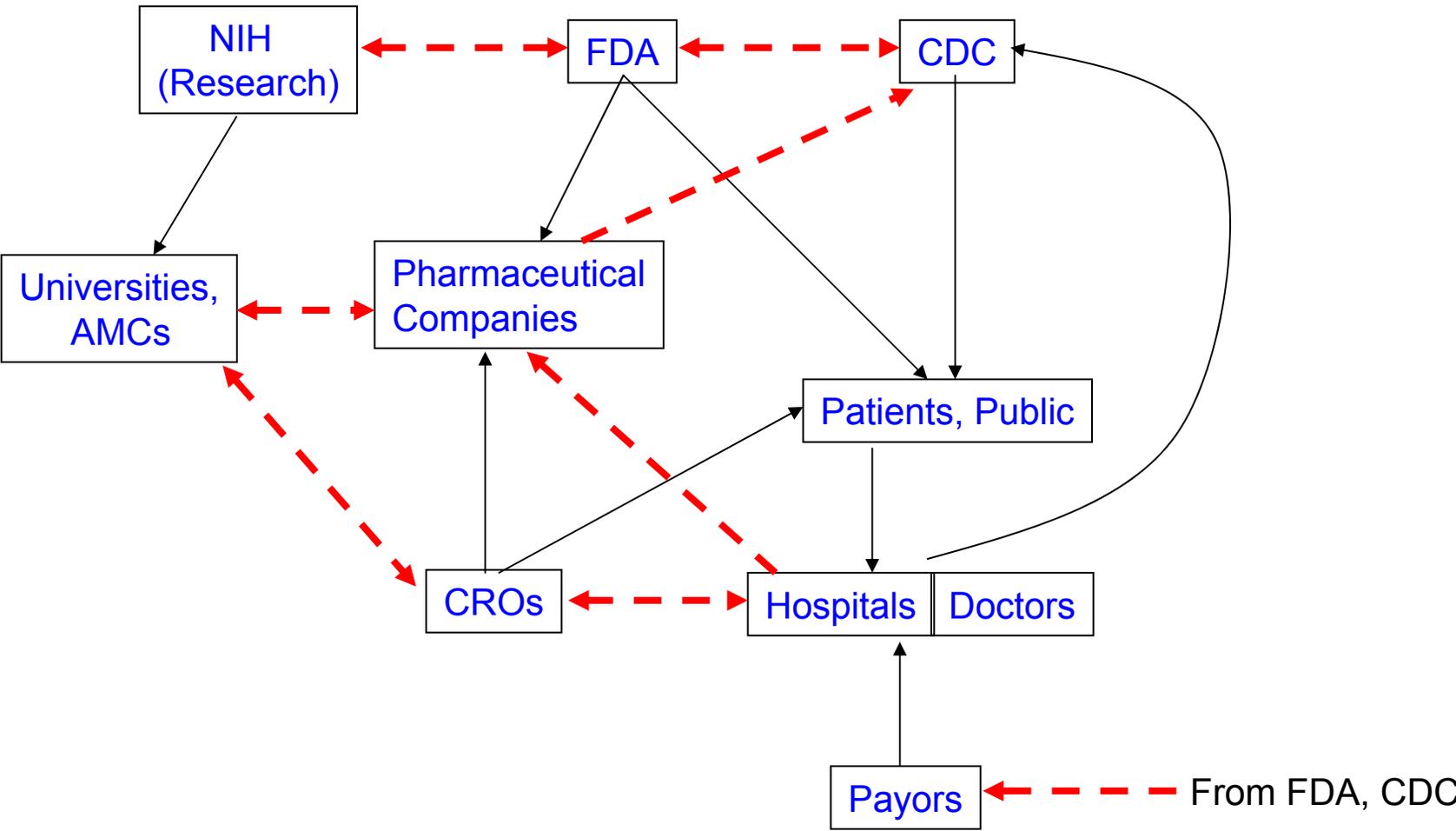
E.g., Analysis of clinical
Care transactions for
Rules, Patient Groups,
Potential Biomarkers

E.g., Creation and Maintenance
of Clinical Decision Support Rules

Future State: A Business Perspective



Future State: A Stakeholder Perspective



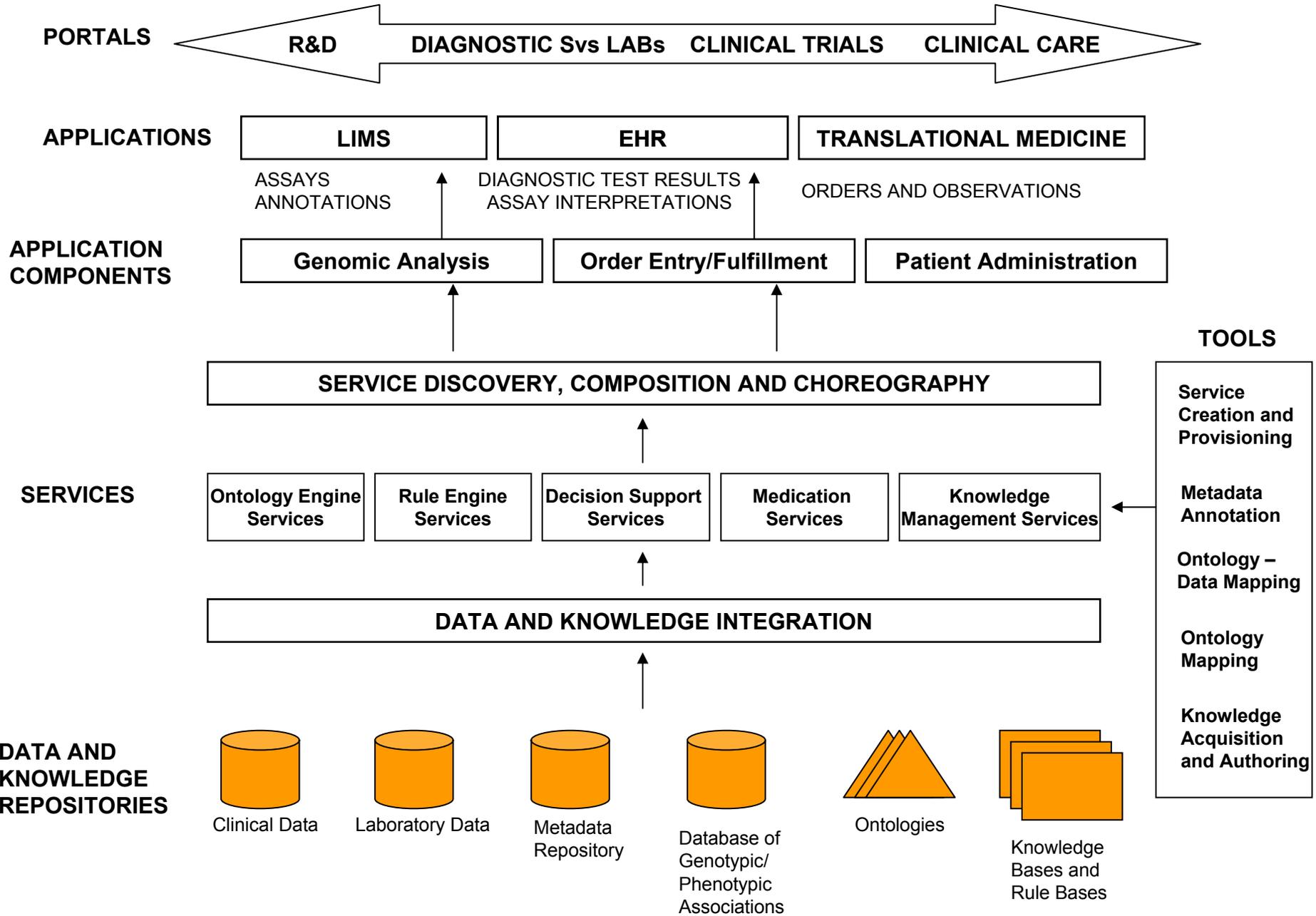
Translation 1: Genomic Research and Clinical Practice

Translation 2: Clinical Research and Clinical Practice

Current State of Clinical Systems: Lack of “Knowledge Orientation”

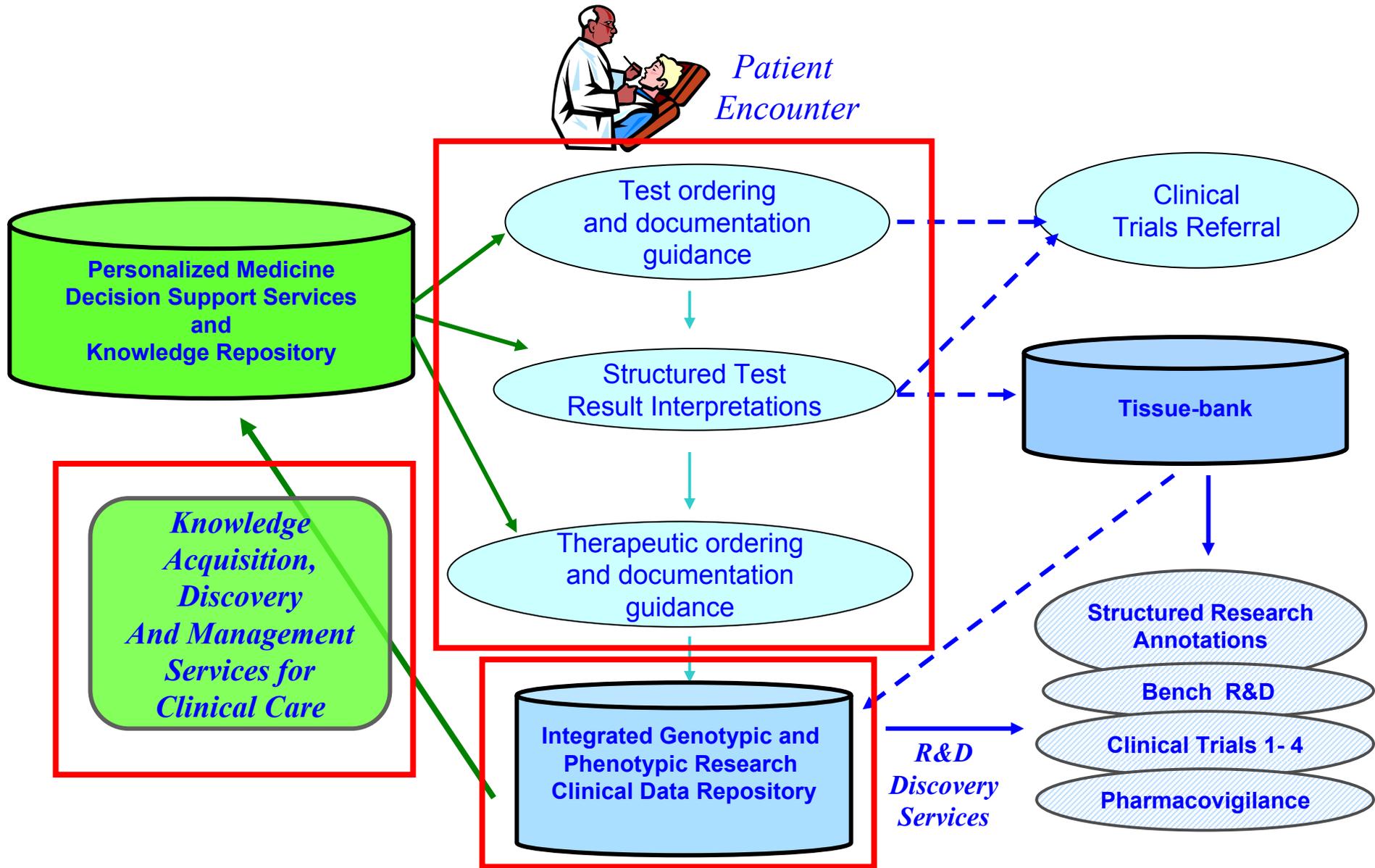
- Knowledge “hardwired” into applications
- Little or no standardization on terminologies, information models or ontologies
- Current knowledge engineering tools update knowledge directly in transactional environments
- No support for versioning, provenance, change propagation.
- System implementations have inadequate knowledge to meet current workflow and quality needs
- Resources required for converting “reference” knowledge into “executable” knowledge is vastly underestimated
 - Medical Knowledge doubles every 19 years (22 months for AIDS literature)
 - Physician needs 2 million facts to practice
 - Introduction of 300+ Molecular Diagnostic tests drastically increases the number of decision support variables!

Clinical Systems: Goal Architecture



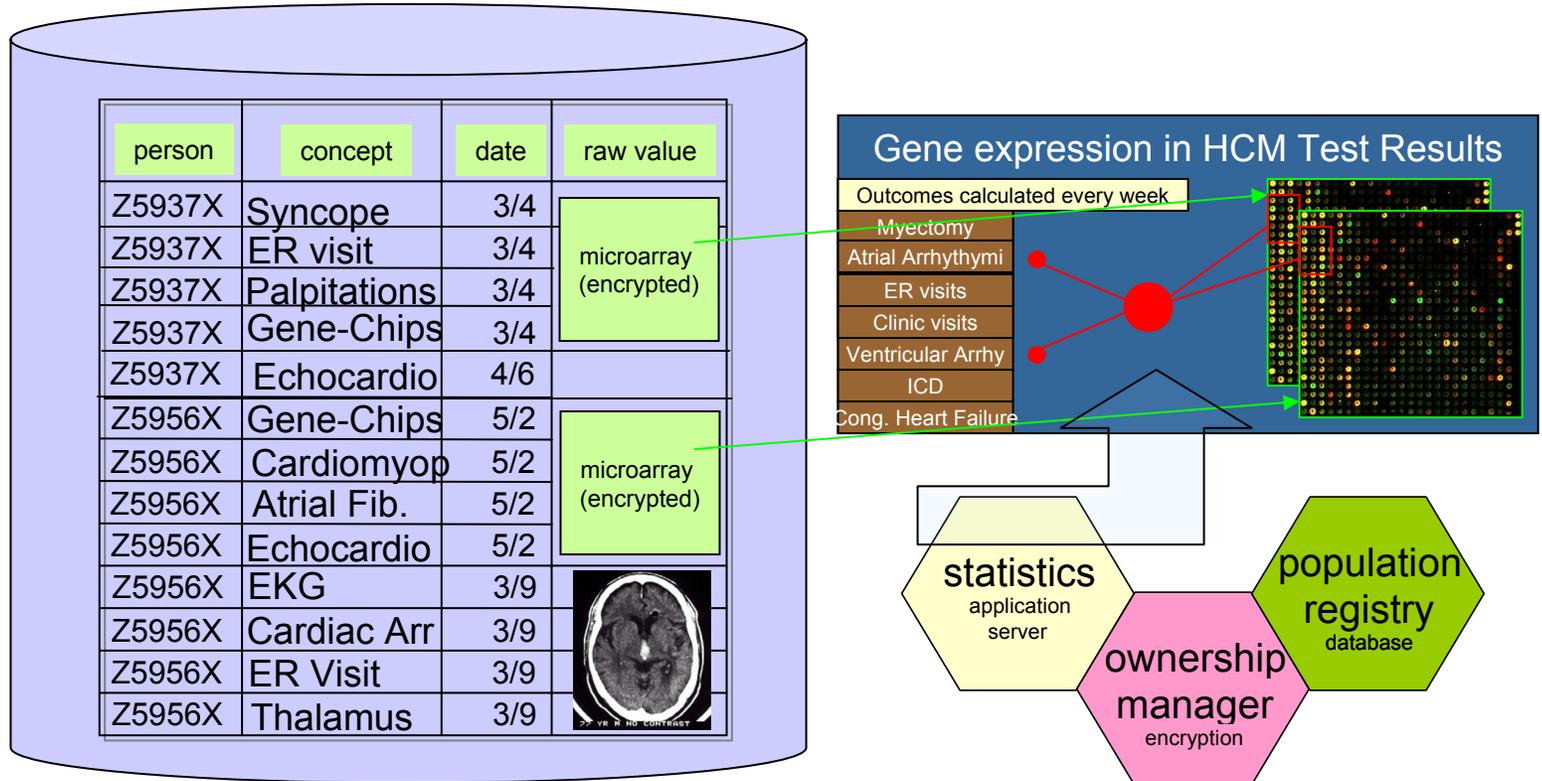
Translation 1: Genomic Research and Clinical Practice

Use Case Flow: Need for Shared Semantics



Data Integration

Connecting Dx, Rx, Outcomes and Prognosis Data to Genotypic Data



Actionable Decision Support

LMR Smart Form - Microsoft Internet Explorer provided by Partners HealthCare System

Address: http://is.partners.org/prototype/dtaylor/marchdmsf/smartform3.htm

LMR Smart Form

Patient: GUBERNATH, JANETTA DOB: 08/25/1947 Age: 58
MRN: 0000001 (MGH) Sex: F Tel: (H) 617-555-1212

Conditions to include: DM CAD ARI

Summary Graphs Note Preview Patient-friendly

CC Carry forward all note content from: Most recent note 3/18/05

HPI Lab Results

Order	12/20/04	11/10/04	9/14/04	6/4/03
Glucose (mg/dL)	175	185	-	145
A1C (4.4%-6.4%)	8.1	8.2	-	8.3
Total Chol (<200 mg/dL)	210	-	240	190
HDL (>45 mg/dL)	59	-	60	53
LDL (<100 mg/dL)	112	-	115	118
Trig (<200 mg/dL)	125	-	125	125
SGOT (U/L)	10	7	-	-
BUN (mg/dL)	12	11	-	-
Cr (mg/dL)	1.2	1.1	-	-
ualb/Cr ratio (mg Ald/g Cr)	-	-	-	-

Needs Attention

- A1C high (8.1 on 12/20/04)
- LDL high (112 on 12/20/04)
- Total Chol high (210 on 12/20/04)
- ualb/Cr overdue (Last 11/9/03)
- Foot exam overdue (Last 4/14/03)
- Eye exam overdue (Last 10/6/03)
- Need current BP
- BMI high (34.0 today)
- Home glucose monitoring not documented

A1C

A1C high (8.1 on 12/20/04)

Adjust glycemic therapy

- Refer to CDE
- Have patient report AM FBG after first 3-5 days
- Patient ed: What is insulin?
- Patient ed: Giving an insulin injection

Cancel Complete

Echo triggers guidance to screen for possible mutations:
- MYH7, MYBPC3, TNN2, TNNI3, TPM1, ACTC, MYL2, MYL3

Knowledge Maintenance

- Need for a Knowledge Repository to support Clinical and Genomic Decision Support
- Evolution of Biomedical Knowledge
 - Clinical Knowledge changes over time, e.g., value ranges for Clinical Normality
 - New knowledge is created, e.g., new molecular diagnostic test hits the market.
- Need for rapid knowledge change and maintenance

Data Integration: Ontology

OWL ontologies that blend knowledge from the Clinical and Genomic Domains

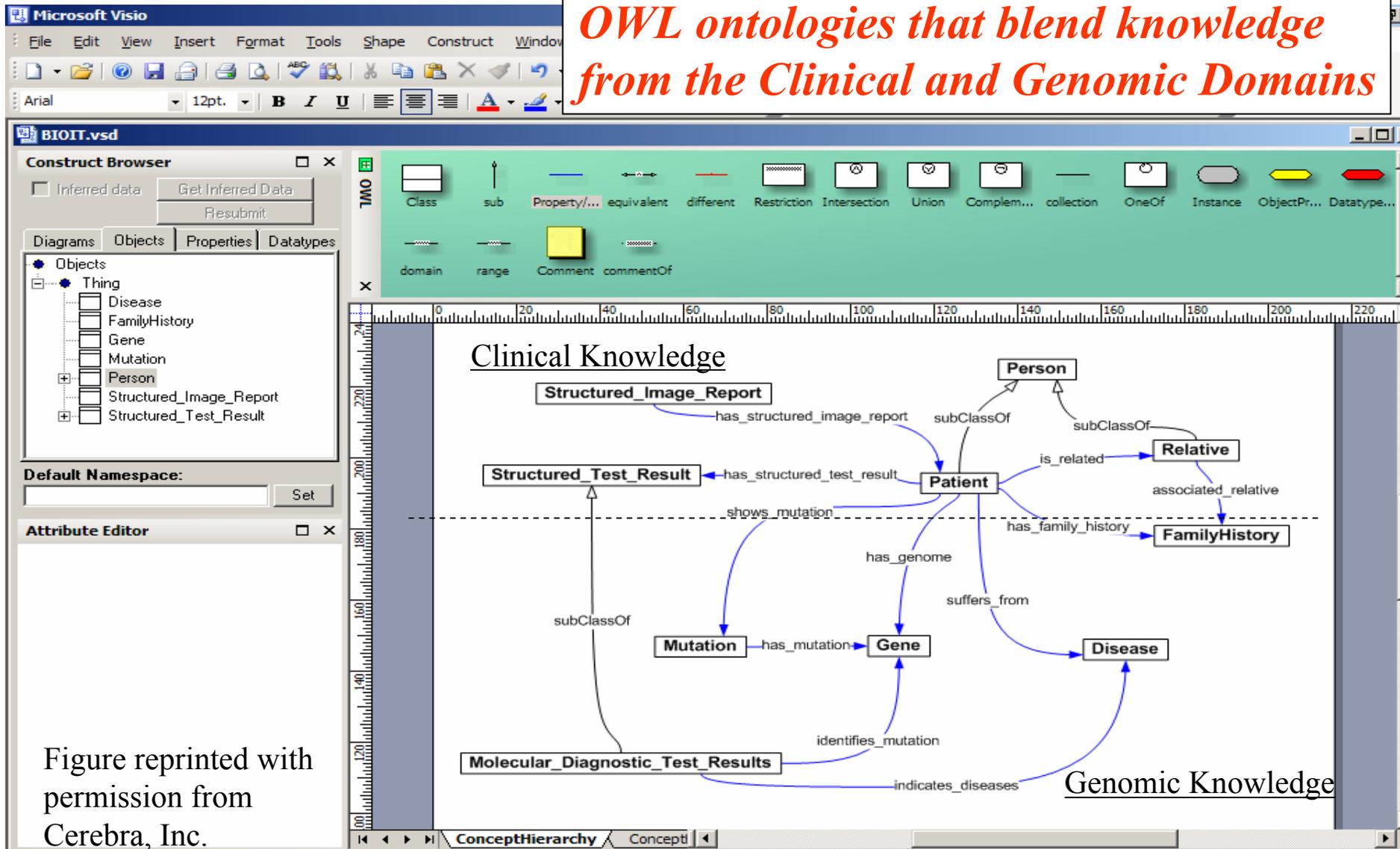
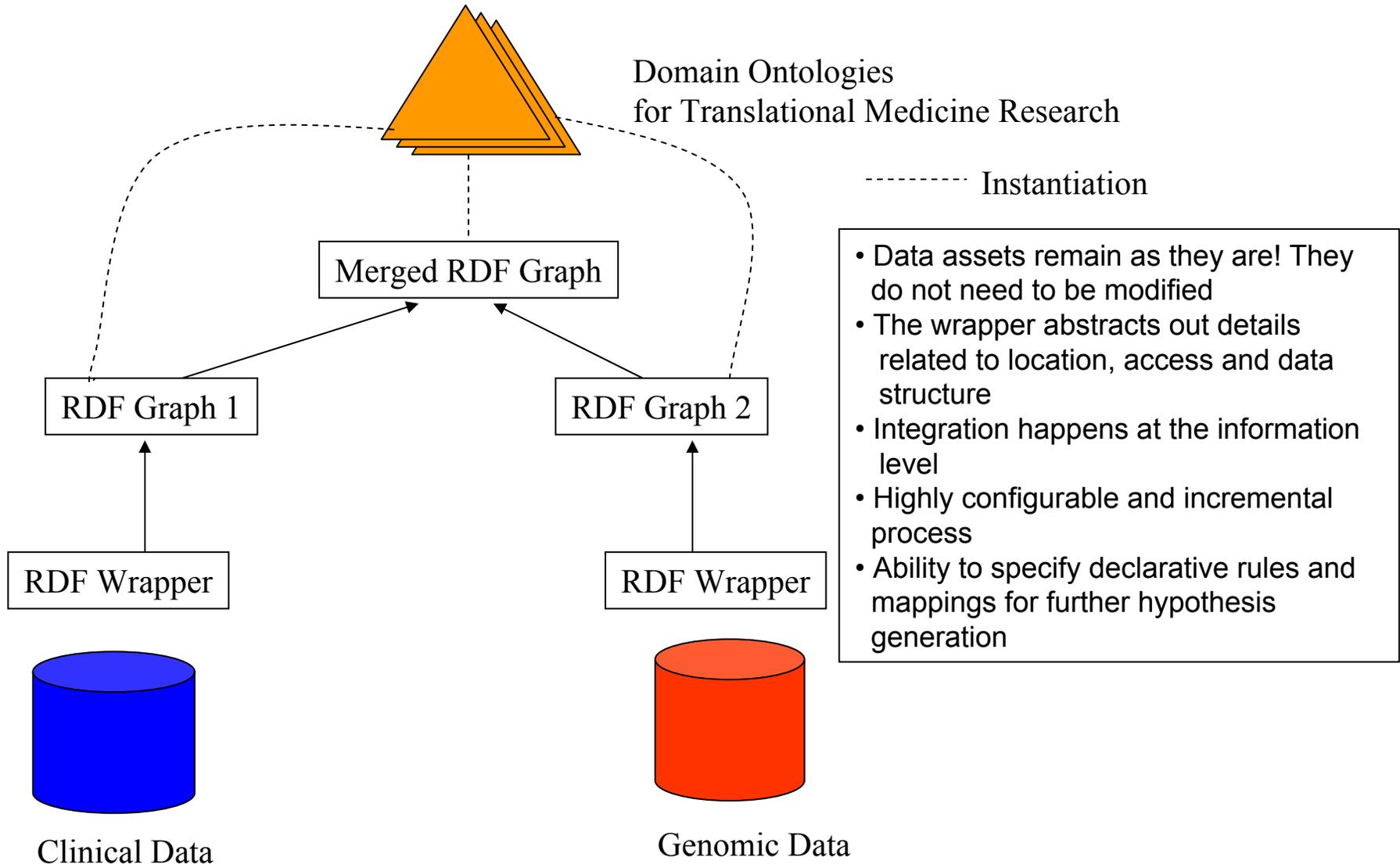
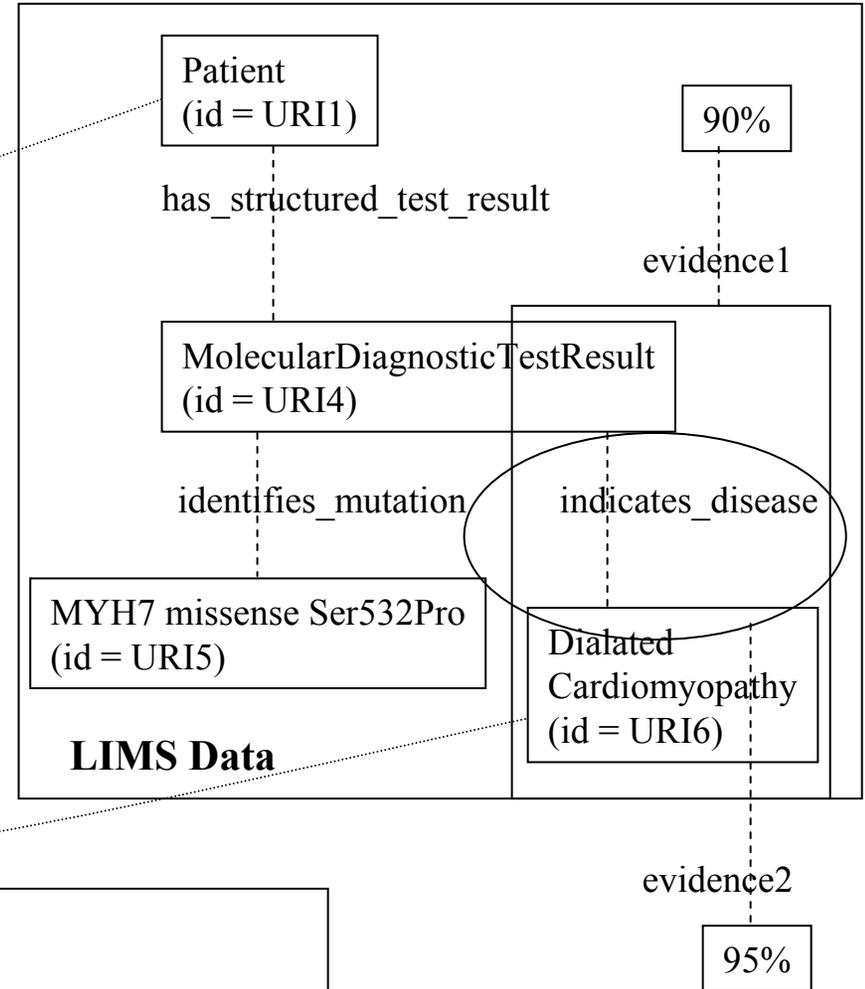
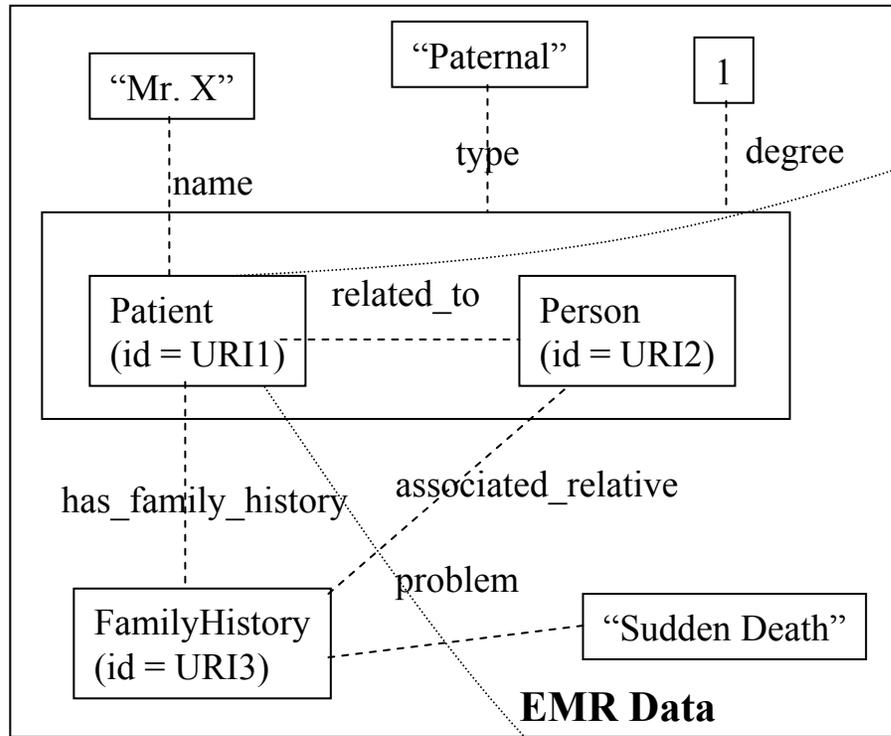


Figure reprinted with permission from Cerebra, Inc.

Data Integration: Architecture



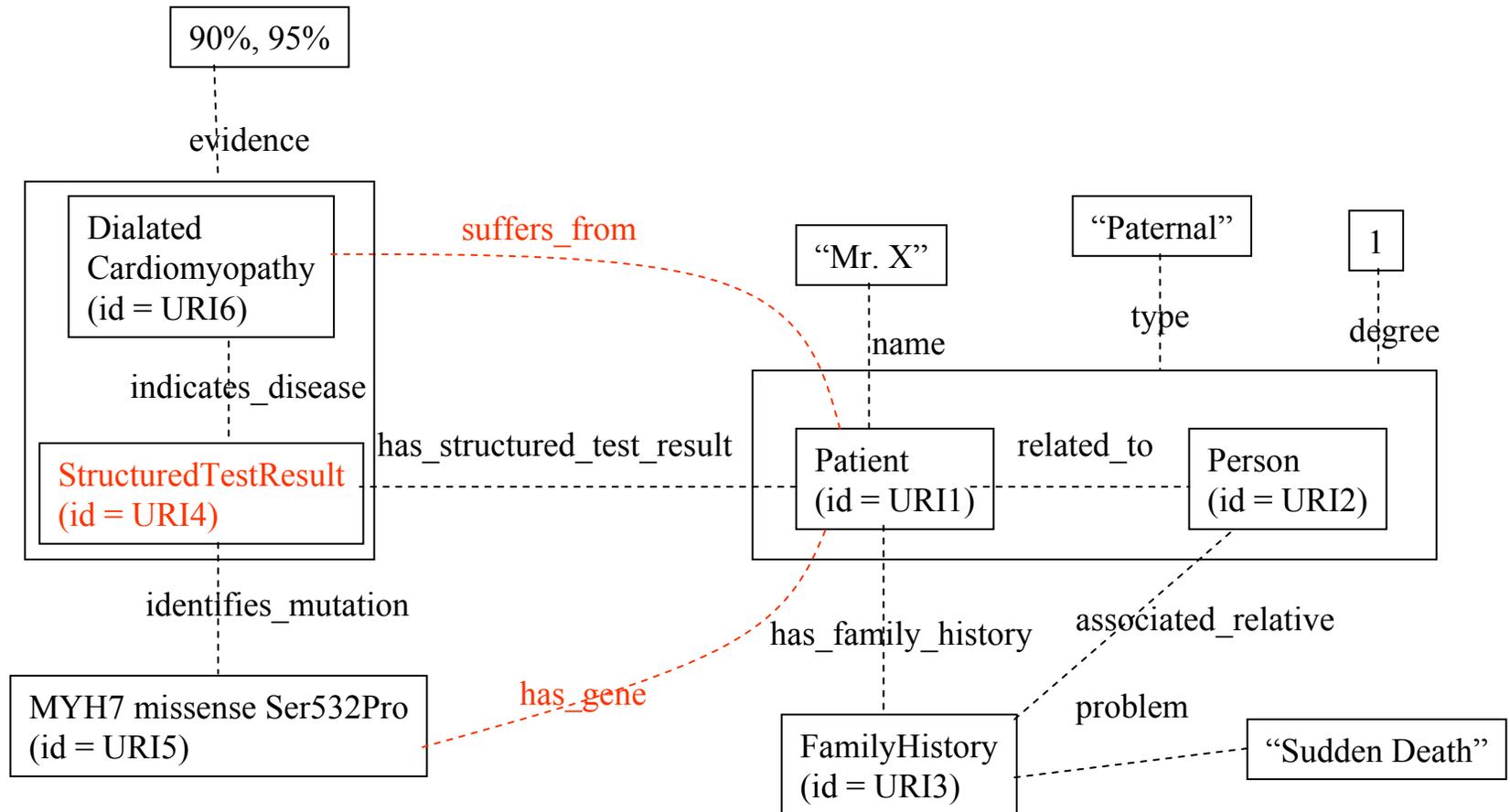
Bridging Clinical and Genomic Information



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

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: 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;
```

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;
```

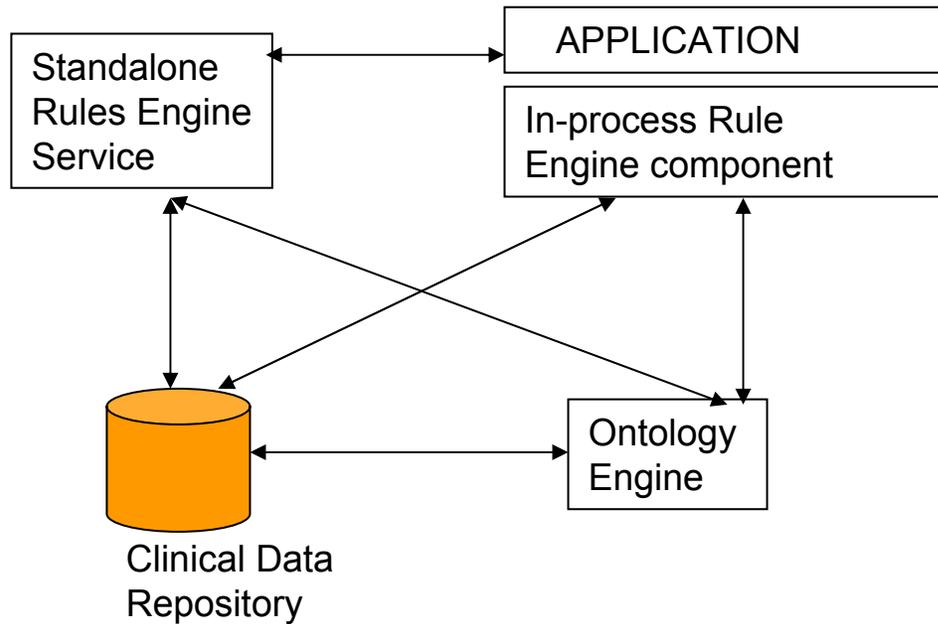
Flexible Clinical Decision Support

```
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")
```

```
IF the_patient.has_ldl_result() > 120
AND the_patient.get_state() = "Fibric Acid Contraindication"
THEN
  the_patient.set_therapy("Zetia Lipid Management Protocol")
```



Application Architecture



- Introduction of new component (Ontology Engine) could impact performance negatively
- Could be mitigated by co-location of Rules and Ontology Engines
- Use of load balancing servers (multiple copies of ontology engine) to improve performance
- Smart Data Caching is a critical need.

Knowledge Base Simplification and Maintenance

- Identification of “Rule Design Patterns”
- Definitions are specifications of conditions that describe:
 - Patient States, e.g., “Patient with Fibrin Acid Allergy”
 - Physiological States, e.g. Normal range of LDL, Bilirubin, etc.
- Actions/Recommendations are specifications that propose therapies, medications, referrals, etc.
 - E.g., Ordering of fibrate therapies for patients with contraindication to fibrin acid
- Decoupling of definitions from decisions enables greater knowledge re-use
 - Context: Ambulatory Care, In-patient
 - Disease States
 - Indications and contraindications for interventions
 - Formularies, Resource Availability
- Enables better change management!

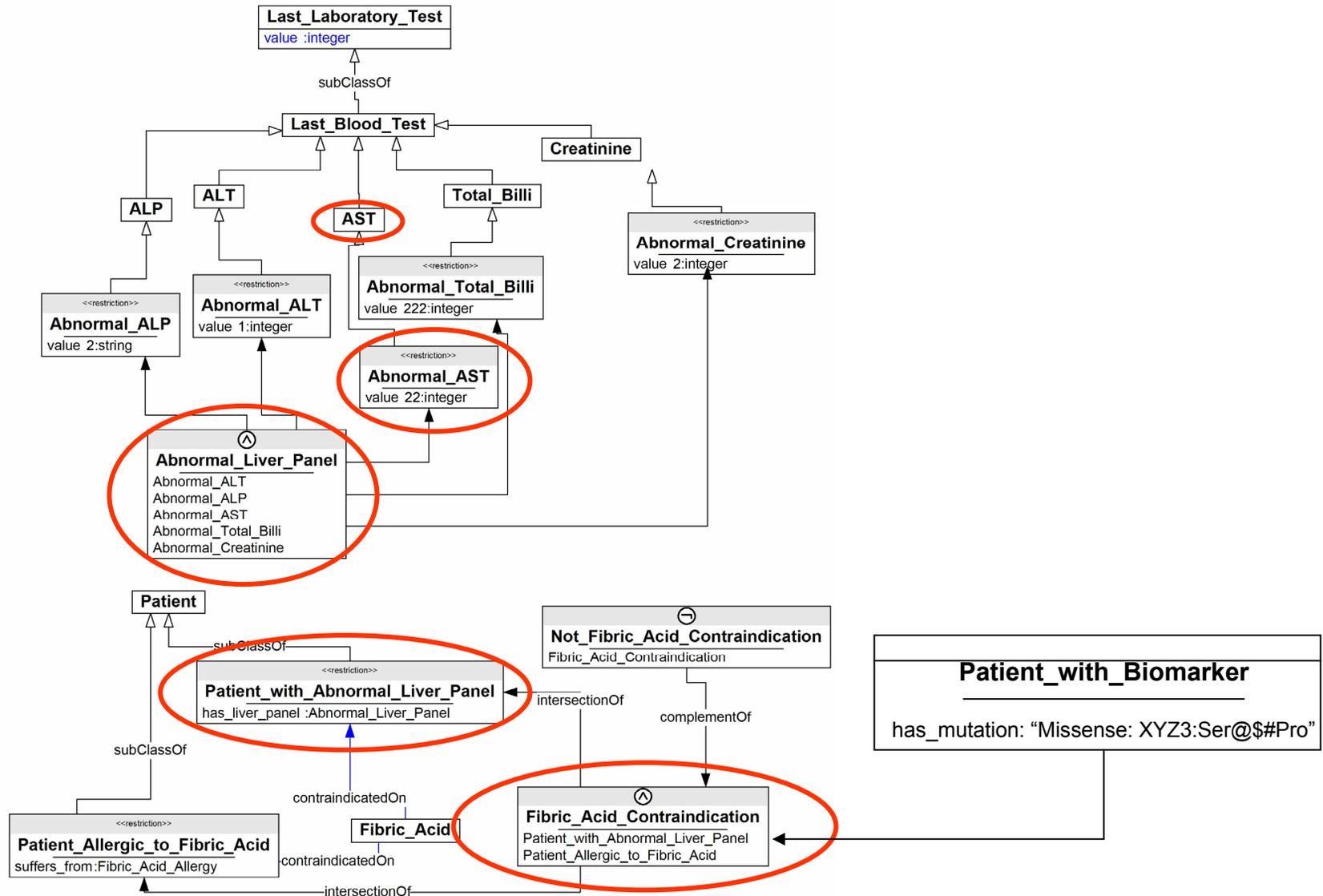
Knowledge Base Maintenance

- Rule simplification promotes ease of authoring
- Encapsulation of rule conditions in definitions makes rule base maintenance easier, Consider:

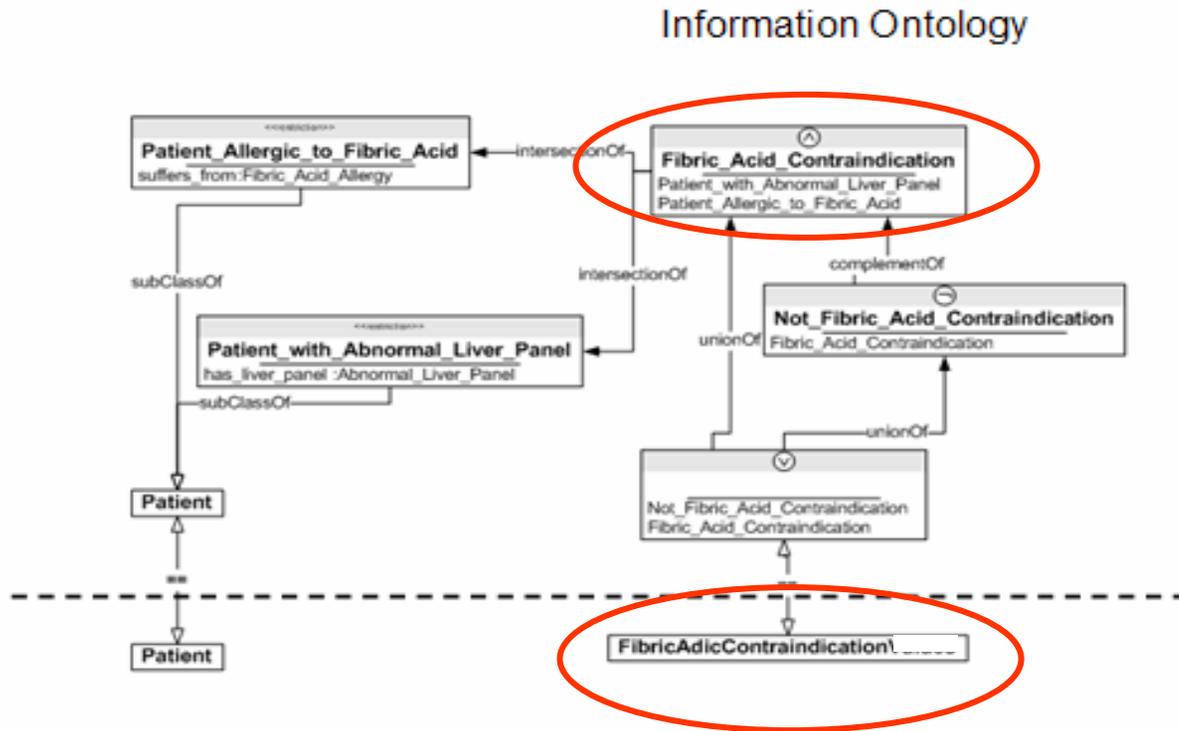
IF A and B and C and D₁ THEN Action₁
IF A and B and C and D₂ THEN Action₂
...
IF A and B and C and D_K THEN Action_K

- ***What if A changes to A' ?***
- Alternative:
 - Let Definition ≡ A and B and C
 - IF Definition and D₁ THEN Action₁
 - IF Definition and D₂ THEN Action₂
 - ...
 - IF Definition and D_K THEN Action_K

Knowledge Change and Provenance



Knowledge Change and Provenance

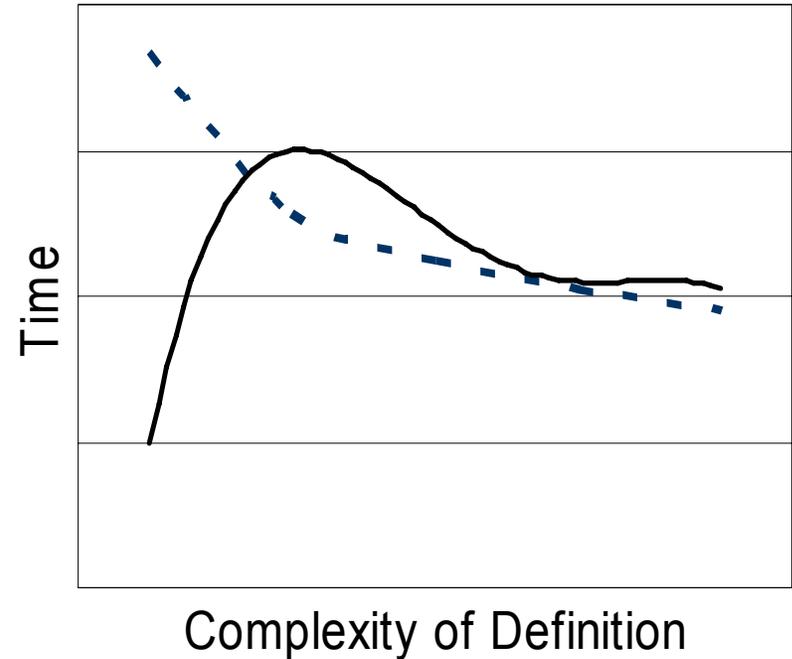
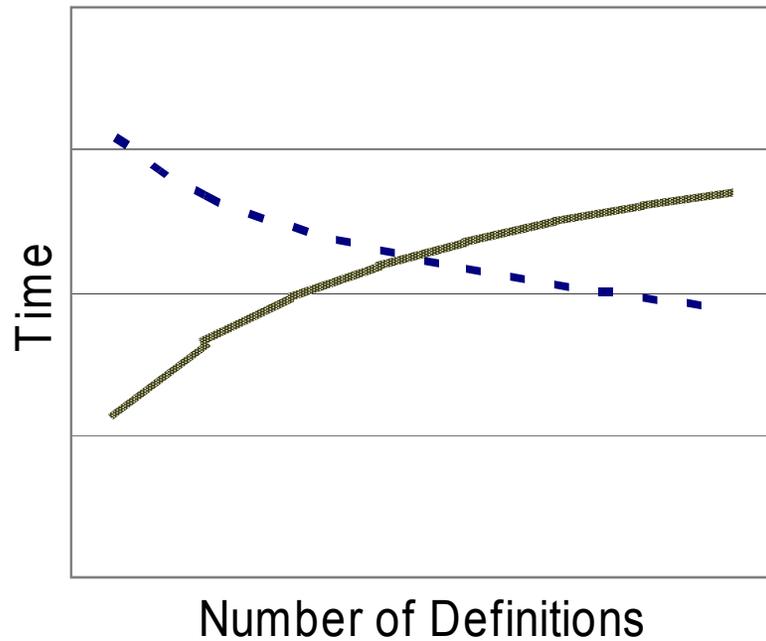


Rule base

Value Proposition

- Simplification of Application Software Complexity
 - Significant chunks of functionality can be implemented using semantic web technologies such as OWL and RDF engines
 - Has impact on Software maintenance
- Simplification of Knowledge Base Complexity
 - Enables easier authoring and maintenance of the knowledge base
- Ability to incrementally integrate new data in a flexible and cost-effective manner
- Ability to handle rapid change in complex knowledge
- Common “Knowledge Standard” for Clinical Decision Support and Quality Reporting

Evaluation: Initial Experiences



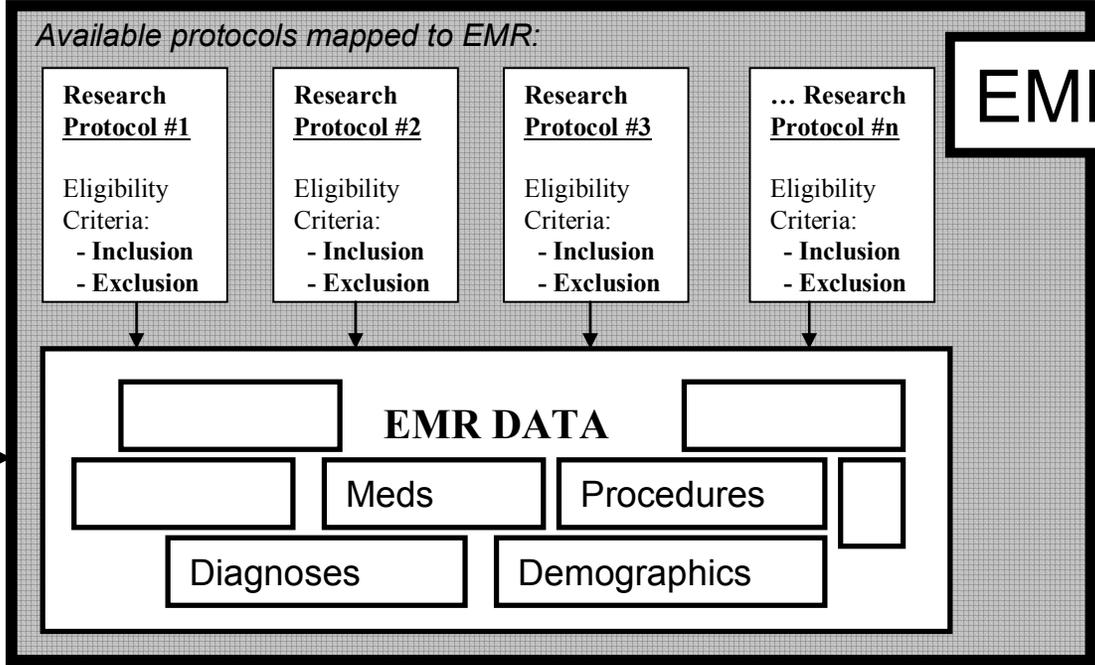
- - - Authoring Execution

Is the time and efficiency gained in authoring offsets the cost required to enhance clinical decision support performance to acceptable levels?

Translation 2: Clinical Research and Clinical Practice

<http://esw.w3.org/topic/HCLS/ClinicalObservationsInteroperability>

Secondary Scenario, (Patient-Centric) Eligibility Screening



EMR instructs physician for further action

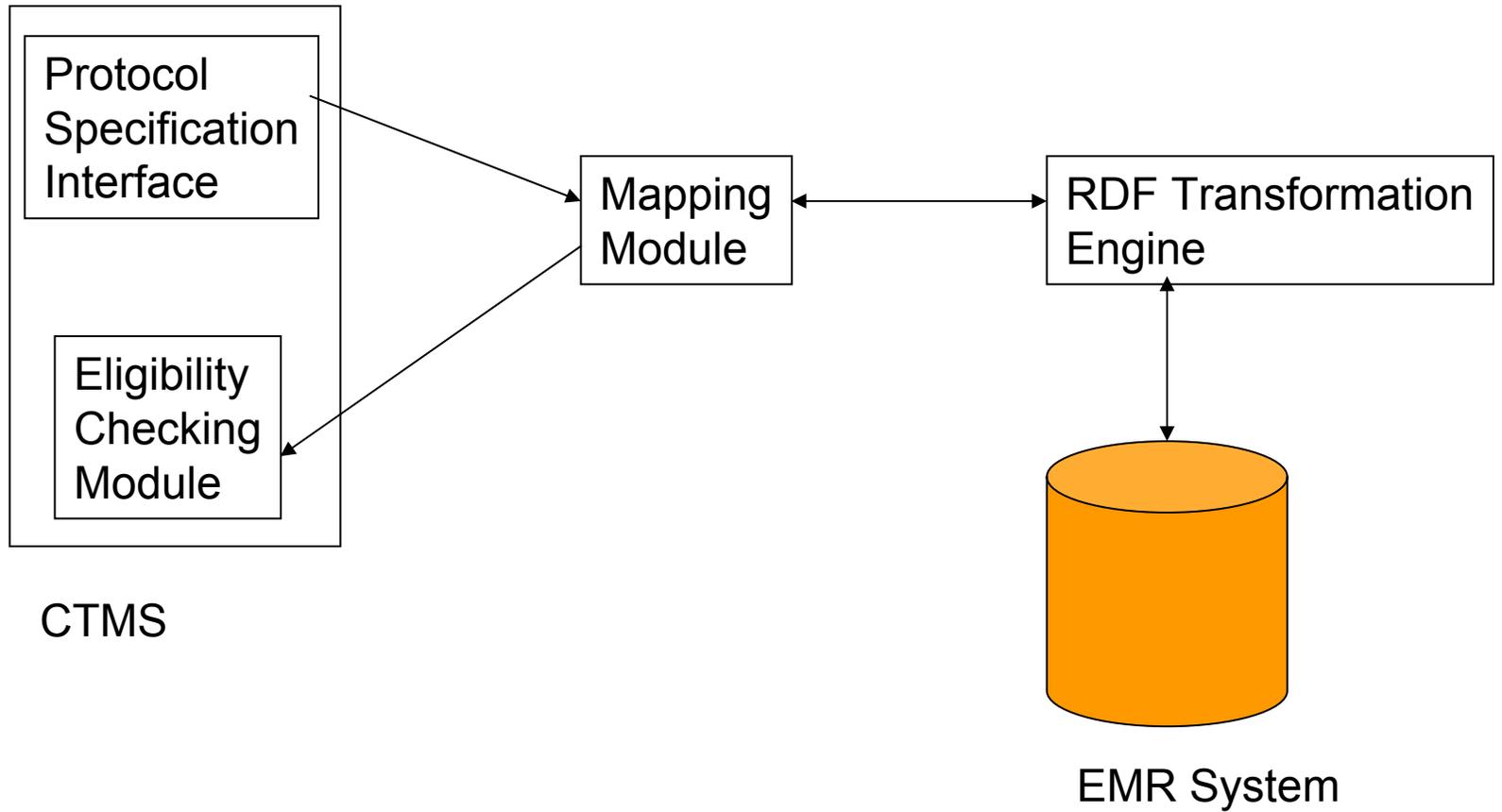
Protocol #	Potentially Eligible for Protocol	# Criteria Met / Total Criteria in Protocol	Criteria #1 (Pass/Fail/Researcher Needs to Evaluate)	No Criteria #2 (Pass/Fail/Researcher Needs to Evaluate)	Criteria #3 (Pass/Fail/Researcher Needs to Evaluate)	...
1	Yes	6/8 criteria met	Pass	Pass	Pass	...
2	No	3/8 criteria met	Pass	Fail	Pass	...
3	Yes	5/8 criteria met	Pass	Pass	Fail	...
...

Further Clinical Evaluation

Refer patient to researcher

Refer re-searchers to patient

Architecture



Goals: Demonstration of Re-use

- Re-use of data from the EMR for Clinical Research
- Re-use of existing vocabularies, e.g., NCI Thesaurus, Snomed, MedDRA
- Re-use of pre-existing information models e.g., HL7/RIM/DCM, CDA, SDTM
- Identify and Re-use software components that can be used to enable a wide range of use cases
 - Patient Recruitment
 - Adverse Drug Event Detection
 - Tracking a Patient through a Clinical Trial

Model Re-use:

Precise, Generalized and Extensible Specification

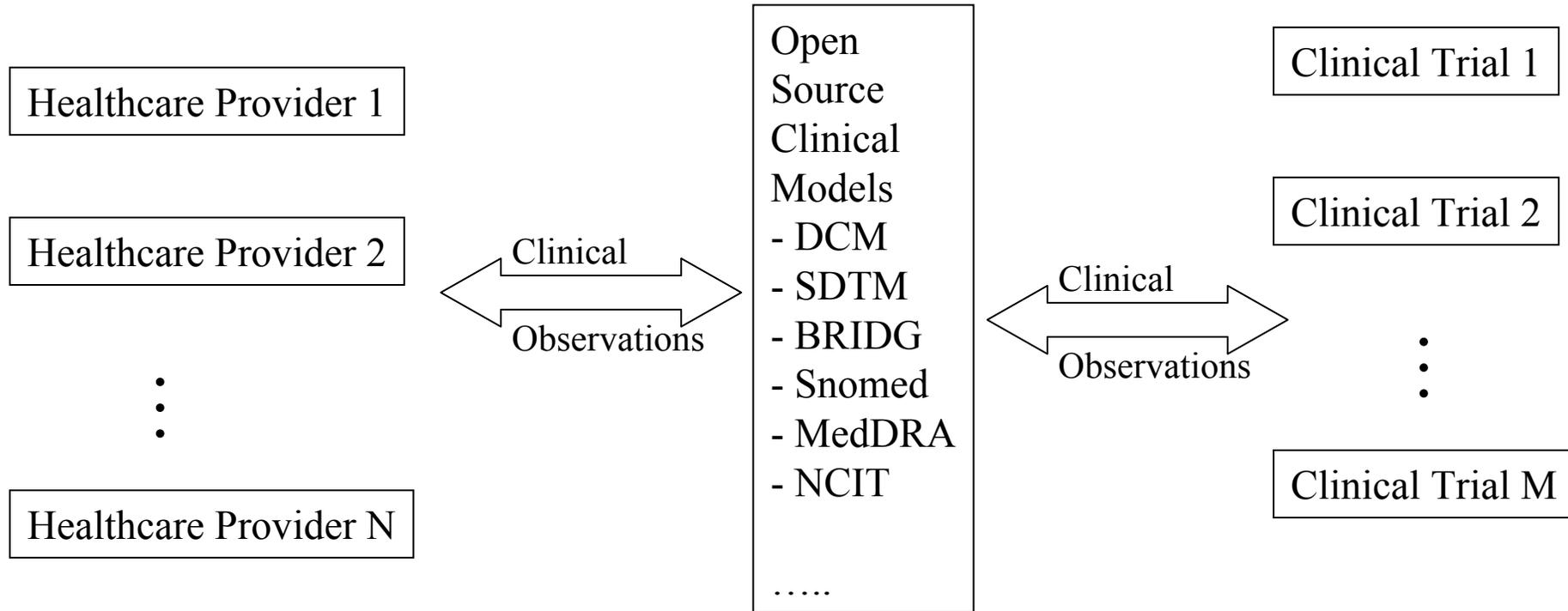
A Systolic Blood Pressure measurement is a pressure measurement that has a value from 0 to 220 and units are mmHg

```
SystolicBloodPressureMeasurement  
equivalentClass  
ClinicalElement  
that key value "SnomedCodeForSystolicBP"  
and magnitude only float[>= 0.0, <= 220.0]  
and units value mmHg
```

A Sitting Systolic Blood Pressure Measurement is a systolic blood pressure measurement taken when a patient is sitting

```
SittingSystolicBloodPressureMeasurement  
equivalentClass  
SystolicBloodPressureMeasurement  
that bodyPosition value Sitting
```

Shareable Open Source Models of Clinical Data



Re-use of Industry Standards

DCM:

SystolicBloodPressureMeasurement
subClassOf
key value “SnomedCodeForSystolicBP”
and magnitude only float[>= 0.0, <= 220.0]
and units value HL7:PQ:mmHg

SDTM:

SystolicBloodPressureMeasurement
equivalentClass
VSTEST
that VSTESTCD value “NCITCodeForSYSBP”
and VSORRESU value mmHg

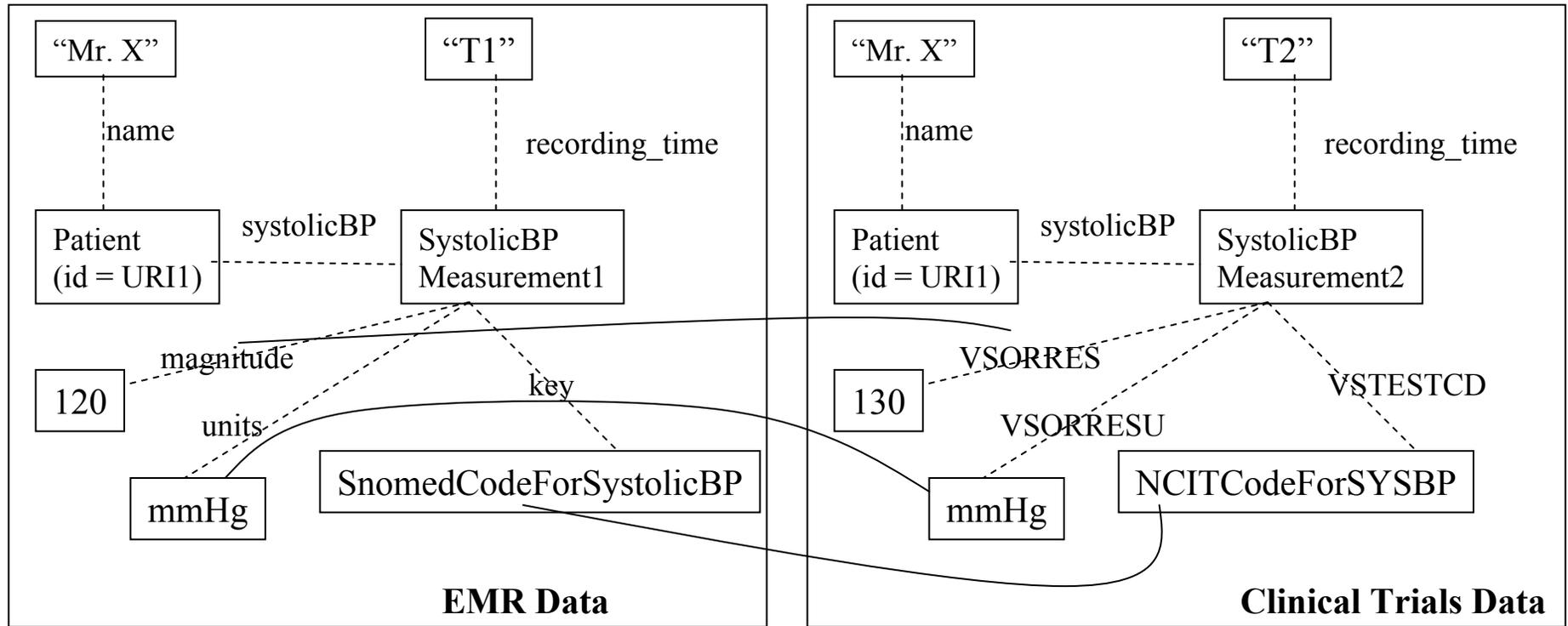
Alignment/Mappings:

DCM:SystolicBloodPressureMeasurement equivalentClass
SDTM:VSTEST that VSTESTCD value “NCITCodeForSYSBP”

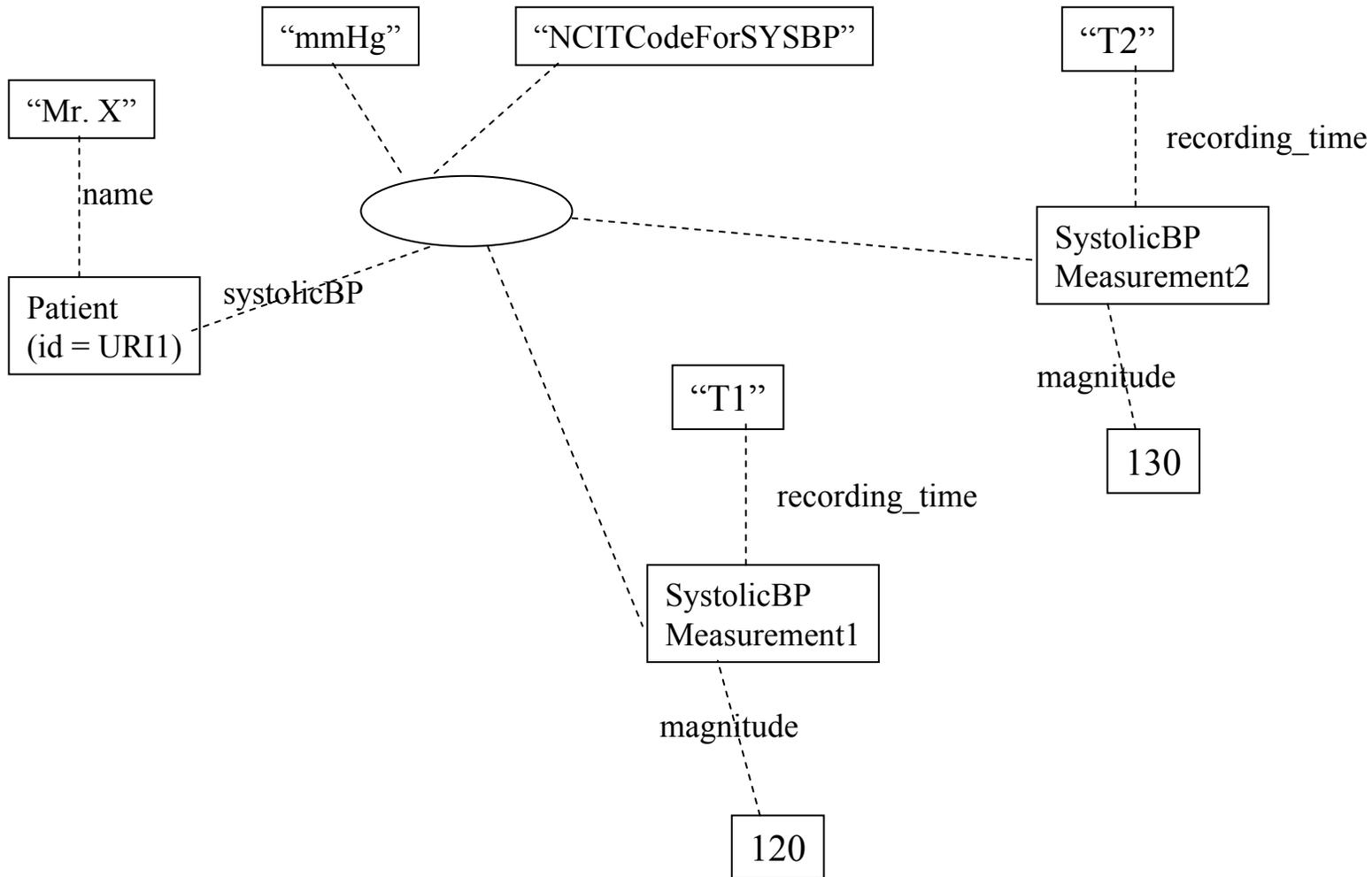
DCM:key equivalentProperty SDTM:VSTESTCD
DCM:units equivalentProperty VSORRESU
DCM:magnitude equivalentProperty VSSORRES

“SnomedCodeForSystolicBP” sameAs “NCITCodeForSYSBP”
HL7:PQ:mmHg sameAs VSORRESU:mmHg

Enabling Clinical Observations Interoperability



Enabling Clinical Observations Interoperability



Precise Protocol Specification

Prophylactic Irradiation to the Contralateral Breast for BRCA Mutation Carriers Undergoing Treatment for Breast Cancer

<http://www.clinicaltrials.gov/ct/show/NCT00496288?order=2>

Ages Eligible for Study: 30 Years - 90 Years, Genders Eligible for Study: Female

Inclusion Criteria:

- Female patient diagnosed with stage I-III breast cancer (AJCC 6), undergoing breast irradiation as part of her adjuvant therapy.
- The patient must be a carrier of a deleterious mutation in BRCA 1/2.
- ...

Exclusion Criteria:

- Metastatic breast cancer.
- Previous irradiation of the breast or chest wall.
- Pregnancy.
- Patients with active connective tissue diseases are excluded due to the potential risk of significant radiotherapy toxicity.
- ...

Precise Protocol Specification

Patient

that hasAge only float[>=30, <=60]

and hasGender value “Female”

and hasDiagnosis some StageI-IIIBreastCancer

and hasTherapy some BreastIrradiation

and hasMutation some (mutationType value deleterious and mutationGene value BRCA1/2)

and not (hasDiagnosis some (BreastCancer that cancerType value Metastatic))

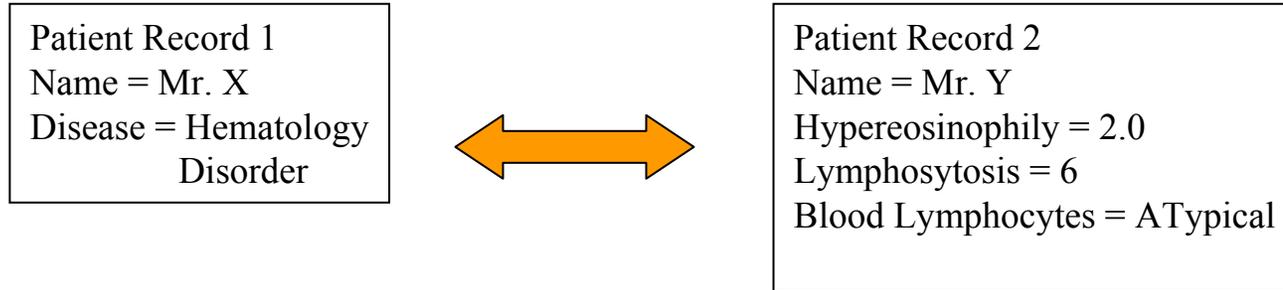
and not (hasTherapy some Irradiation that hasLocation some (Chest or BreastWall))

and not (hasCondition some Pregnancy)

and not (hasDisease some (Disease that hasLocation some ConnectiveTissue
and type value Active))

...

Identify Patients in the absence of explicit data about a clinical condition



Which of these two patients have Hematology Disorder?

Assert the following Mapping:
PatientWithHematologyDisorder
equivalentClass
Patient
that hypereosinophily only float[>1.5]
and lymphosytosis only float [> 5]
and bloodLymphocytes value ATypical

The OWL Ontology Engine will infer the rest.

Conclusion: Semantics a “Transformational” Enabler

- Data and Knowledge Integration *across Biomedical Research, Clinical Research and Clinical Practice* is a critical requirement for the Next Generation Healthcare Enterprise
 - The ability to capture and re-use information semantics is a critical enabler!
 - The ability to perform “as needed”, incremental and cost effective integration
 - The ability to support flexible and rapid change management
 - Increased productivity for authoring different forms of knowledge
- Rapid adoption of innovations from Genomic Research into Clinical Practice is crucial for improving patient outcomes and quality of care and is likely to transform the state and impact of healthcare
 - The rate of knowledge change will increase dramatically as Genomic Knowledge explodes!
 - Automated Semantics-based Knowledge Update and Propagation will be key in keeping the knowledge updated and current