

**Computational Thinking to Support Clinicians and Biomedical Scientists**  
**June 21–22, 2011**

# Automated Reasoning for Application of Clinical Guidelines

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# GLINDA: GuideLine INteraction Detection Architecture

- Computational methods for reasoning about evidence-based practice
- Mechanisms for dealing with the messiness of clinical situations
  - Application of multiple clinical-practice guidelines
  - Adjustments for patient co-morbidities
  - Adjustments for interactions among interventions



# GLINDA Project Team

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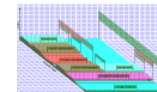
# Clinical Context of our Work

- Populations are aging worldwide
- Older adults tend to have multiple chronic conditions
  - 75 million people in the US have two or more concurrent chronic conditions
- Management of multiple co-morbidities presents challenging problems
  - Competing therapeutic goals
  - Interventions that interact
  - Difficulty achieving parsimonious treatment plans

# Role of Clinical Practice Guidelines

- Clinical practice guidelines define evidence-based best practices
- Lots of work on automating CPGs

EON, InterMed (GLIF), SAGE,  
PROforma, Asbru, ...



- Almost all CPGs—and all systems to automate treatment in accordance with CPGs—focus on single diseases

WINDOW FRAME


**ATHENA Hypertension Advisory**
References Sources

Patient Name
XXXX-XX-XXXX
[View Patient Summary](#)

Recommendations
Lifestyle
Adherence
Assumptions
Patient Summary

**Blood Pressure apparently not under control:**  
Based on last measurement of **145/92** taken 87 days ago on mm/dd/yyyy

**CARDIO RISK FACTOR:**  
**23% High**

\*Estimated 10 Year cardiovascular risk factor for this patient [Explain](#)

Enter a new BP:  [Update](#)  
Date: MM/DD/YR ☐ Write back to Vista

**Blood Pressure and Prescription History**


**Recommendations**
[Other Patient Information and Alerts](#)

- Consider intensifying drug treatment: **BP Elevated** based on most recent available BP
- There appears to be a **Strong Contraindication** to a currently prescribed drug, evaluate clinical significance
- Bronchospasm is a **Strong Contraindication** or use of beta adrenergic receptor antagonists, although many patients tolerate and therefore benefit from this drug therapy

Review lifestyle modifications with the patient. See the [Lifestyle](#) page.

**Therapeutic Possibilities**

**Discontinue** [atenolol](#)

**AND start one of the following drugs**

- [ACE Inhibitors \(lisinopril\)](#)
- [\(non-DHP\) Calcium Channel Blocker \(diltiazem\)](#)

**Add one or more of the following drugs**

- [ACE Inhibitors \(lisinopril\)](#)
- [\(non-DHP\) Calcium Channel Blocker \(diltiazem\)](#)

**Increase dosage of hydrochlorothiazide**

**Indications**

- Heart Failure [EVIDENCE](#)
- CKD
- Heart Failure [EVIDENCE](#)
- CKD [EVIDENCE](#)
- CKD
- Heart Failure [EVIDENCE](#)
- CKD [EVIDENCE](#)

**Contraindications**

- Brochospastic disease
- Heart Failure
- Heart Failure

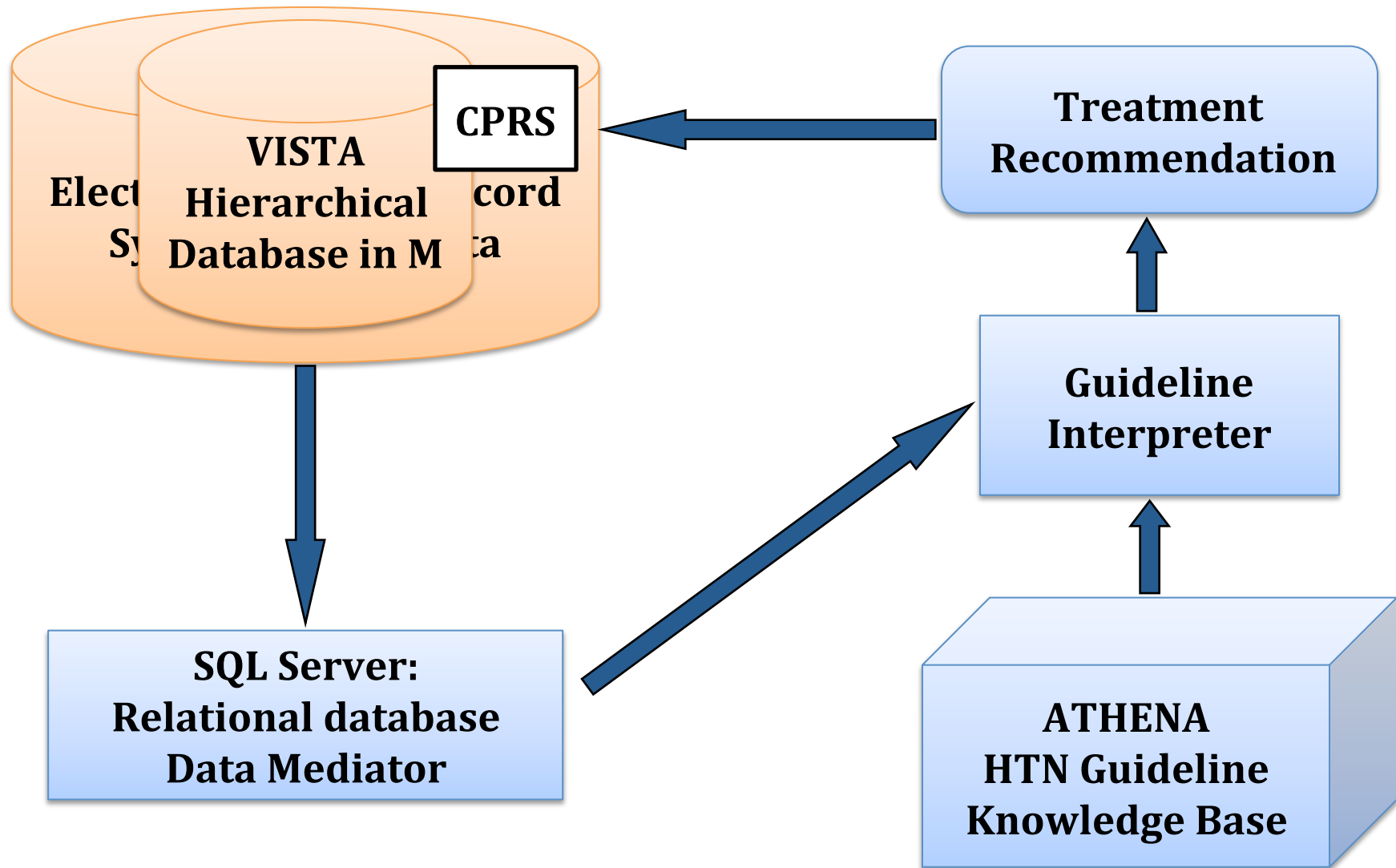
☐ Do not display advisory for this clinic visit again

[Exit](#)

☐ Compelling Indication
☐ Relative Indication
☐ Relative Contraindication
☐ Strong Contraindication
☐ Adverse Effects

Don't forget you know the patient better than we do message utpat lorem ipsum dolor sit amet, consectetur adipiscing

# Simplified ATHENA Architecture



## Identifier

VA/JNC-VII Hypertension Guideline

## Title

The clinical information from this system is advisory only and is intended to supplement the knowledge of health care professionals regarding the management of hypertension. It is not intended to replace sound clinical judgment or individualized patient care in delivery of healthcare services.

## Authors

NIH NHLBI Joint National Committee  
Mary Goldstein, MD  
Brian Hoffman, MD  
Susana Martins, MD MSc

## Version

February, 2009

## Clinical Algorithm

◆ hypertension management diagram

## Eligibility Criteria

- ◆ presence of diagnosis of hypertension
- ◆ absence of renovascular disease
- ◆ no diagnosis of pregnancy
- ◆ Absence of Secondary Hypertension
- ◆ absence of spinal cord injury

## Goal

- ◆ BP target patient with diabetes mellitus
- ◆ BP target for patient without diabetes mellitus

## Patient Characterization

- Risk\_Group\_A
- Risk\_Group\_B
- Risk\_Group\_C
- Home\_BP

## Drug Usages

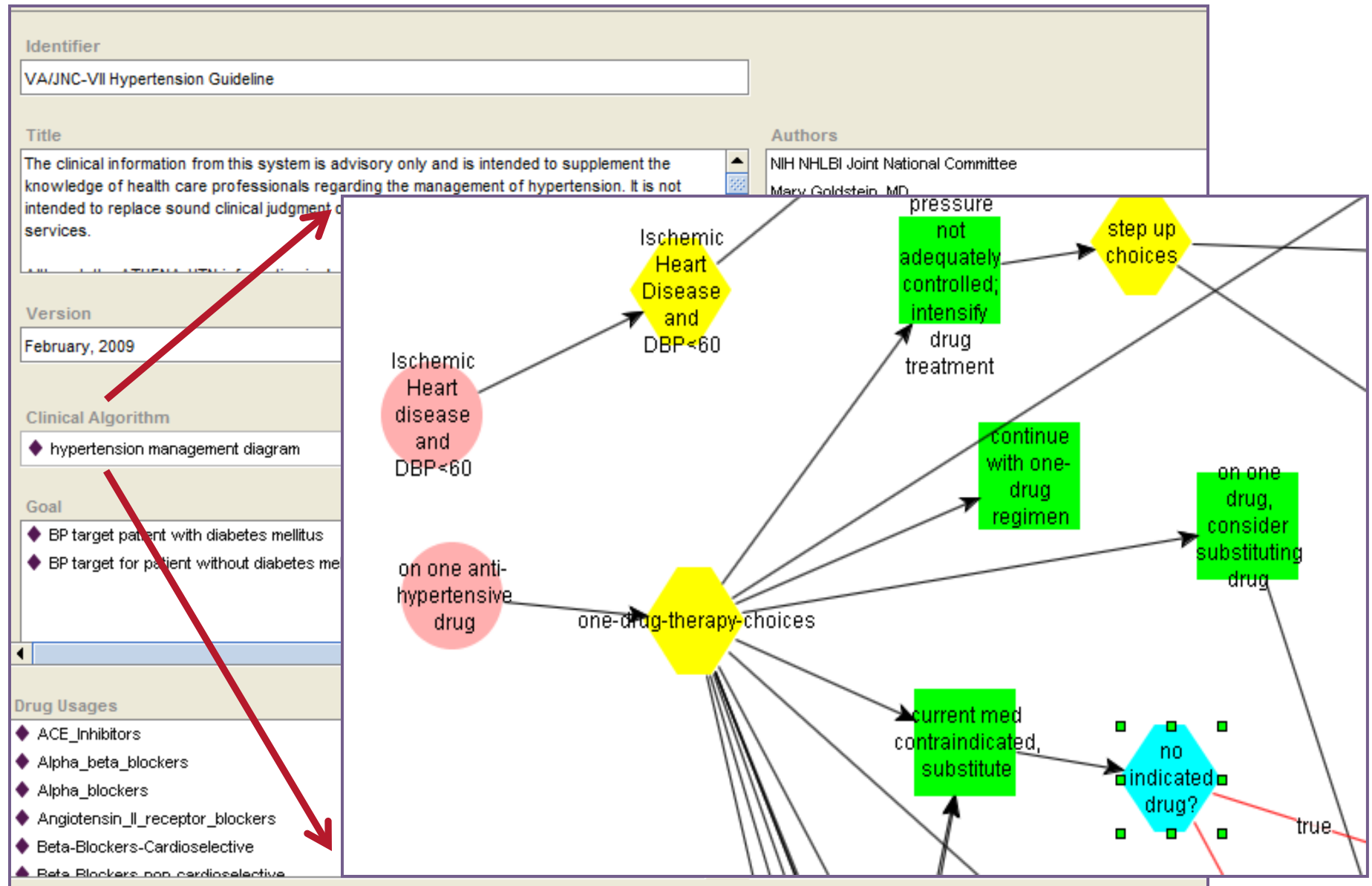
- ◆ ACE\_Inhibitors
- ◆ Alpha\_beta\_blockers
- ◆ Alpha\_blockers
- ◆ Angiotensin\_II\_receptor\_blockers
- ◆ Beta-Blockers-Cardioselective
- ◆ Beta-Blockers-non-cardioselective

## Guideline Drugs

- ◆ acebutolol
- ◆ amiloride
- ◆ amlodipine
- ◆ amlodipine besylate
- ◆ atenolol
- ◆ captopril



# ATHENA HTN Knowledge Base



Visit Not Selected  
Current Provider Not Selected  
Primary Care Team Unassigned

Active Problems  
Obesity, Unsp  
Chronic Airway Obstru  
Unspecified Drug-Indu  
Depressive Disorder N  
Diabetes  
Hypertension

ATHENA Hypertension Advisory

Patient SSN [ ] Name [ ] Patient Summary

Most Recent BP in Database 158/85 Date [ ]

ENTER a New BP [ ] Date [ ] Update Advisory

**Guideline Goal: SBP < 140 and DBP < 80 [ presence of diabetes mellitus ]**  
**BP apparently NOT UNDER CONTROL, based on most recent available BP.**

Recommendations Precautions Assumptions Lifestyle Adherence Glossary

**Recommend ADDING antihypertensive medication: BP ELEVATED based on most recent available BP.**  
**RECOMMENDATIONS DO NOT APPLY TO PREGNANT WOMEN (or women likely to become pregnant)**

Compelling Indication Relative Indication Strong Contraindication Relative Contraindication Adverse Events

Consider one of the following therapeutic possibilities:	Click here for important ...	Reasons	Click here to provide ...
Add Thiazide Diuretic (HCTZ)	Info	✓ Diabetes	Feedback
Add ACE Inhibitors(lisinopril)	Info	✓ 1st line drug for hypertension	Feedback
Add Cardioselective Beta Blocker (atenolol)	Info	✓ Diabetes_Mellitus	Feedback
Add DHP Calcium Channel Blocker (felodipine, nifedipine)	Info	~ Diabetes_Mellitus	Feedback
Add Angiotensin II Receptor Blocker (irbesartan)	Info	~ Diabetes	Feedback

Your comments for the Guidelines Team (optional and welcome!)

☐ Do not display Advisory for this clinic visit again.

Recommendations considered No Read Not a clinical priority today

Complete clinical information may not be available through the computer system. Please use all the information that you have about the patient together with your clinical judgment to decide on the best therapy for this patient.

Cover Sheet Problems Meds Orders Notes Consults Surgery D/C Summ Labs Reports

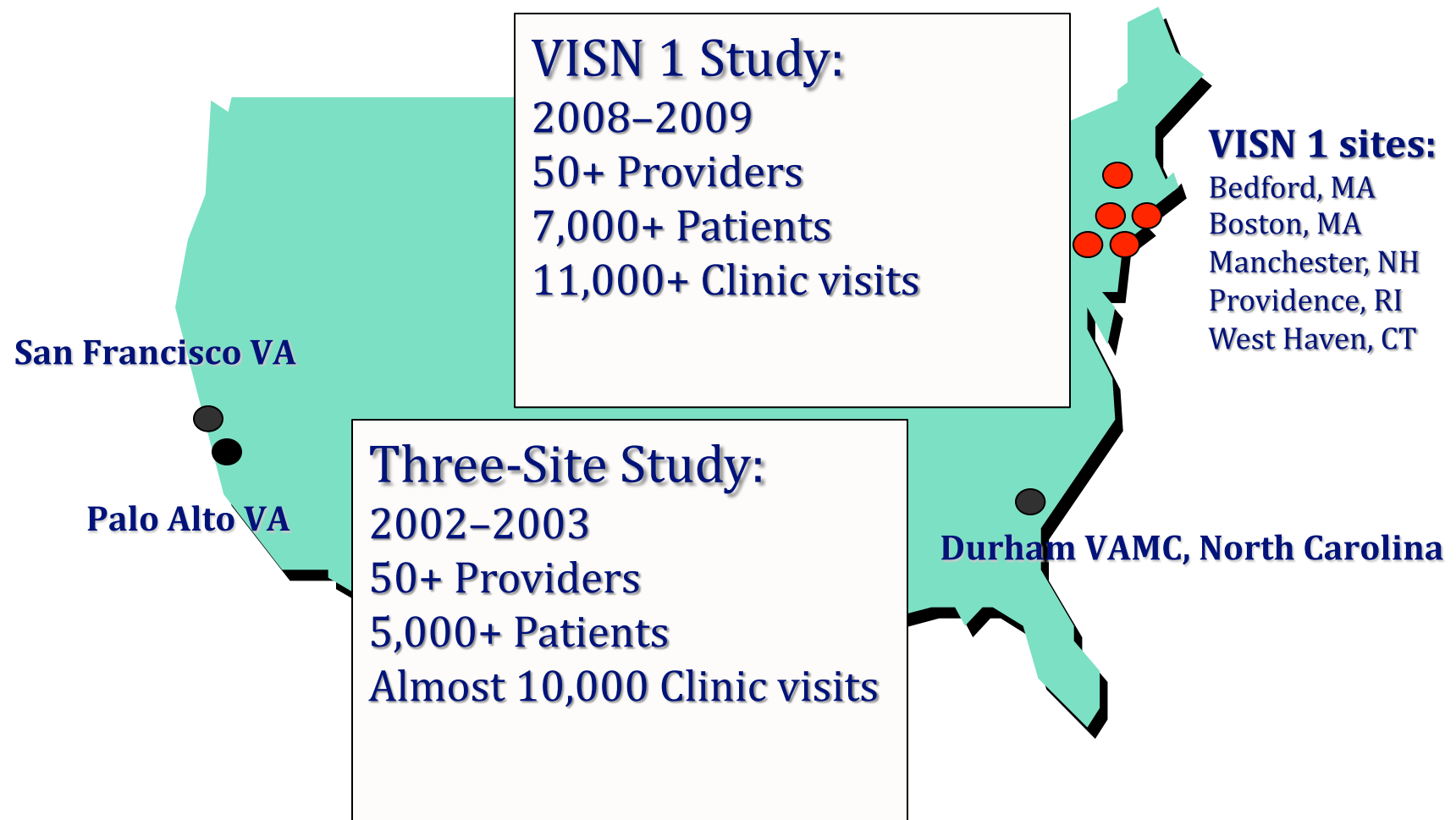
SYNTHETIC PATIENT DATA ONLY

Goals

Messages

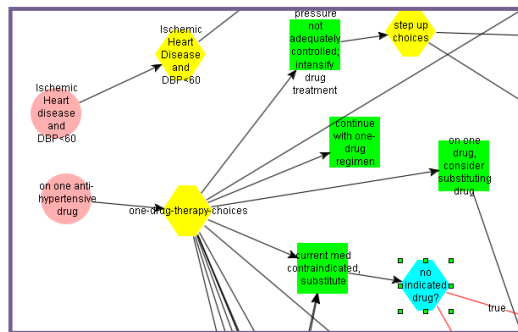
Action Choices

# ATHENA-HTN Evaluation Studies

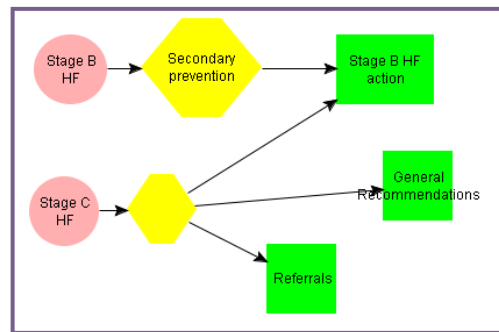


# Encoded Guidelines

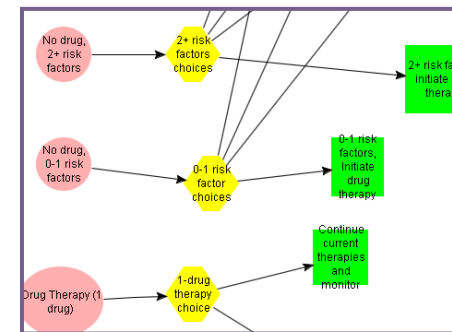
## ATHENA Hypertension



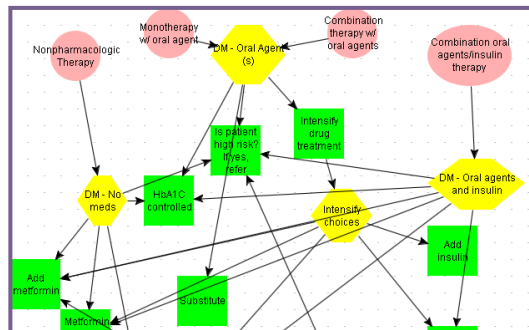
## ATHENA Heart Failure



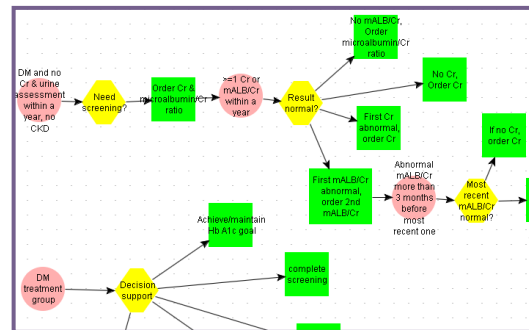
## ATHENA Hyperlipidemia



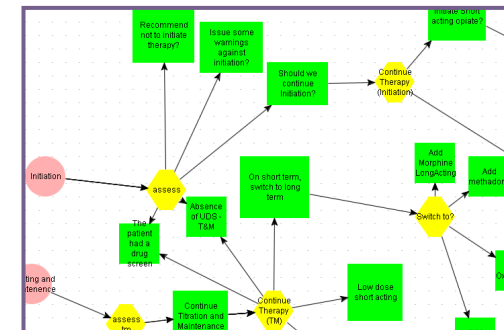
## ATHENA Diabetes



## ATHENA Kidney Disease



## ATHENA Opioid Therapy



# Limitations of Single-Disease Guidelines

[Boyd et al. JAMA 2005]

- Simultaneous application of multiple guidelines leads to suboptimal care
  - Hypothetical 79-year-old woman with chronic obstructive pulmonary disease, Type 2 diabetes, osteoporosis, hypertension, and osteoarthritis
  - If the relevant CPGs were followed, the hypothetical patient would be prescribed 12 medications and a complicated, pharmacologically inappropriate regimen
- Application of CPGs needs to
  - Detect and repair conflicting interactions
  - Prioritize recommendations





# Recommendations for Hypertension

Therapeutic Possibilities	Indications	C
CLICK ON DRUGS FOR IMPORTANT		
Add one or more of the following drugs		
<u>DHP Calcium Channel Blocker (felodipine, nifedipine SA)</u>		
	 MI (BP not controlled), Diabetes Mellitus	
<u>(non-DHP) Calcium Channel Blocker (diltiazem)</u>	 MI (BP not controlled)	

# Recommendations for Hyperlipidemia

Therapeutic Possibilities	Indications	Contraindications
CLICK ON DRUGS FOR IMPORTANT		
Add one or more of the following drugs		
<a href="#">Statin</a>	✓ LDL not within guideline goal	
<a href="#">Bile Acid Sequestrant</a>	~ LDL not within guideline goal	
<a href="#">Nicotinic Acid</a>	~ LDL not within guideline goal	⊖ Diabetes Mellitus

# Recommendations for Diabetes

<b>Substitutions</b>  Discontinue <u>METFORMIN</u>	 DM-Type2(DM-Type2)	 Creatinine > 1.5 and Ma (Creatinine > 1.5 and M. [Creatinine(1.8/2011-6- 8@ Sex(Male)])
 <b>AND start one of the following drugs</b>  <u>GLIPIZIDE(GLIPIZIDE)</u>	 DM-Type2	
 <b>Add one or more of the following drugs</b>  <u>GLIPIZIDE(GLIPIZIDE)</u>	 DM-Type2	

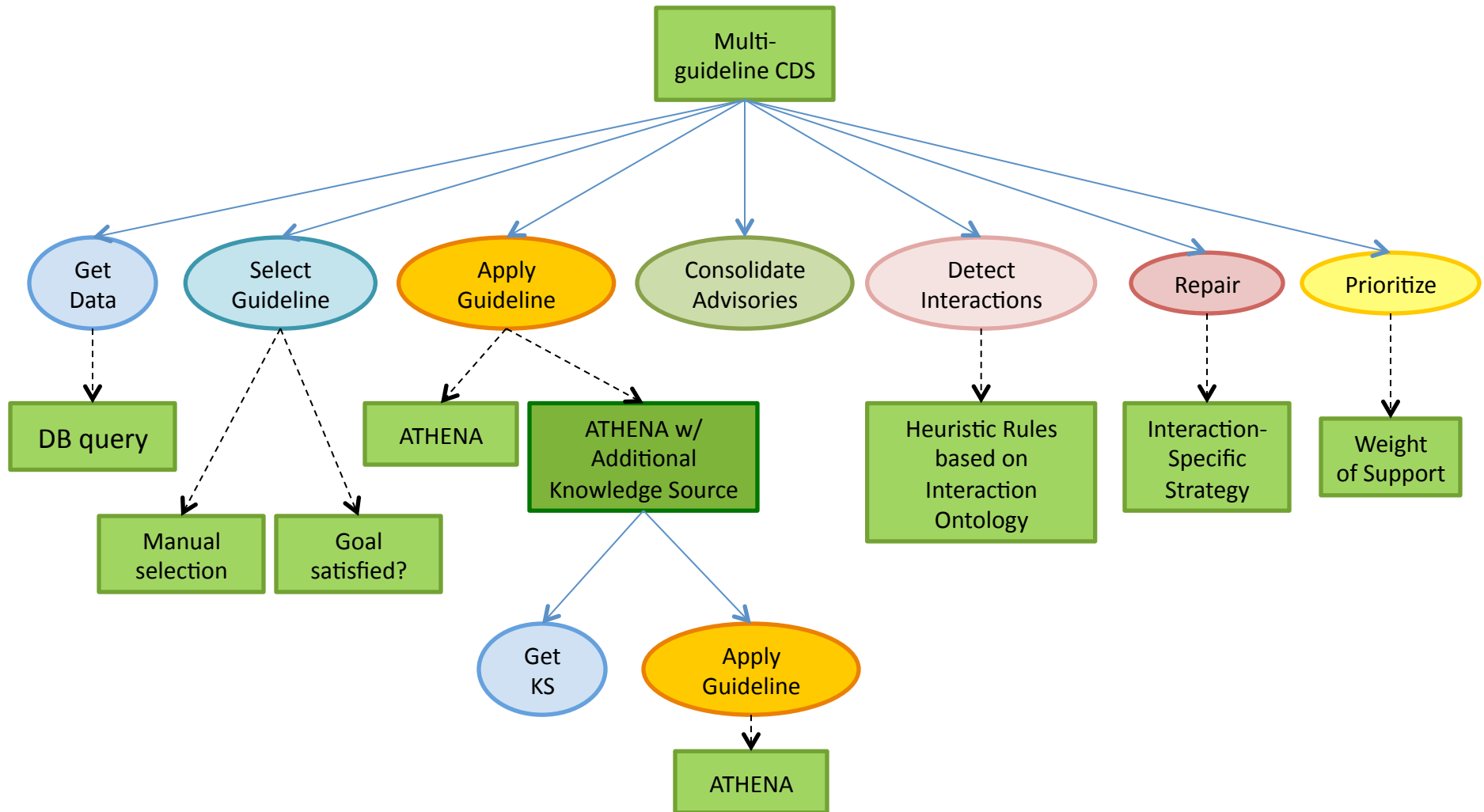


# Overview of GLINDA Approach

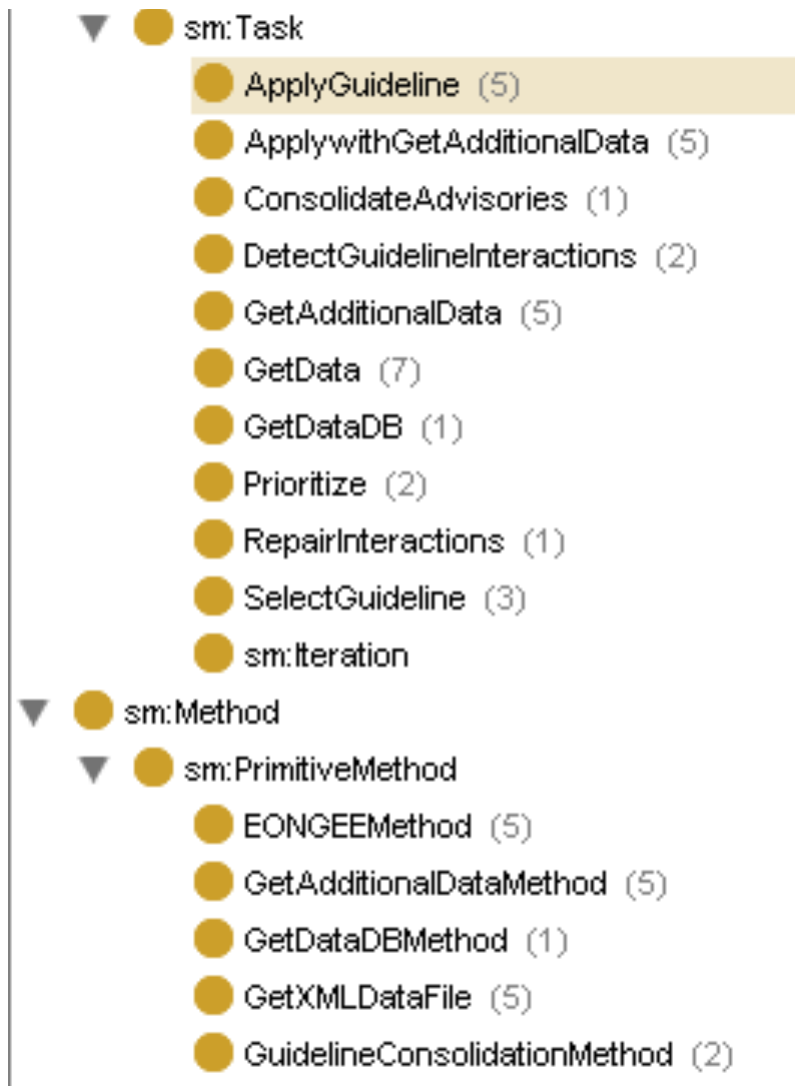
- Incorporate our extensive experience with ATHENA CDS in an agent-oriented architecture
- Use task—method decomposition to create agent-oriented model of procedural elements
- Develop ontology of guideline interactions
- Develop agents for detecting conflicts, repairing conflicts, prioritizing and integrating treatment recommendations



# GLINDA Task–Method Decomposition



# Modeling tasks and methods in Protégé



# Modeling tasks and methods in Protégé

The image shows the Protégé software interface. On the left is a class hierarchy tree. The 'sm:Task' class is expanded, and 'ApplyGuideline (5)' is selected and circled in red. The main window is the 'INDIVIDUAL EDITOR for 'Apply HTN Guideline Task' (instance of ApplyGuideline)'. The 'For Individual:' field contains the URL 'http://bmir.stanford.edu/glinda/taskmethod.owl#ApplyHTNGuideline\_task'. The editor contains several property lists:

- sm:label**: Apply HTN Guideline Task
- sm:hasMethod**: EONGEEMethod\_Hypertension
- sm:subtaskOf**: GLINDA workflow, Simple Apply Multiple Guidelines Test, Simple Apply One Guideline Test, SubAlgorithm\_HTN
- sm:inputsSpecification**: CaseData\_Tag, Current\_Time\_Tag, HTNTrigger\_tag, ProtegeServerAccess\_tag
- sm:outputSpecification**: HTNAdvisory\_tag

At the bottom of the editor are icons for saving, undo, redo, and a search icon.

# Modeling tasks and methods in Protégé

The image shows the Protégé software interface for modeling tasks and methods. On the left is a class hierarchy tree:

- sm:AnalysisEntity
  - sm:Algorithm (13)
  - sm:BranchPoint
  - sm:Connector
  - sm:Task
    - ApplyGuideline (5)
      - ApplywithGetAddition
      - ConsolidateAdvisories
      - DetectGuidelineInterac
      - GetAdditionalData (5)
      - GetData (7)
      - GetDataDB (1)
      - Prioritize (2)
      - RepairInteractions (1)
      - SelectGuideline (3)
      - sm:Iteration
- sm:Method
  - sm:PrimitiveMethod
    - EONGEEMethod (5)
      - GetAdditionalDataMeth
      - GetDataDBMethod (1)
      - GetXMLDataFile (5)
      - GuidelineConsolidation
      - HeuristicGuidelineInteractionDetection
      - SelectGuidelineMethod (3)
    - sm:DataQueryMethod
    - sm:DataTransformationMethod
    - sm:TaskDecompositionMethod

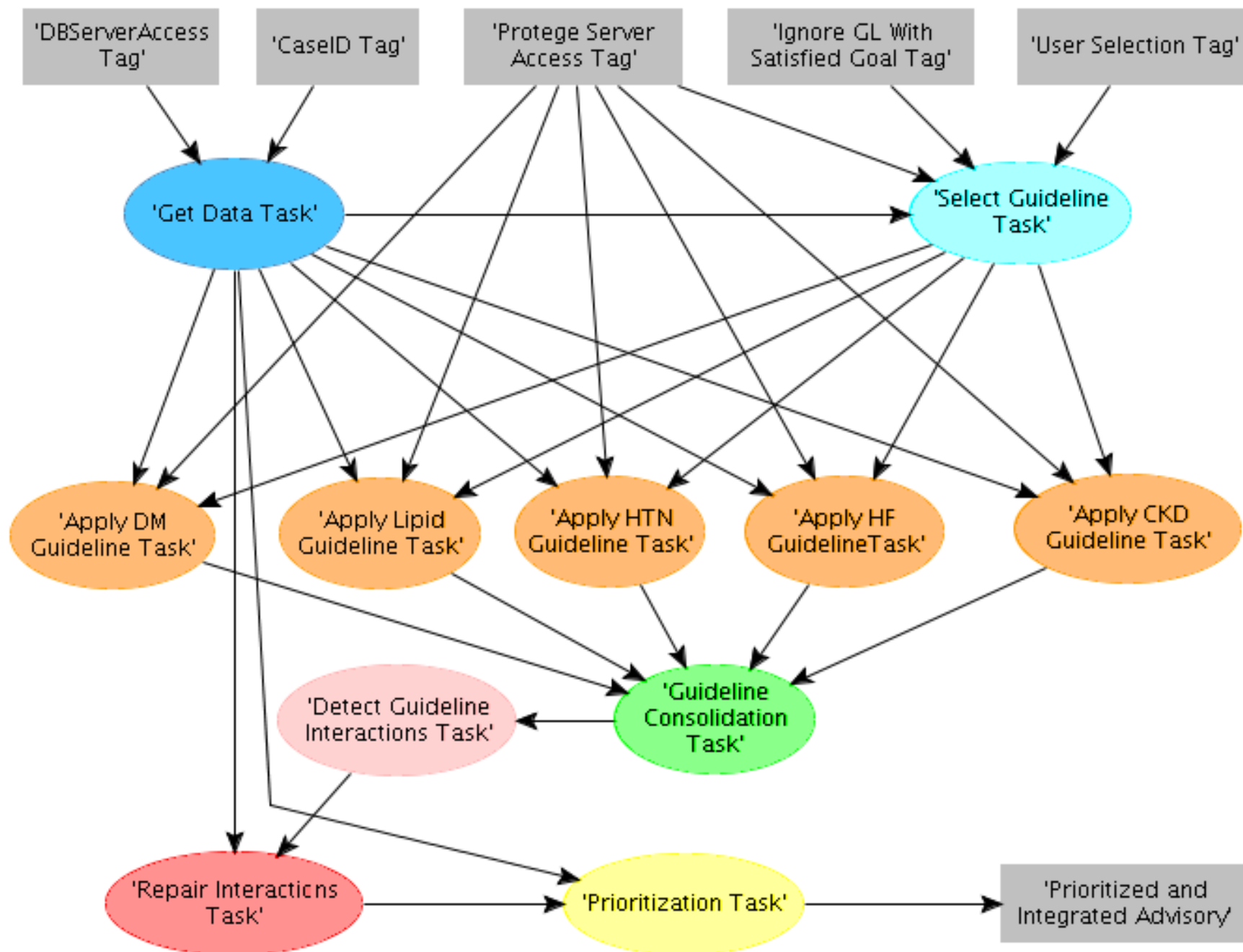
The main window is the 'INDIVIDUAL EDITOR for 'Apply HTN Guideline Task' (instance of ApplyGuideline)'. It contains the following fields:

- For Individual:** [http://bmir.stanford.edu/glinda/taskmethod.owl#ApplyHTNGuideline\\_task](http://bmir.stanford.edu/glinda/taskmethod.owl#ApplyHTNGuideline_task)
- sm:label:** Apply HTN Guideline Task
- sm:subtaskOf:** GLINDA workflow (circled in red)
- sm:hasMethod:** EONGEEMethod\_Hypertension
- sm:inputsSpecification:**
  - CaseData\_Tag
  - Current\_Time\_Tag
  - HTNTrigger\_tag
  - ProtegeServerAccess\_tag

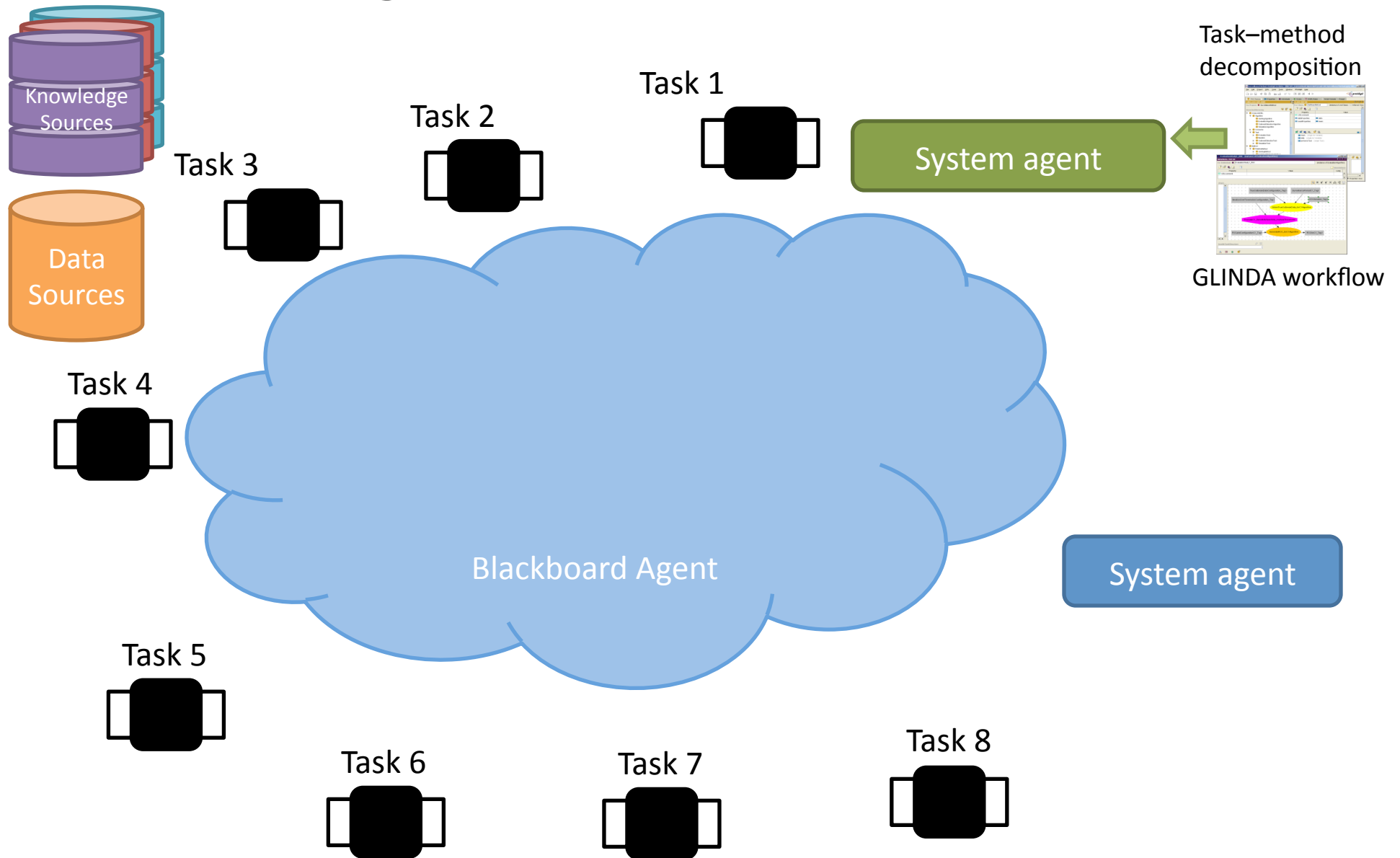
On the right, a workflow diagram is shown. It is a directed graph with nodes representing tasks and tags. The nodes are:

- Tags (grey rectangles): 'DBServerAccess Tag', 'CaseID Tag', 'Protege Server Access Tag', 'Ignore GL With Satisfied Goal Tag', 'User Selection Tag'.
- Tasks (colored ovals):
  - 'Get Data Task' (blue)
  - 'Select Guideline Task' (cyan)
  - 'Apply DM Guideline Task' (orange)
  - 'Apply Lipid Guideline Task' (orange)
  - 'Apply HTN Guideline Task' (orange)
  - 'Apply HF Guideline Task' (orange)
  - 'Apply CKD Guideline Task' (orange)
  - 'Detect Guideline Interactions Task' (pink)
  - 'Guideline Consolidation Task' (green)
  - 'Repair Interactions Task' (red)
  - 'Prioritization Task' (yellow)
  - 'Prioritized and Integrated Advisory' (grey rectangle)

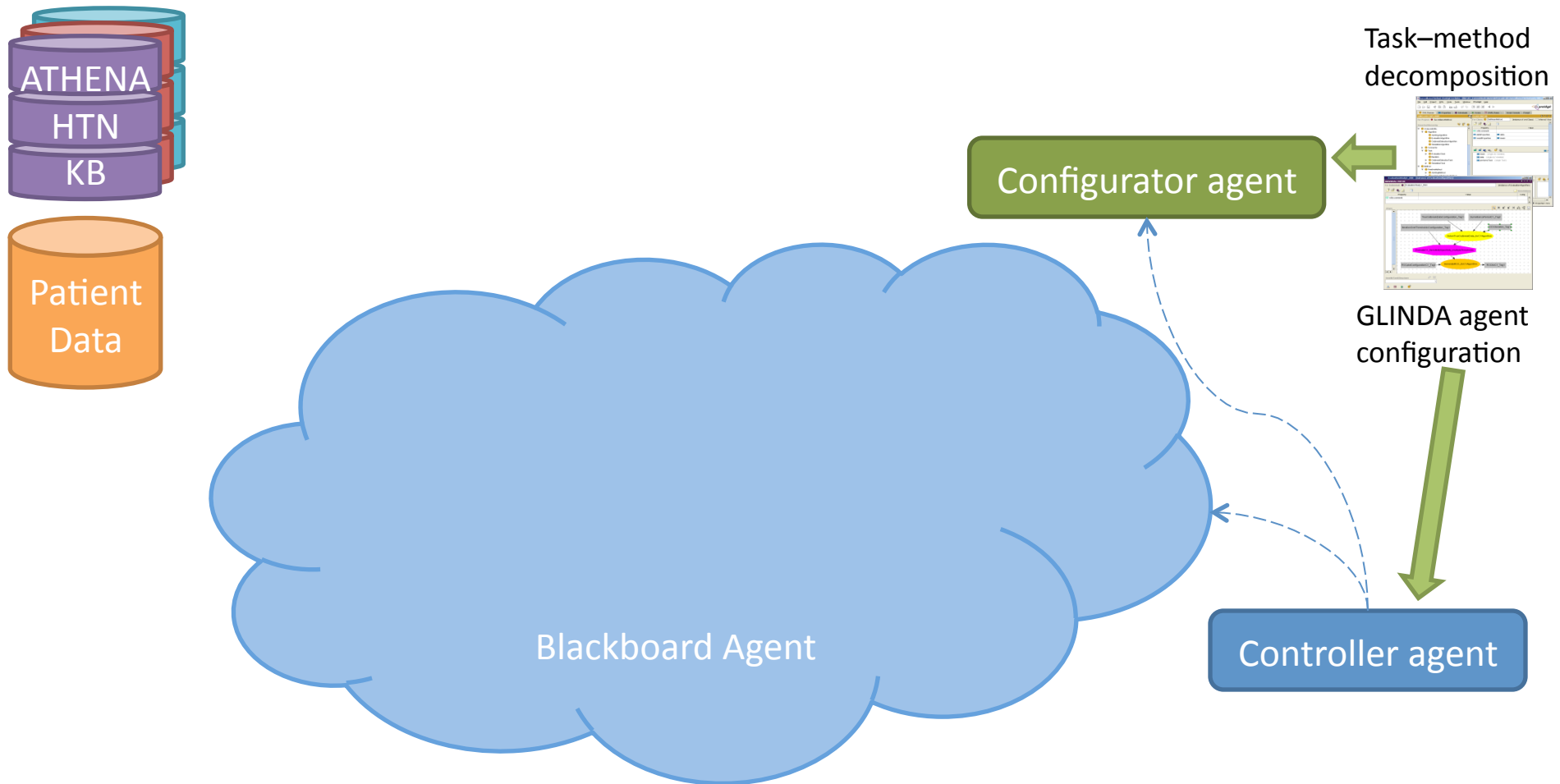
The diagram shows a complex network of dependencies between these tasks and tags, with arrows indicating the flow of information or control.



# Implementation of Tasks and Methods in an Agent-Oriented Architecture

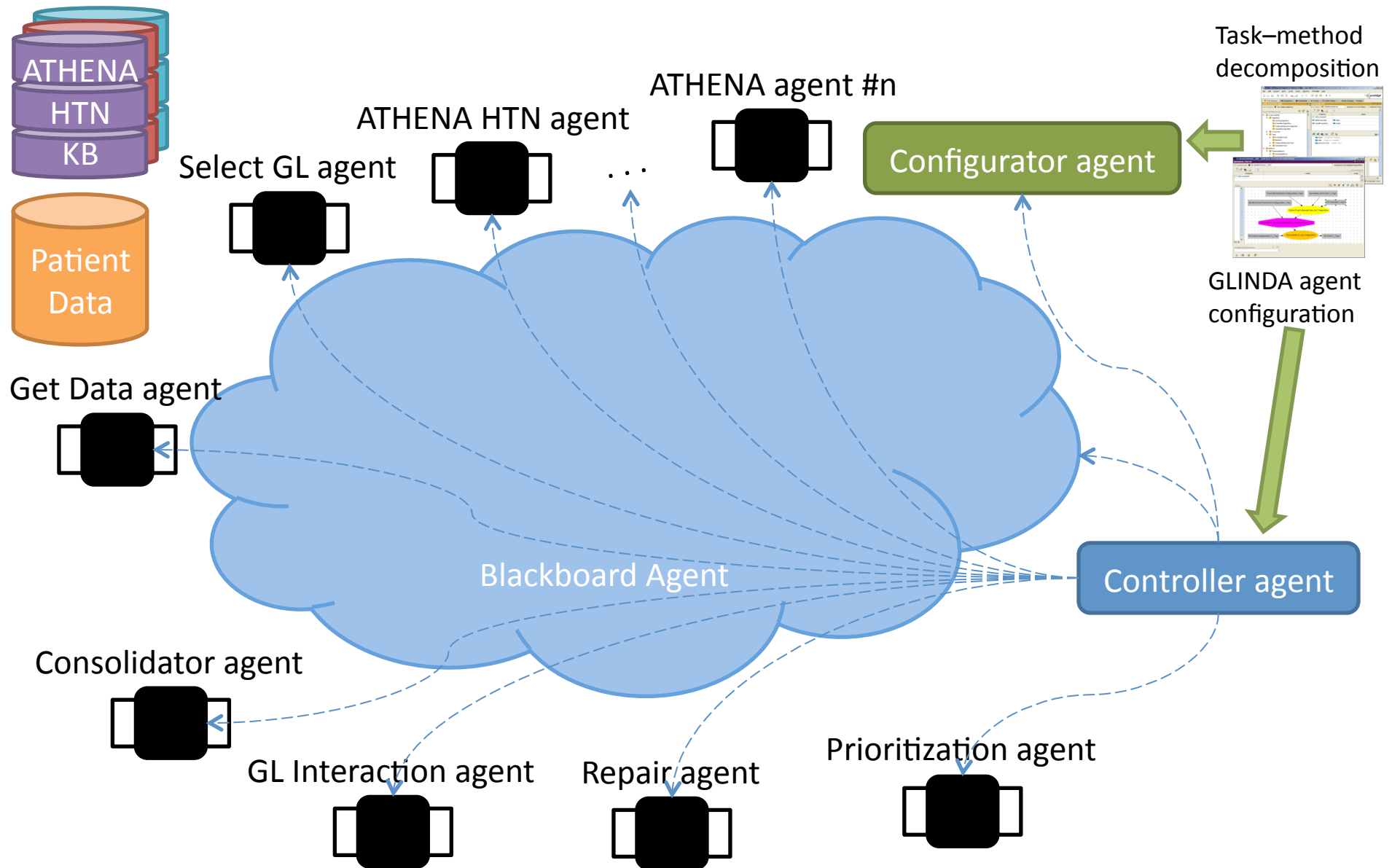


# Running GLINDA – Initializing ...

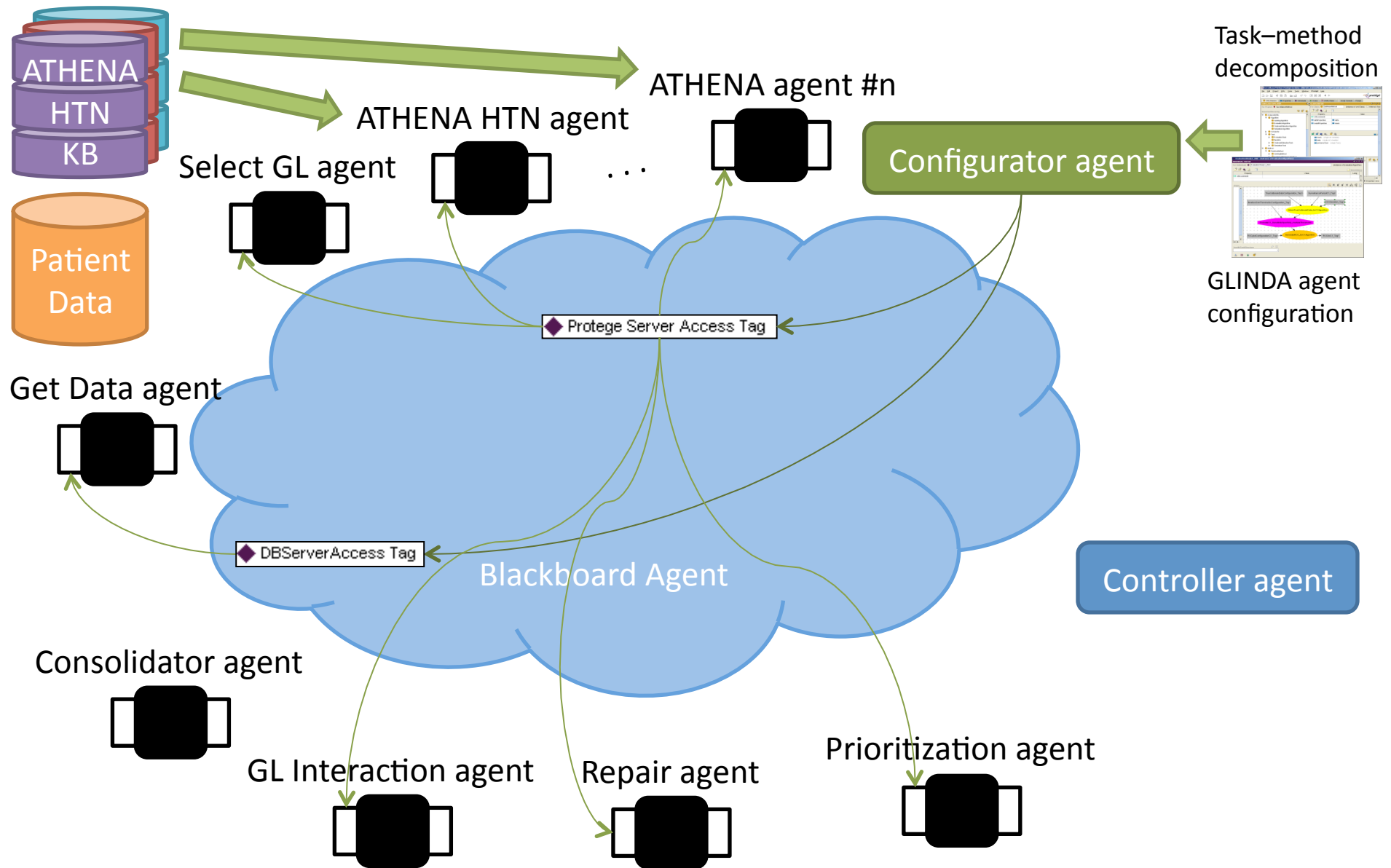




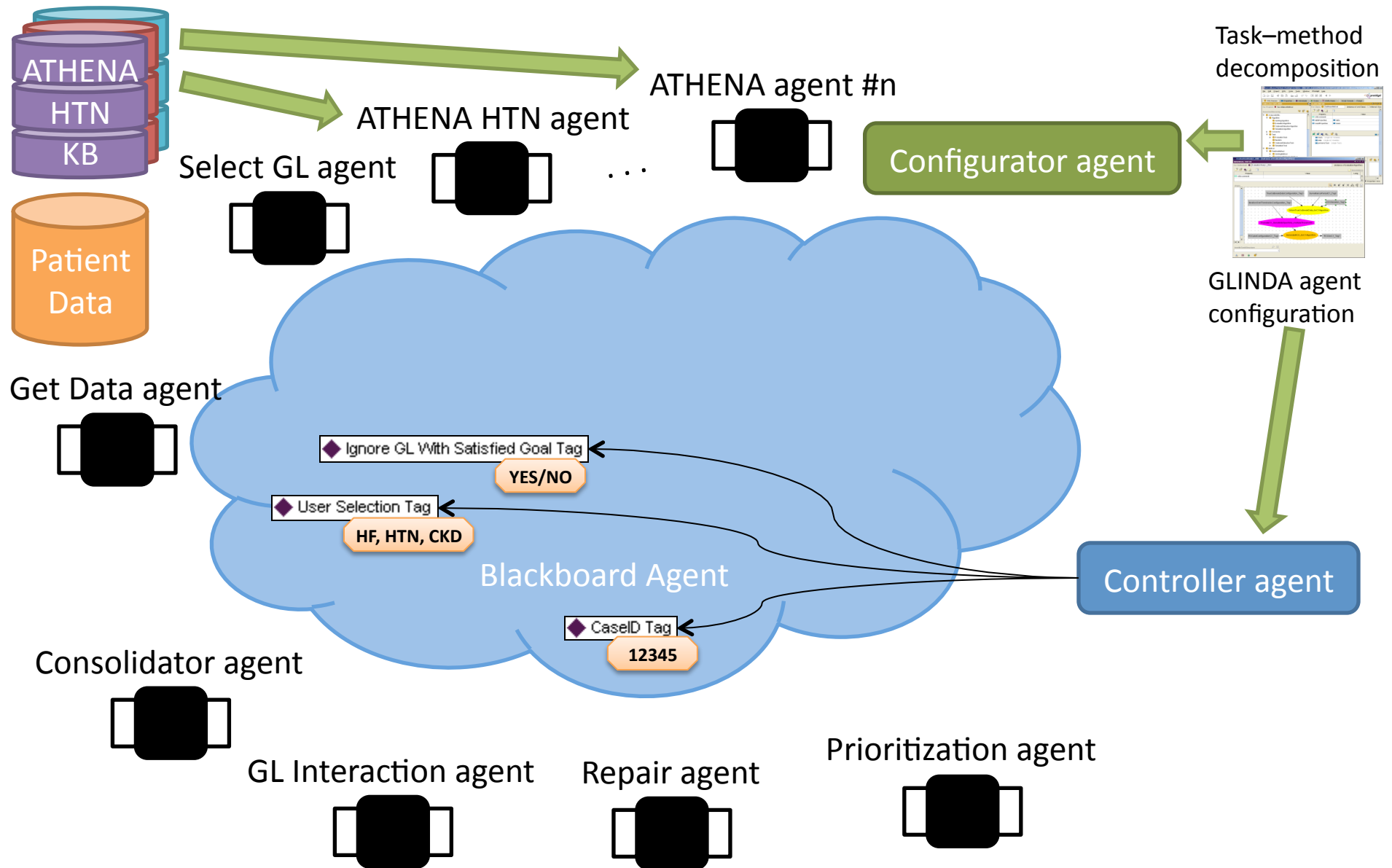
# Running GLINDA – Creating Agents



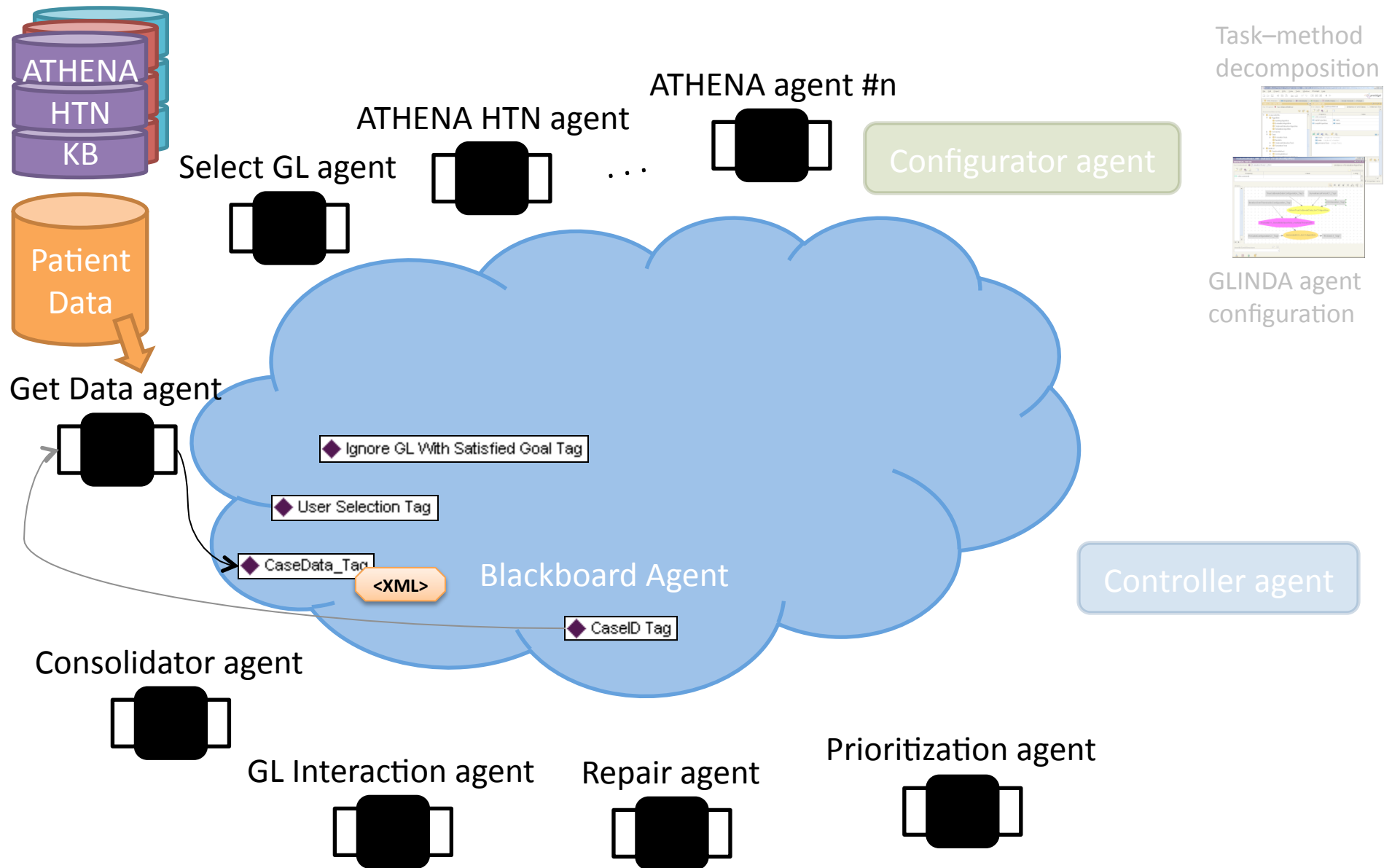
# Running GLINDA – Configuring Agents



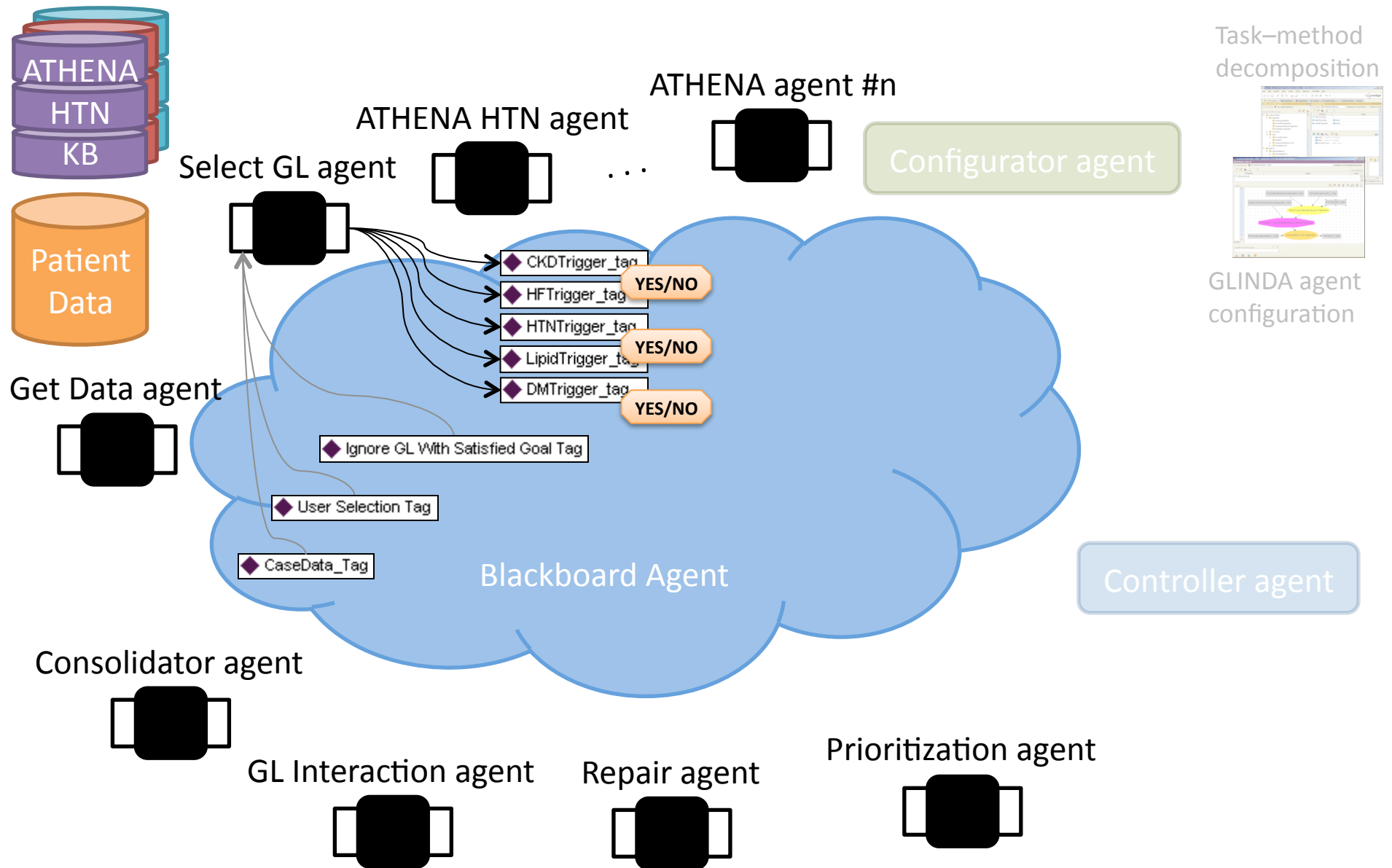
# Running GLINDA – Activating Agents



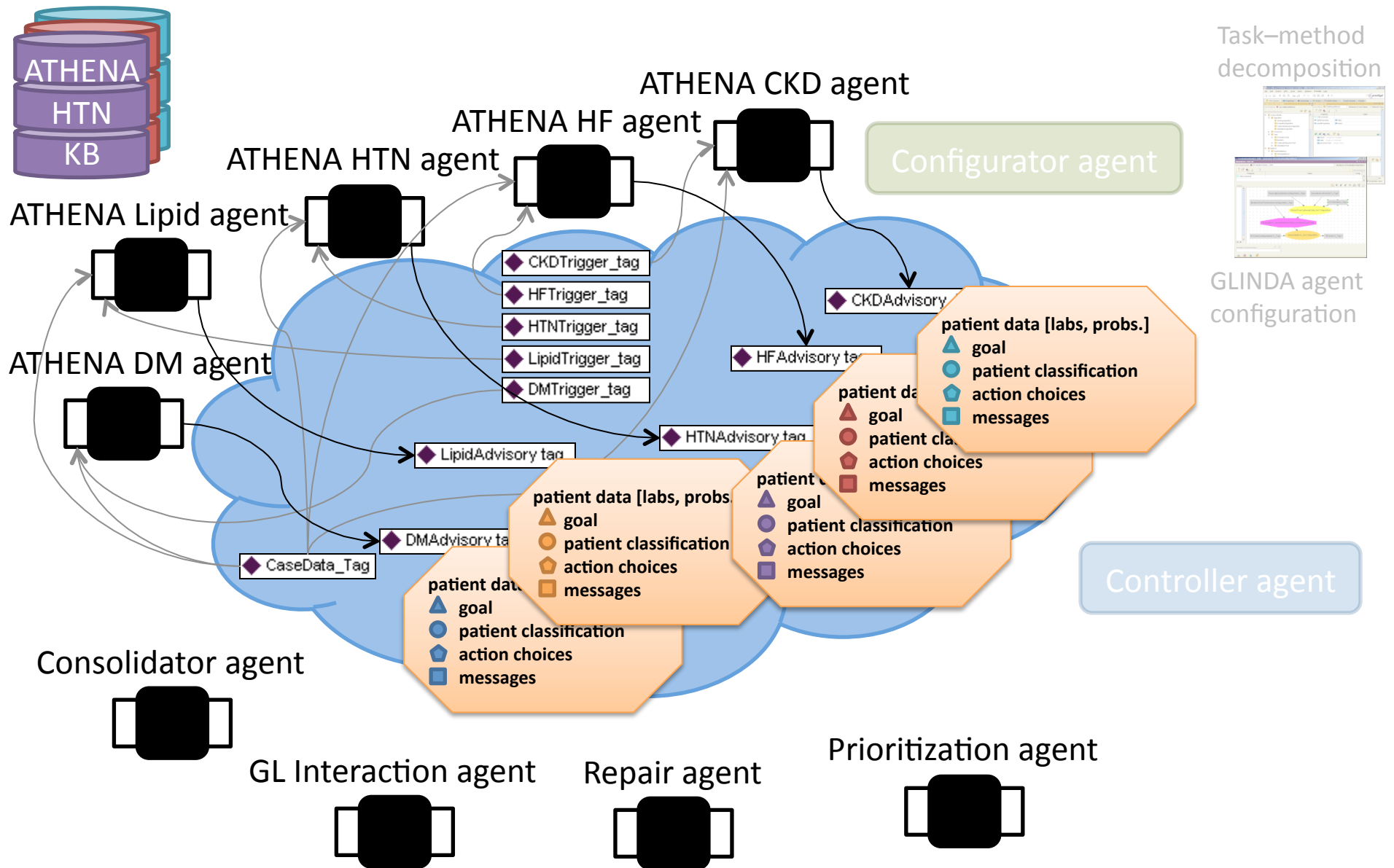
# Running GLINDA – *Get Data*



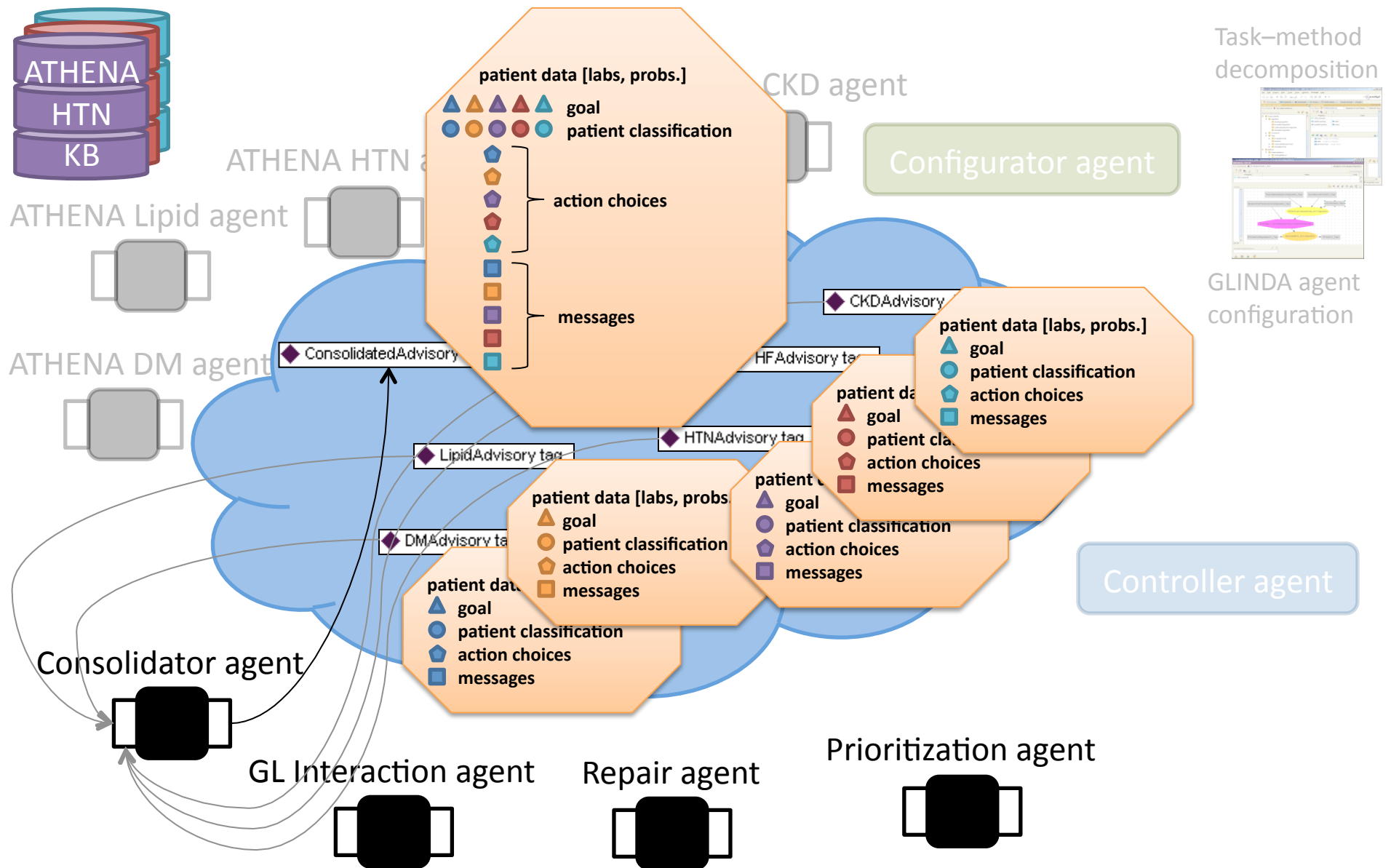
# Running GLINDA – *Select Guideline*



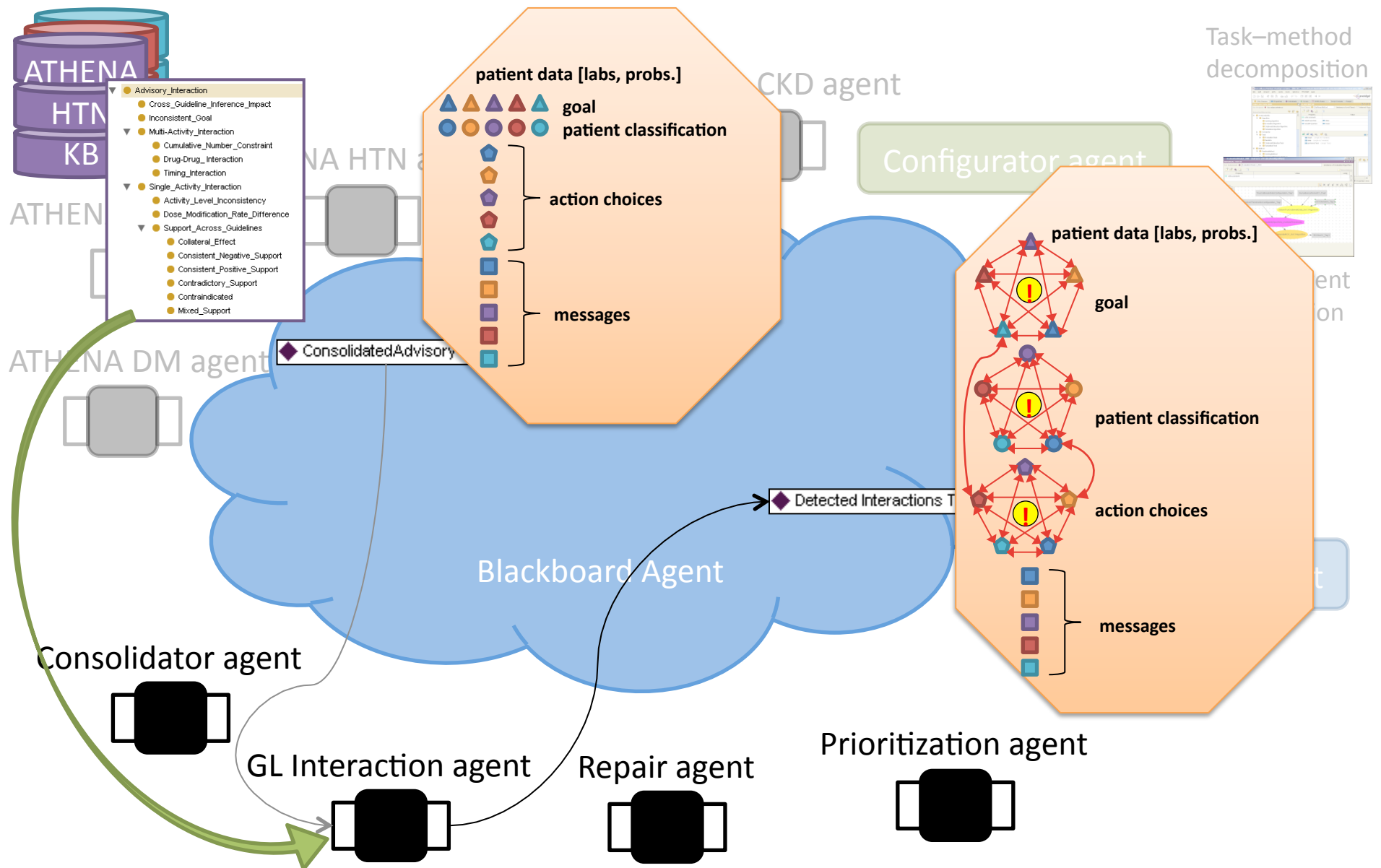
# Running GLINDA – Run ATHENA Agents



# Running GLINDA – Consolidate Advisories

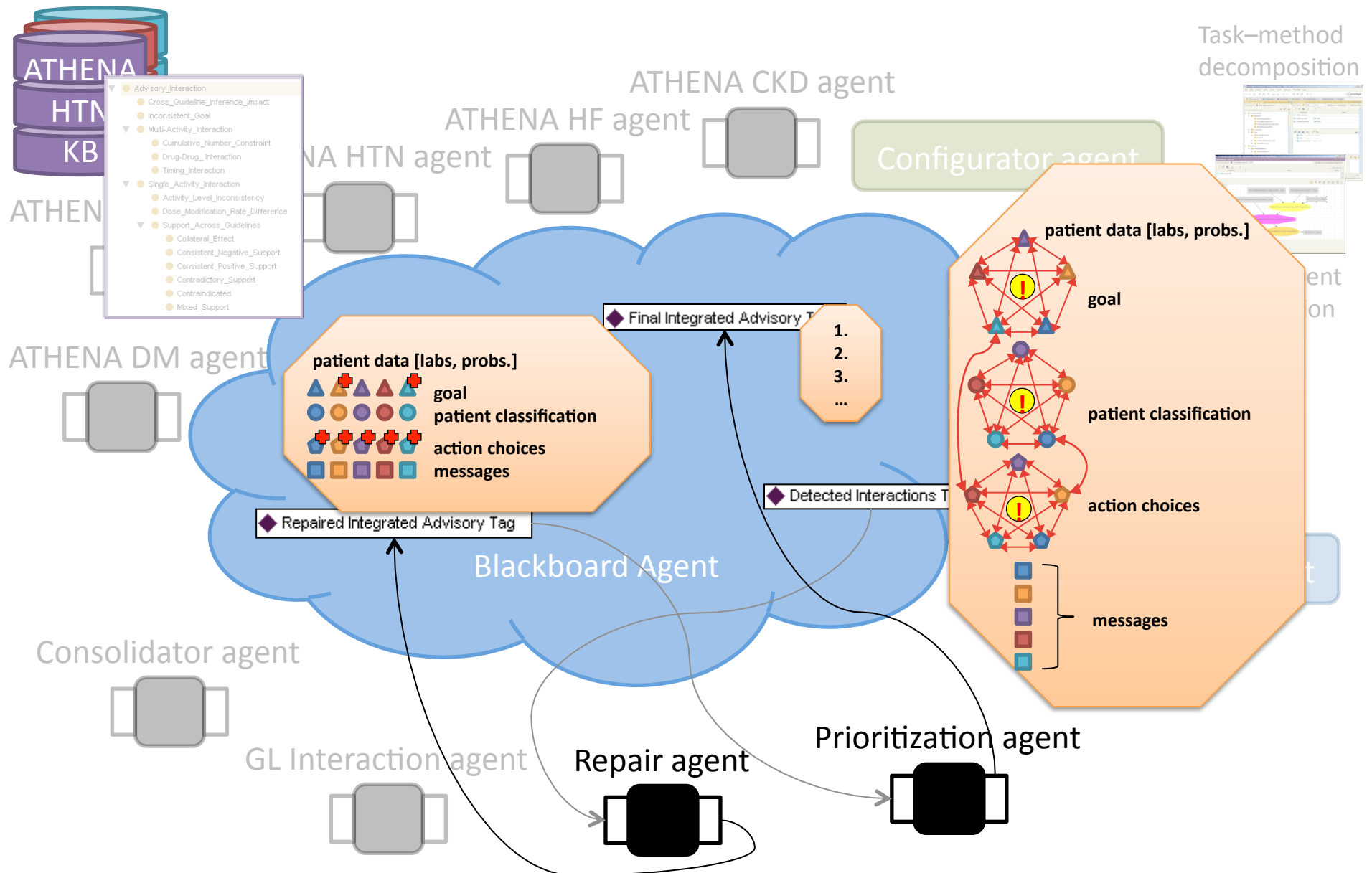


# Running GLINDA – Calculate Interactions





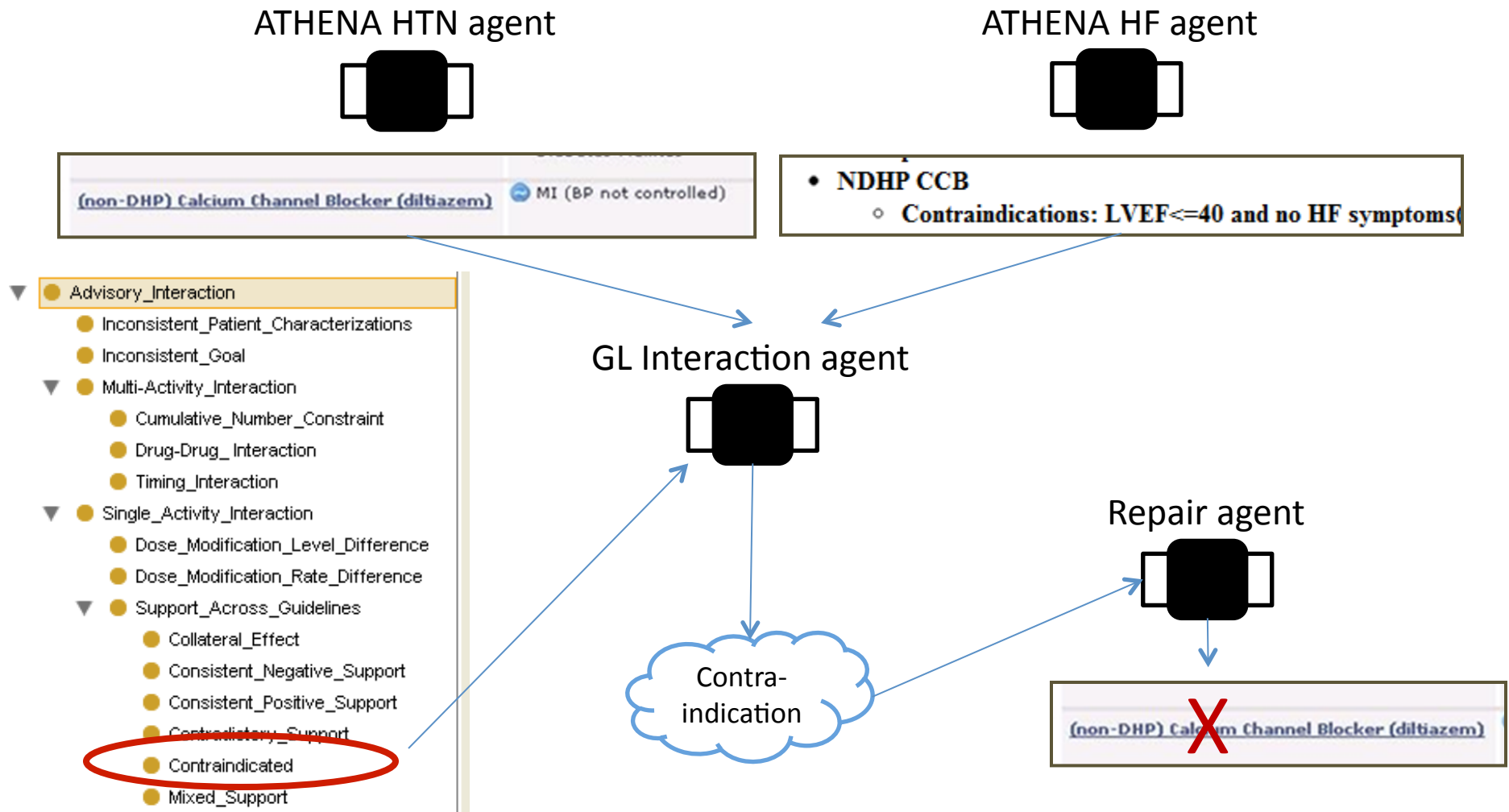
# Running GLINDA – Repair and Prioritize



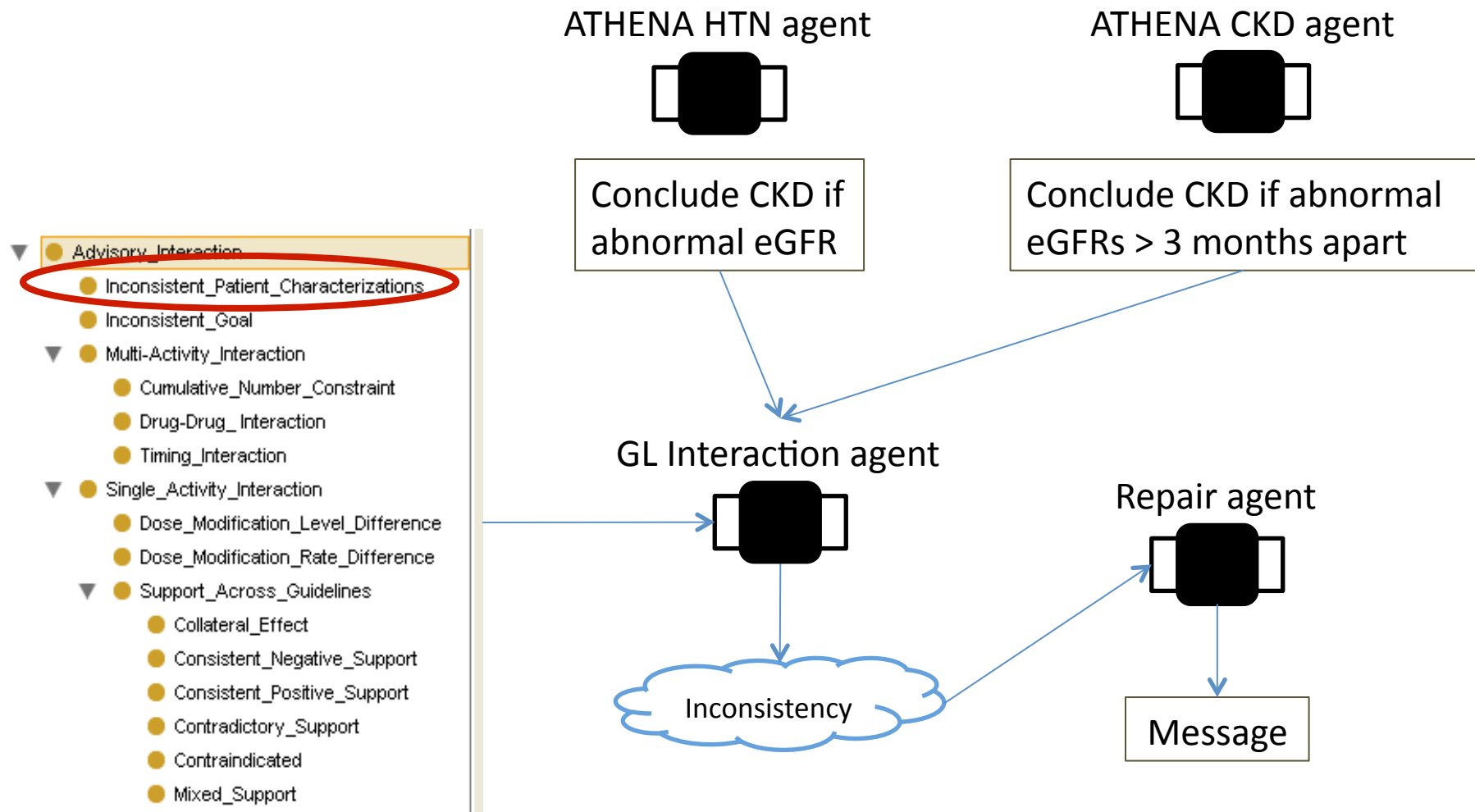
# Ontology of Cross-Guideline Interactions Among Recommendations

- ▼ ● Advisory\_Interaction
  - Inconsistent\_Patient\_Characterizations
  - Inconsistent\_Goal
- ▼ ● Multi-Activity\_Interaction
  - Cumulative\_Number\_Constraint
  - Drug-Drug\_Interaction
  - Timing\_Interaction
- ▼ ● Single\_Activity\_Interaction
  - Dose\_Modification\_Level\_Difference
  - Dose\_Modification\_Rate\_Difference
- ▼ ● Support\_Across\_Guidelines
  - Collateral\_Effect
  - Consistent\_Negative\_Support
  - Consistent\_Positive\_Support
  - Contradictory\_Support
  - Contraindicated
  - Mixed\_Support

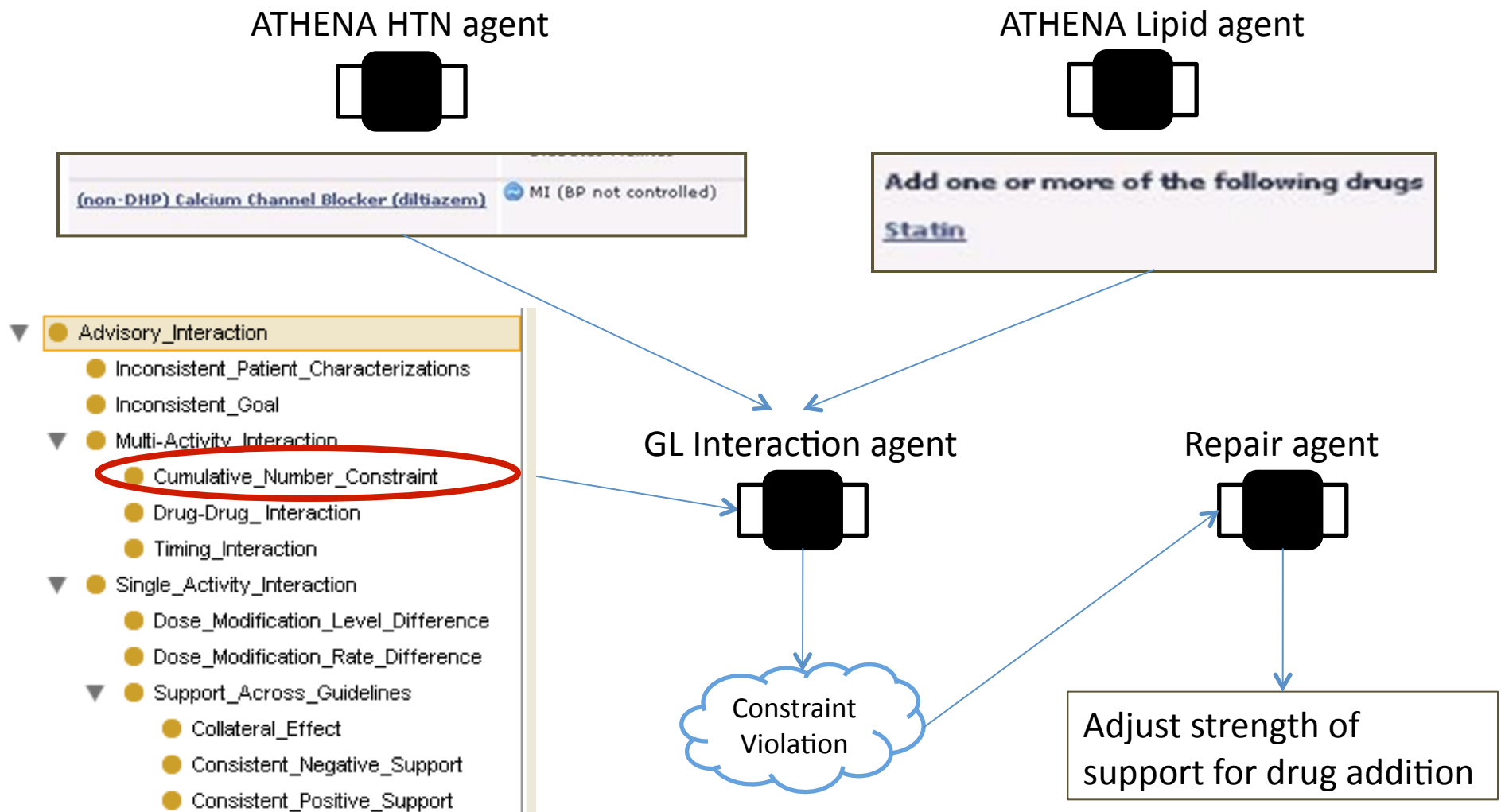
# Example 1: Contradictory Recommendations

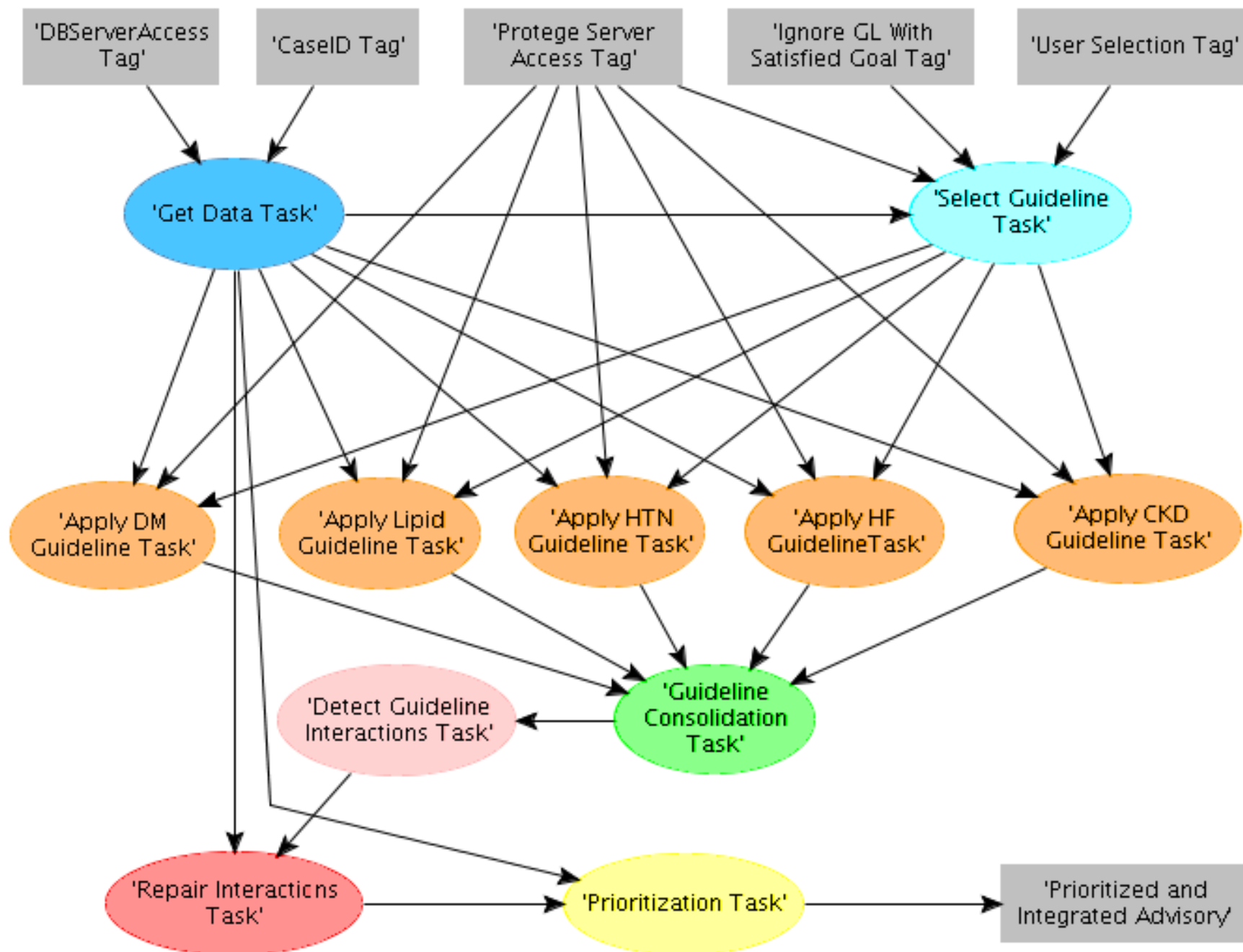


# Example 2: Inconsistent Patient Characterizations



# Example 3: Cumulative Number of Interventions





# Use of patient data to drive our work

- We extracted 2455 complex, deidentified patient cases from the Stanford Translational Research Integrated Database Environment (STRIDE)
- We are applying our method for interaction detection to 226 selected cases selected for their combination of diseases and number of drugs
- Formative evaluation of system performance drives knowledge-base evolution

# Conclusions

- Systems that assist with guideline-based care need to address the messiness of actual clinical situations
- An agent-oriented architecture allows for
  - Reasoning about comorbidities, application of multiple guidelines, and situation-specific interactions
  - Flexibility in experimenting with alternative computational workflows
- Creating GLINDA will drive development of formal models for computational thinking about
  - Guideline interactions
  - Repair mechanisms
  - Prioritization of interventions





**This work has been supported by the National Library of Medicine**  
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