Phenotype Aphril:
Week 1: Phenotype Development

How to get a 'black box' to reliably and reproducibly Phenotype and do it better than humans?

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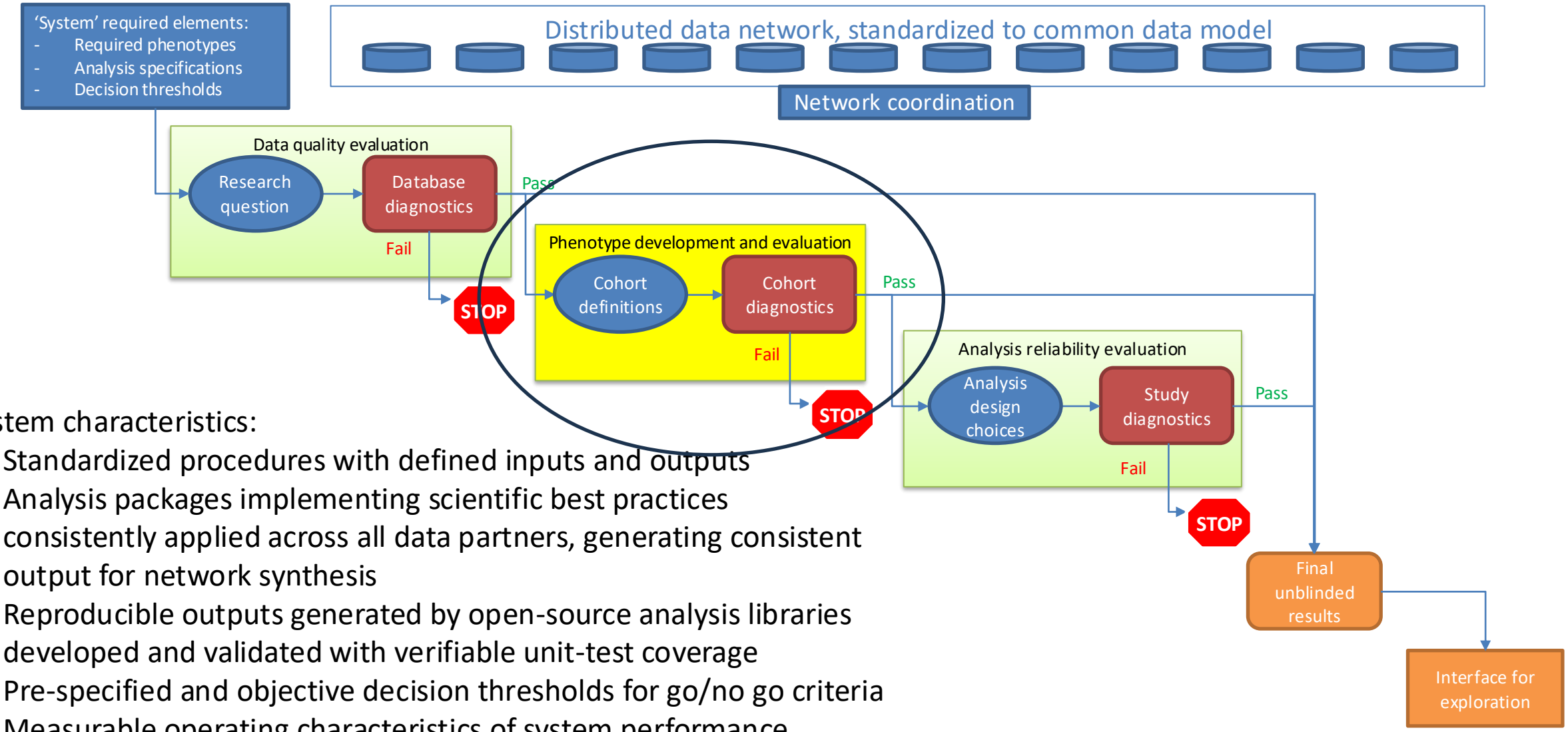
April 7th 2026

coreason

Engineering open science systems that build trust into the real-world evidence generation and dissemination process



System characteristics:

- Standardized procedures with defined inputs and outputs
- Analysis packages implementing scientific best practices consistently applied across all data partners, generating consistent output for network synthesis
- Reproducible outputs generated by open-source analysis libraries developed and validated with verifiable unit-test coverage
- Pre-specified and objective decision thresholds for go/no go criteria
- Measurable operating characteristics of system performance

Plans for Phenotype Aphril

- **Week 1: Phenotype development**
  - April 7 community call: Demo – building cohorts in ATLAS
- **Week 2: Phenotype evaluation**
  - April 14 community call: Interactive – case adjudication using KEEPER
- **Week 3: Iterative phenotype development**
  - No community call: build your own AMI cohort definitions!
- **Week 4: Iterative phenotype evaluation**
  - April 28 community call: Review performance of submitted AMI cohort definitions

OHDSI Phenotype Development and Evaluation Workgroup

2026 OKR

Objective 1: Advance the Science of AI-Assisted Systematic Phenotyping (shared with AI work group)

KR 1.1: Conduct Phenotype Phebruary with an objective to help benchmark an iterative, empirically grounded, AI-assisted workflow collaboratively across diverse RWD network sources by Q1 2026.

KR 1.2: Finalize and submit the "Minds Meet Machines" manuscript to a high-impact informatics journal by Q1 2026

KR 1.3: Develop a gold standard for phenotype algorithms for a specific data source that can be used to evaluate independent phenotype development or evaluations pipelines. by Q3 2026

KR 1.4: Develop, test, and validate a robust AI-assisted pipeline for phenotype and development of clinical phenotypes by September 2026.

KR 1.5: Populate the Phenotype Library with >= 100 new phenotypes using AI and demo the learning in the global symposium

Objective 2: OHDSI Library integration

KR 2.1.: Publish a peer-reviewed communication establishing Inter-Library Metadata Standards (lead VA Cipher) to ensure high-fidelity findability and cross-network reproducibility By Q2 2026.

KR 2.2: Refactor the Phenotype Library Submission Architecture to mandate adherence to the new metadata ontologies. By Q4 2026

OHDSI's "Phenotype Phebruary"

A Community-Driven Scientific Challenge for **Reliable** Cohort Definition

PHebruary
(adapts: 2026 'PHapril' sprint)

The Initiative: A Community-Driven Scientific Challenge

Epidemiologists, gemerologists, Clinical experts, clinical experts, Data scientists, collaboratiors, AI developers, collaborators

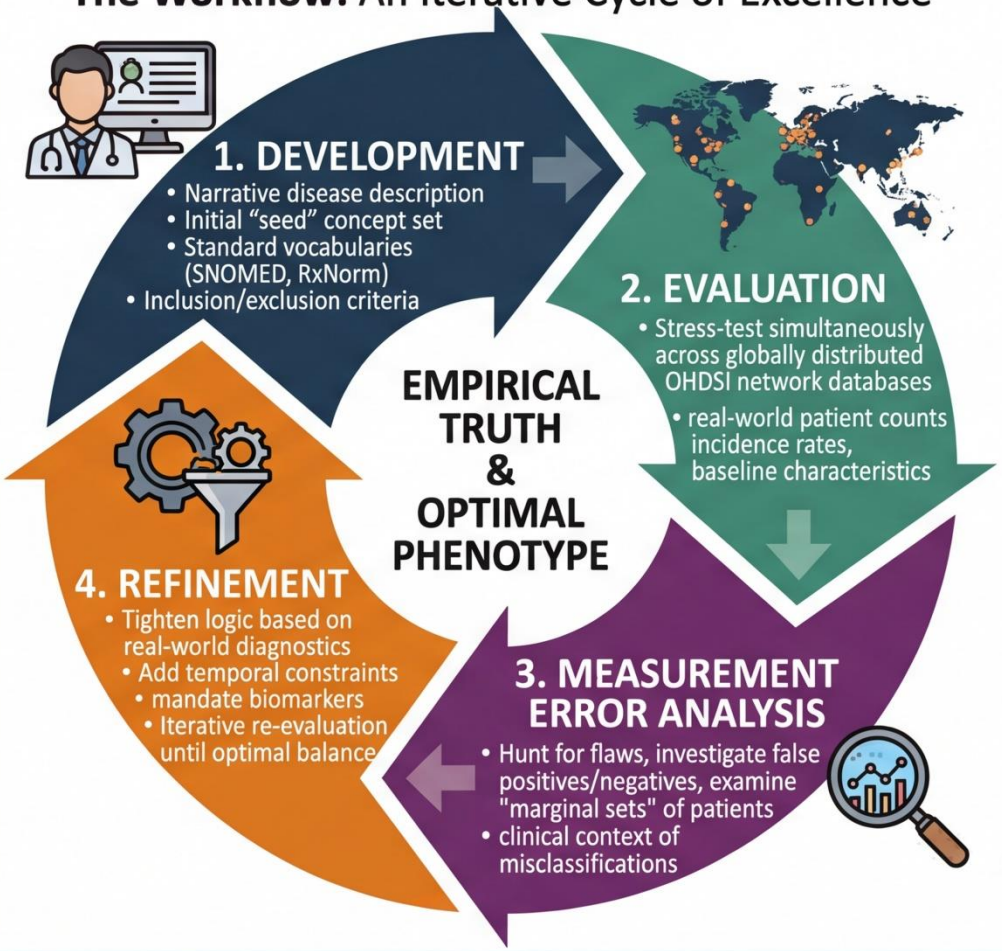
- **Transparency & Rigor** in cohort definition
- Multi-week community-wide challenge
- Establish "gold standard" phenotype definitions

- **Focusing on Specific Conditions** (targets curated complex conditions)
  - crowdsourced examples:
    - Acute Pancreatitis
    - Systemic Lupus Erythematosus (Lupus)
    - Acute Myocardial Infarction (AMI)

Crowdsourcing Truth – live building, collaborative ethos, openly debated clinical intent, local coding nuances.

Ultimate goal is Robust, empirically validated cohort definitions in the open-source OHDSI Phenotype Library

The Workflow: An Iterative Cycle of Excellence



The Toolkit: The Engine of Open Science

ATLAS
web GUI
- Complex definitions
- No raw SQL
- Reproducible JSON files
- Runs on OMOP DBs

CohortDiagnostics
R package, evaluation phase
- Executes across multiple data partners
- Unified diagnostic dashboard
- Index event misclassification
- Semantic drift

The AI Evolution: Minds Meet Machines

KEEPER (Knowledge-Enhanced Electronic Profile Review)
- Automated case adjudication with LLMs
- Validates PPV
- Acts as "AI clinician", evaluates patient meets clinical intent, accelerates error analysis

LIBRARIAN AGENTS
- Automate systematic literature reviews
- Interpret complex clinical guidelines
- Translate plain-text to ATLAS JSON or executable code

MAXIMIZING PRECISION with Proposer-Validator Loops

LLM Proposer (Maximizing Sensitivity):
- suggests data-driven rule expansions for edge cases

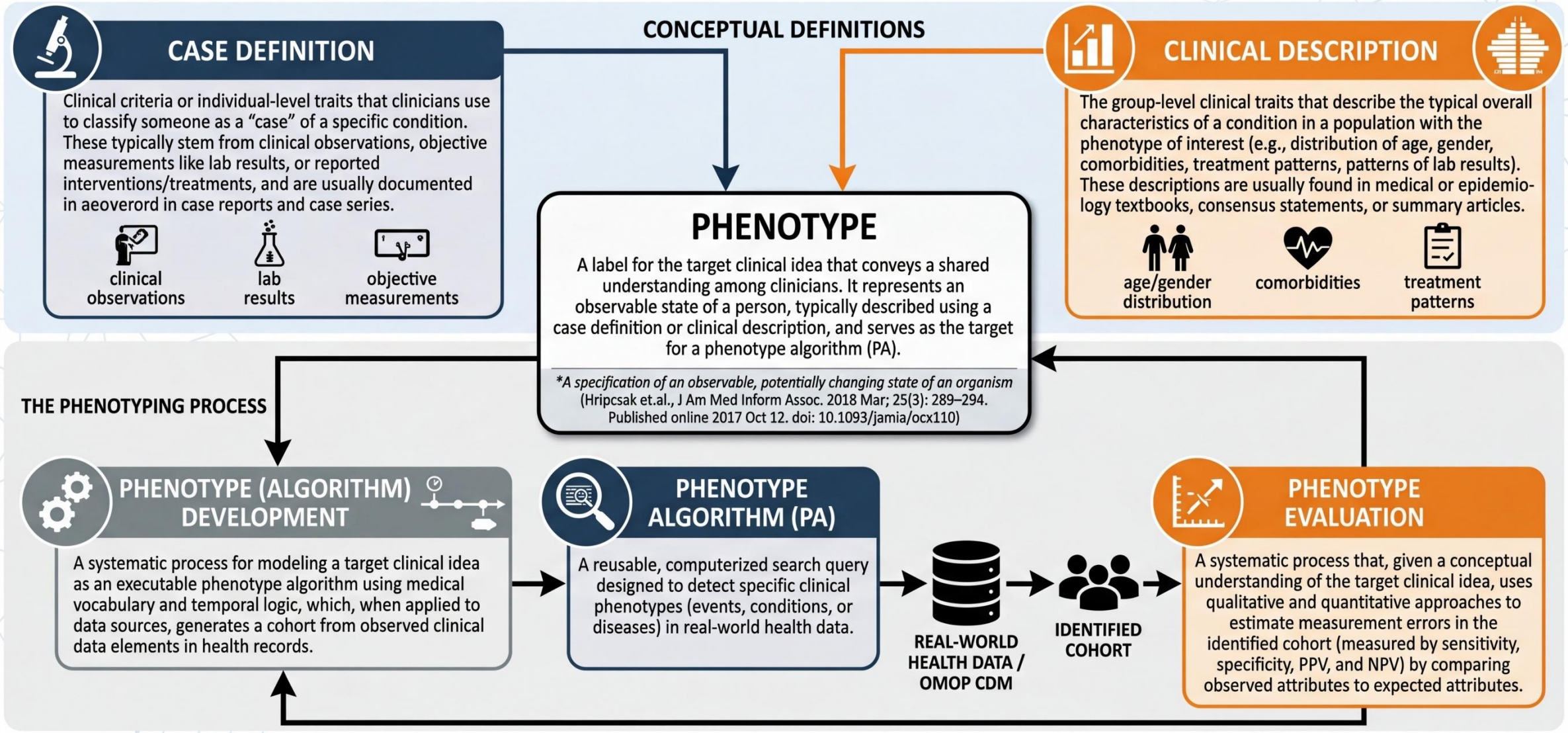
Deterministic/Human Validator (Maximizing Specificity): check marginal data, prevent semantic drift, ensure correct profile

CONCLUSION: The Future of Reliable Real-World Evidence

Generation of reliable RWE hinges on "garbage in, garbage out". Foundational cohorts determine predictive models, drug safety alerts, and causal inference studies. Standardized phenotyping is the bedrock for all reliable observational research. Merging rigorous epidemiology, global standardization, open-source tooling, and AI automation for highly accurate, universally reproducible definitions. Ultimately unlocking the life-saving potential of global health data.

OHDSI

Terminology



Phenotype Development

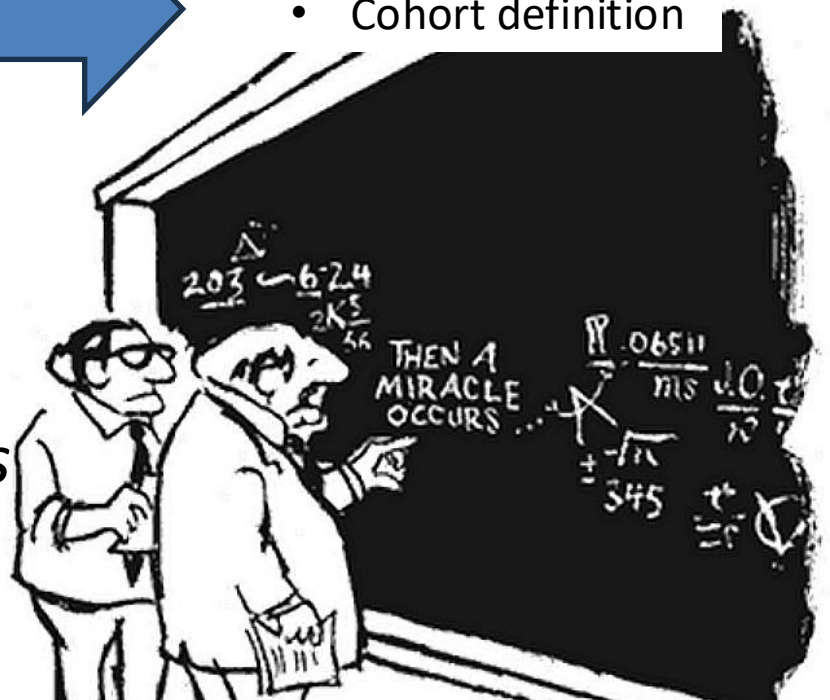
Inputs:
- Clinical idea

Phenotype Development process

Black box

Let the LLM figure it out….

Outputs:
- Cohort definition

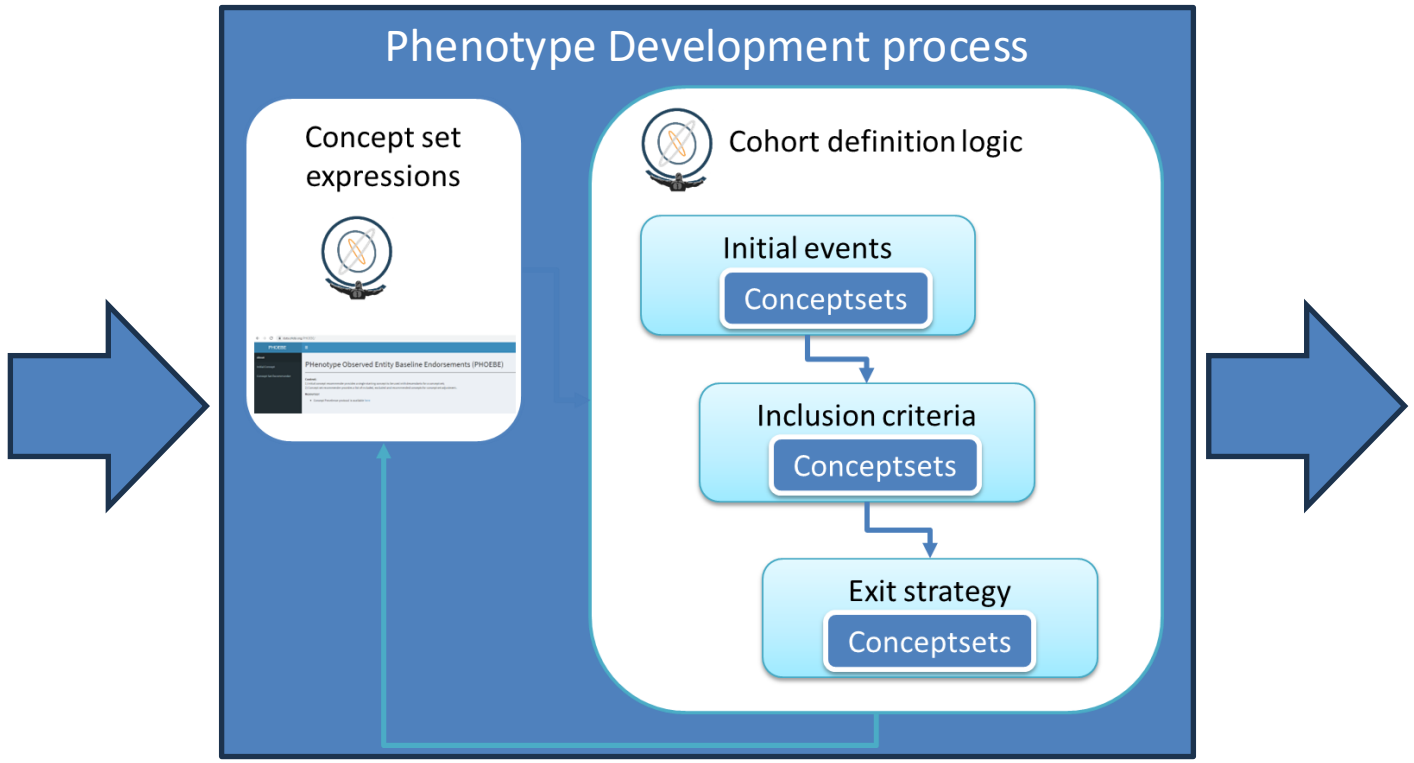


Mind Meets Machine → ConceptSets

OHDSI Global Symposium 2025

Phenotype Development

Inputs:
- Clinical idea



Outputs:
- Cohort definition

Mind Meets Machine → ConceptSets
OHDSI Global Symposium 2025

OHDSI AI-Driven Pherotype Development Workflow

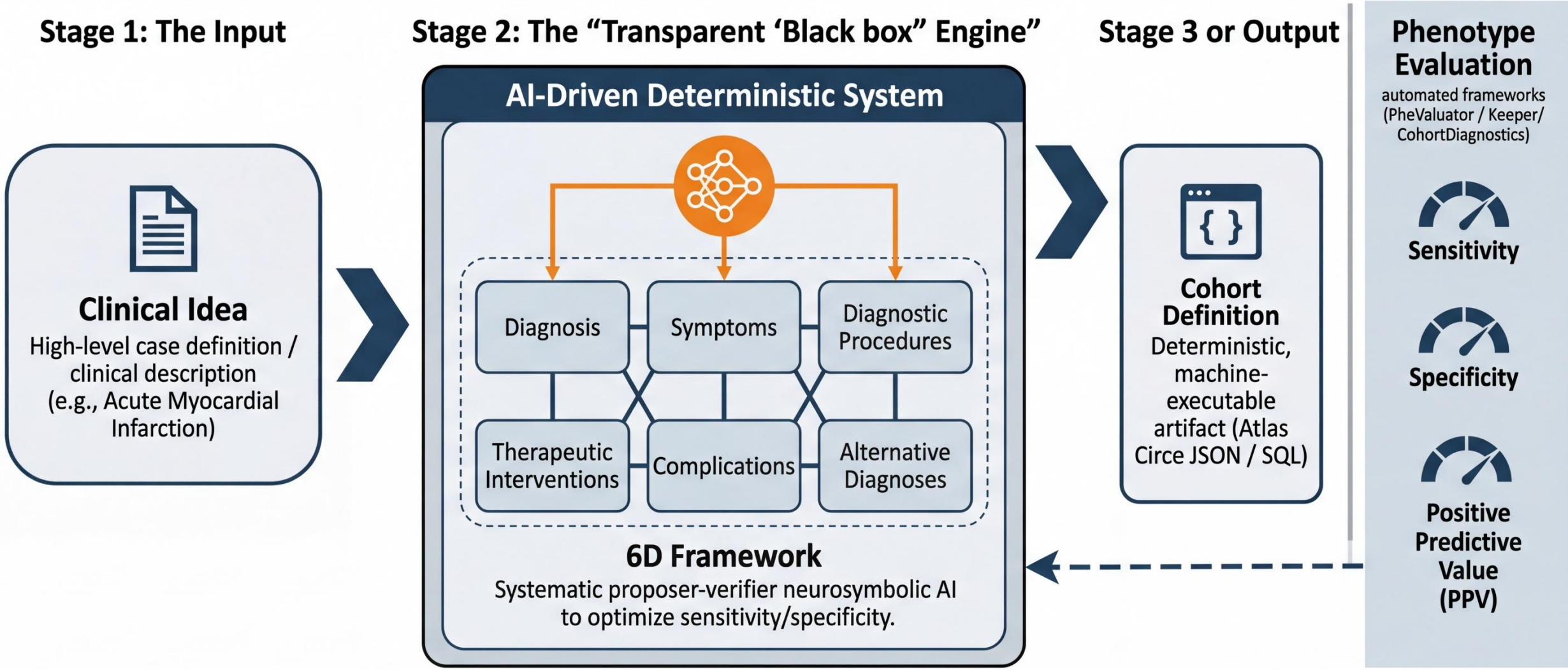


Figure 1: Systematic Workflow for Phenotype Development. This conceptual architecture illustrates the transition from manual, subjective heuristic coding to a standardized, automated pipeline. A raw clinical idea **(Input)** is processed by an **AI-driven system** that **deconstructs the phenotype intent** using a **universal six-dimensional framework. This engine generates a deterministic, machine-executable cohort definition (Output).** Crucially, the development phase is decoupled from evaluation, relying on automated probabilistic tools to objectively measure performance metrics (Sensitivity, Specificity, PPV) and ensure reproducibility.

OHDSI Heuristic Process for Computable Phenotype for AMI

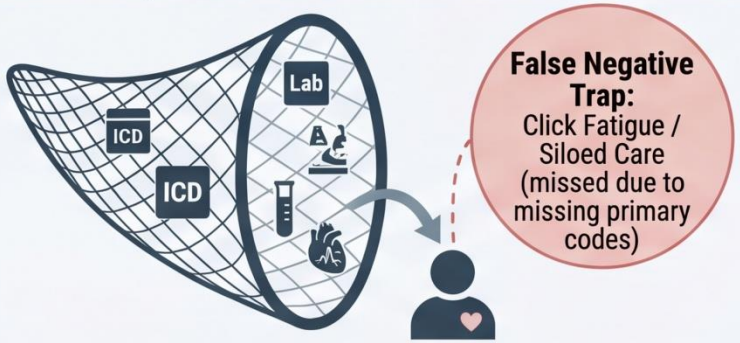
1 Step 1: Capture person events in the database who may have the phenotype

Heuristic: Identify the persons who might have AMI

Aim: Increase sensitivity (minimize false negatives)

Task: Create inclusive concept sets used in cohort entry events

Conceptual



False Negative Trap: Click Fatigue / Siloed Care (missed due to missing primary codes)

AMI Applied Section

Cohort Entry Events (ANY of):

ICD-10
I21 series

Diagnosis Code: AMI in any position

cTn > ULN

Lab: Troponin (hs-cTn) > upper limit of normal

PCI/Angio

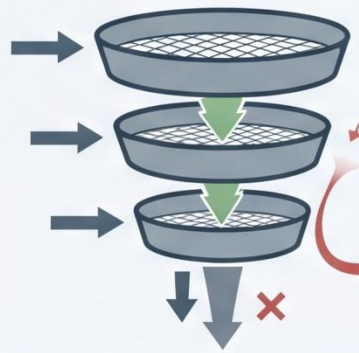
Procedure: Emergent Angiography or Cardiac Stent

2 Step 2: Remove person events that most likely do not have the phenotype

Heuristic: Restrict persons who likely do not have AMI

Aim: Increase specificity / Positive Predictive Value (PPV) (minimize false positives)

Task: Add inclusion/exclusion criteria based on clinical truth



False Positive Trap: ED Rule-Out Coding / Problem List Bloat

Clinical Context: Myocardial Injury (cTn Alone) ≠ MI (4th Universal Definition)

Inclusion/Exclusion Criteria:

Corroborating Evidence: (e.g., If entry = Elevated Troponin, **MUST** also have Ischemic evidence, such as ECG ECG code, Angiogram, or Chest Pain diagnosis)

Setting Restrictions: (Inpatient or ED diagnoses ONLY. Exclude routine outpatient check-ups) VS

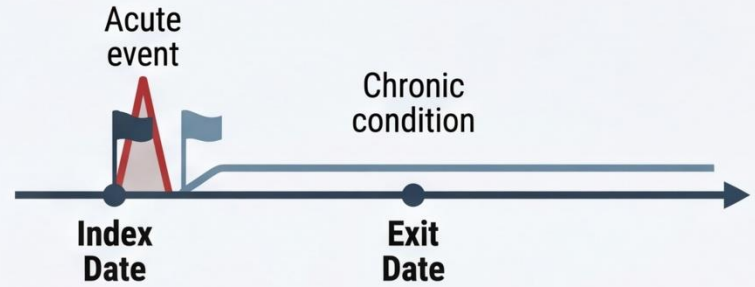
Rule-Out Filter: (Exclude ED codes if discharged same-day with no subsequent cardiac procedures, meds, or admission)

3 Step 3: Shift dates for each person to represent the real biological date

Heuristic: Determine the start and end dates for each AMI episode

Aim: Reduce index date misspecification

Task: Set an exit strategy, refine entry events



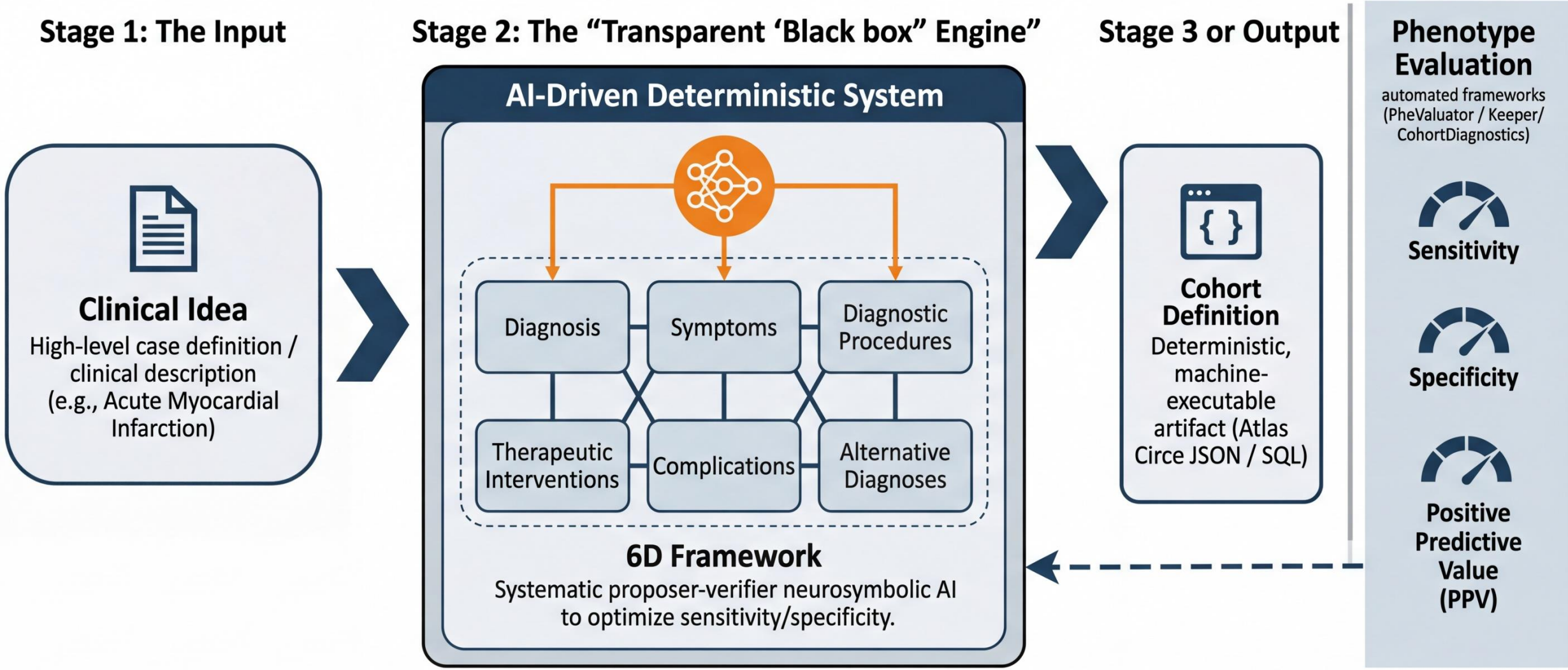
Timeline Strategy (Episode of Care):

Index Date: (admission with first qualifying AMI code or cTn spike)

Exit Strategy: (Force Exit 30 days post-hospital discharge)

Handling Recurrence: (Differentiate new AMI code from copy-forward error: Require NEW cTn spike or NEW acute admission for re-entry)

OHDSI AI-Driven Pherotype Development Workflow



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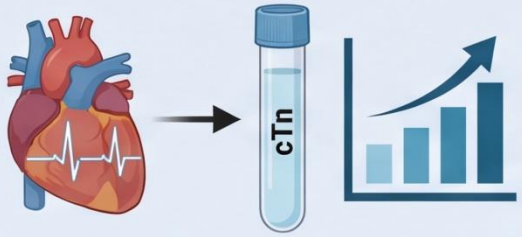
Evolution of the Universal Definition of Myocardial Infarction (MI): From Syndromic to Pathophysiological

AI generated

2007 | 2012 | 2018 | August 2026 (Anticipated)

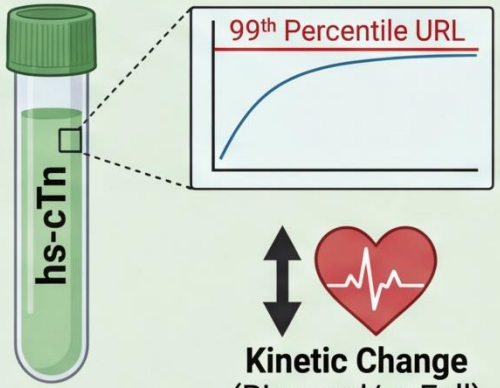
2nd Universal Definition



Gold Standard:
Cardiac Troponin (cTn)
Replaced CK-MB

Introduced **MI Subtypes 1-5**
(Atherothrombotic vs. Non-atherothrombotic)

3rd Universal Definition



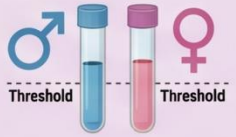
Kinetic Change
(Rise and/or Fall)

Integrated **99th Percentile URL**
Emphasized **Kinetic Changes** for Acute Events

4th Universal Definition
(Contemporary Standard)

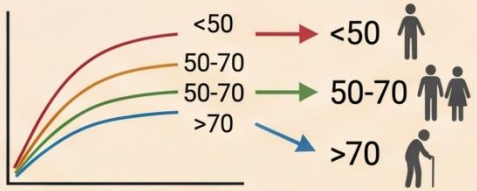
Myocardial Infarction
(Ischemic)

Myocardial Injury
(Non-Ischemic)

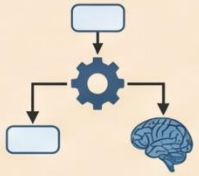


Sex-Specific 99th Percentile URLs
Decoupled Injury from Infarction

Proposed 5th Universal Definition



Age-Specific URLs



MINOCA Refinement & ML Triage Algorithms
(e.g., 0/1-hour)

Global Task Force (ESC, ACC, AHA, WHF)
Transition to **Age-Specific Thresholds**, Enhanced MINOCA Categorization

Catalyst: High-Sensitivity Cardiac Troponin (hs-cTn)

Legacy Assays

Large Molecules
detected only with massive necrosis

The Evolution Was Forced by Ubiquitous hs-cTn Deployment.
Increased Sensitivity for Necrosis Necessitated Structural Changes to Maintain Specificity for Atherothrombotic Ischemia.

hs-cTn Assays

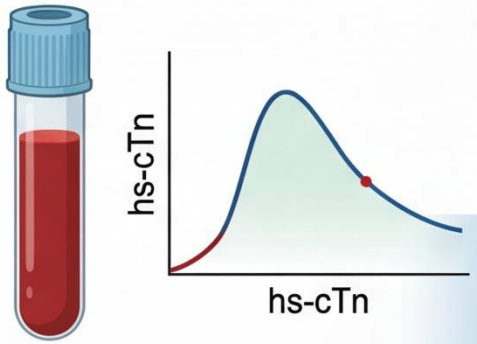
High Sensitivity (Detects Micro-Necrosis), Reduced Clinical Specificity for Ischemia

AI generated

Differentiating Acute Myocardial Injury from Myocardial Infarction (4th Universal Definition)

Corroborating Clinical Evidence of Active Ischemia is Required

Biochemical Necrosis (hs-cTn Delta)



- Diagnostically Insufficient on its own
- Represents Acute Myocardial Injury

+ MUST BE ACCOMPANIED BY

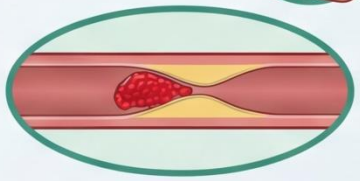
Evidence of Active Myocardial Ischemia (At Least One)

Symptoms
Crushing retrosternal chest pressure, radiating arm/jaw pain, or profound dyspnea equivalents.

New Ischemic ECG Changes
New ST-segment elevation or depression, new T-wave inversions, new Left Bundle Branch Block (LBBB).

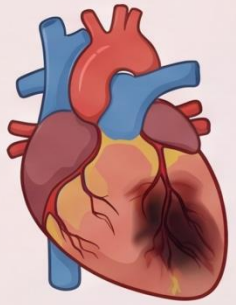
Pathological Q Waves
Indicating established transmural electrical death on ECG.

Imaging Evidence
New loss of viable myocardium or regional wall motion abnormality (RWMA) in a territorial pattern.



Angiographic or Autopsy Evidence
Identification of obstructive intracoronary thrombus (defines Type 1 MI).

Myocardial Infarction (MI)



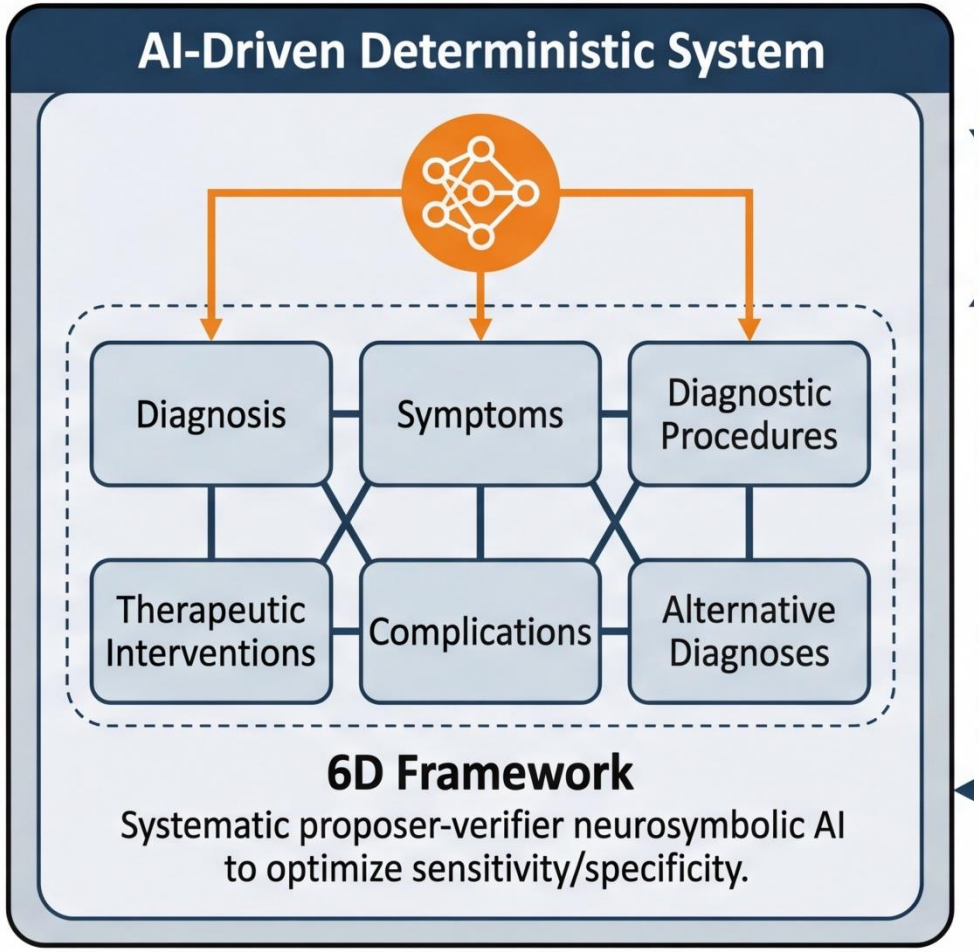
Driven by Active Ischemia.

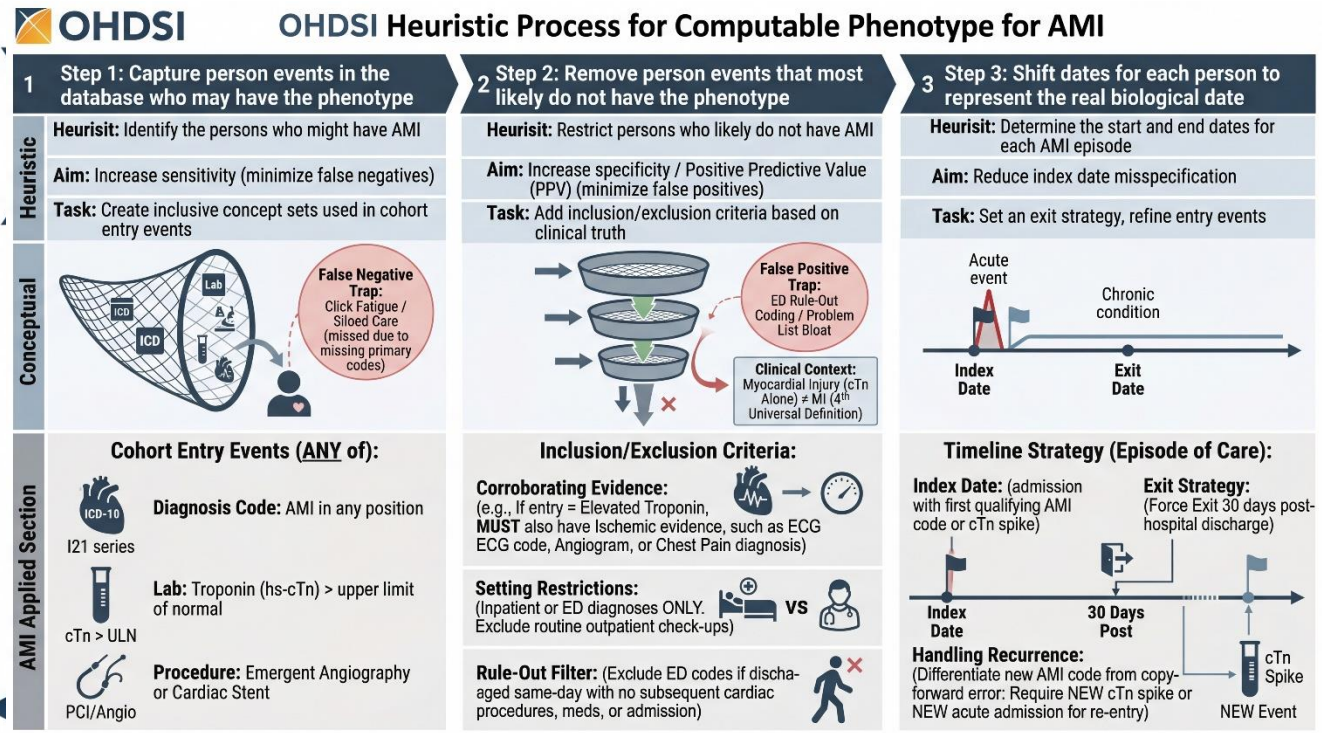
Diagnosed by hs-cTn rise/fall **PLUS** at least one ischemia marker.

Let’s phenotype Acute Myocardial Infarction…

AI generated

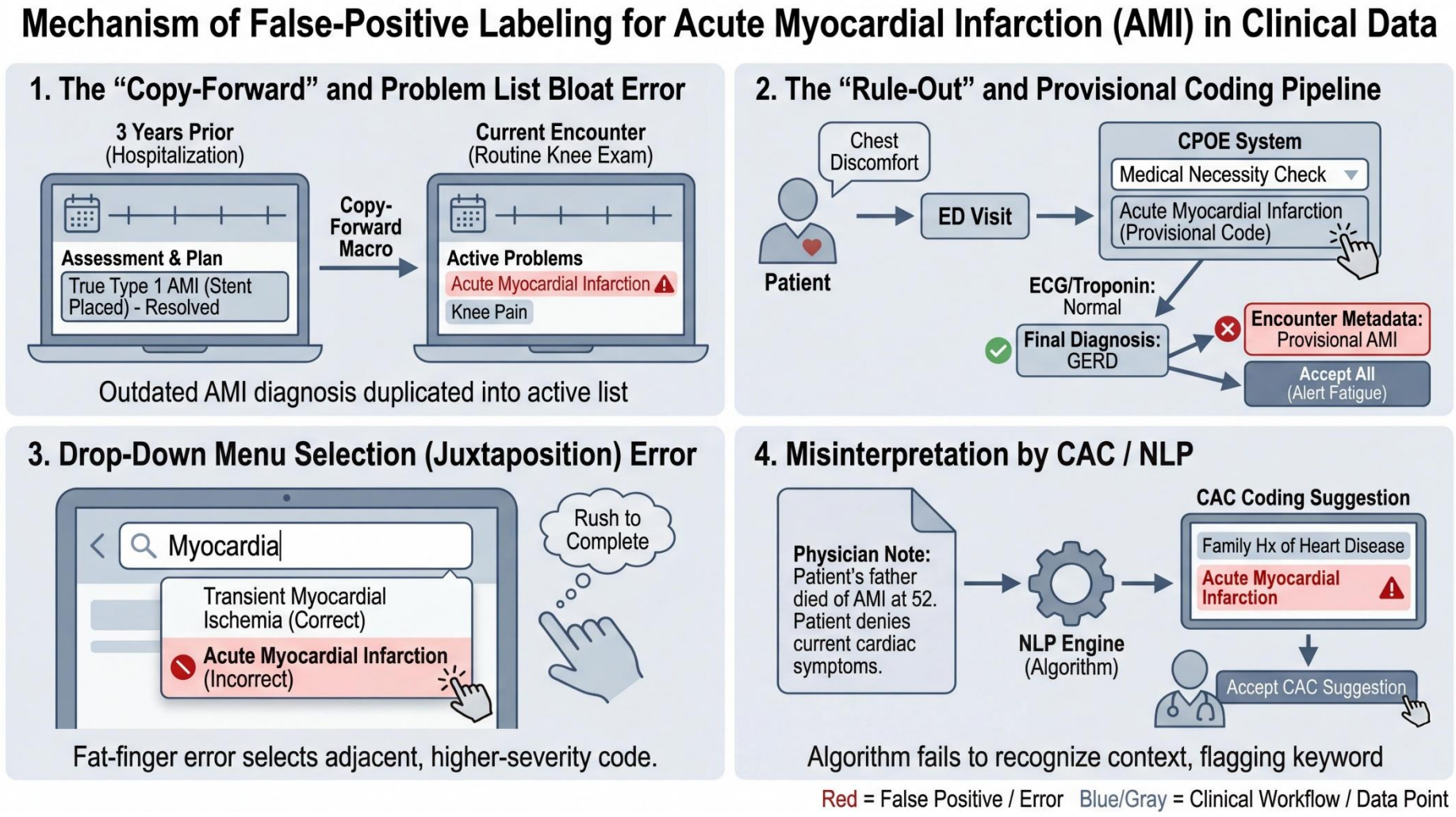
Stage 2: The “Transparent ‘Black box” Engine”





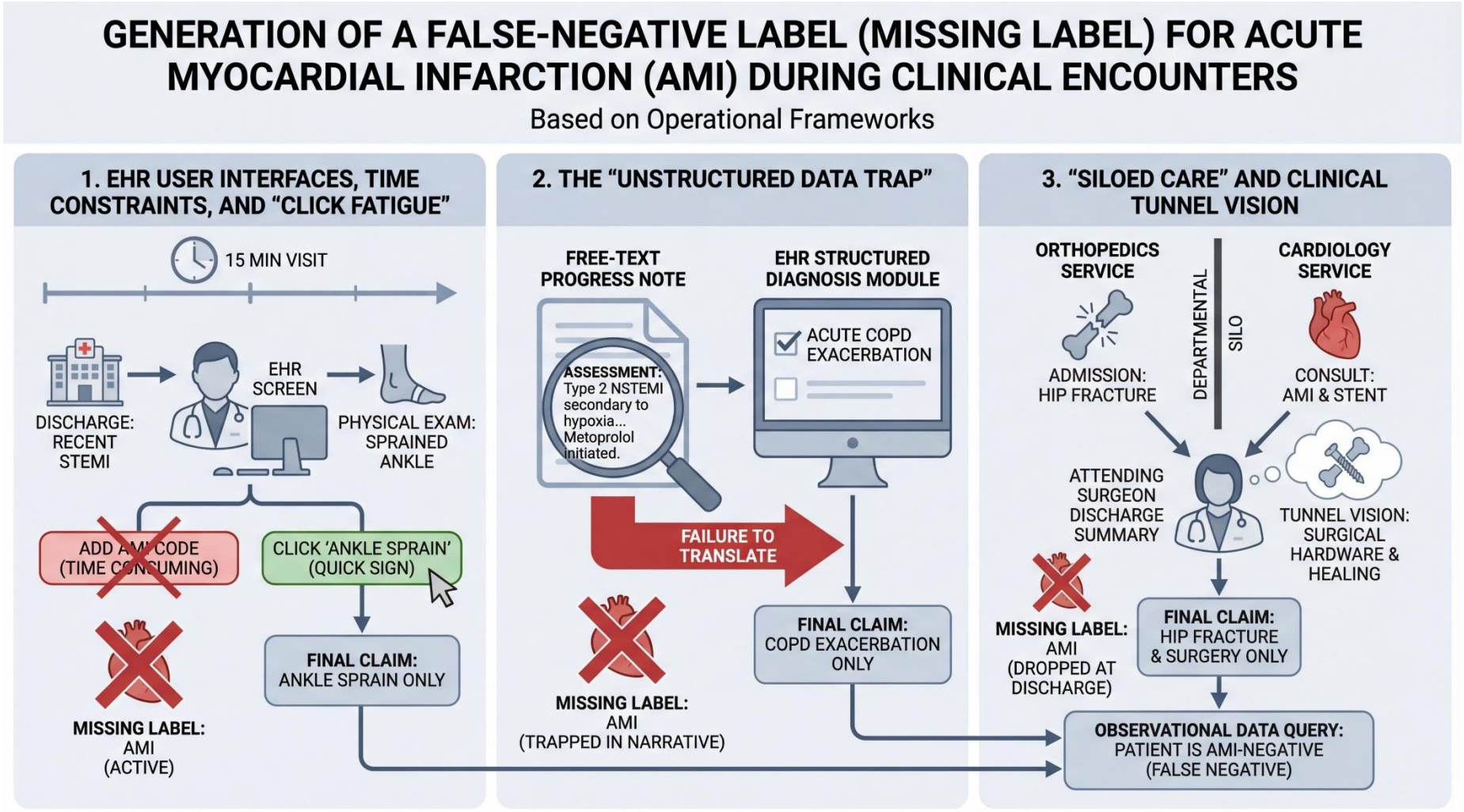
AI generated

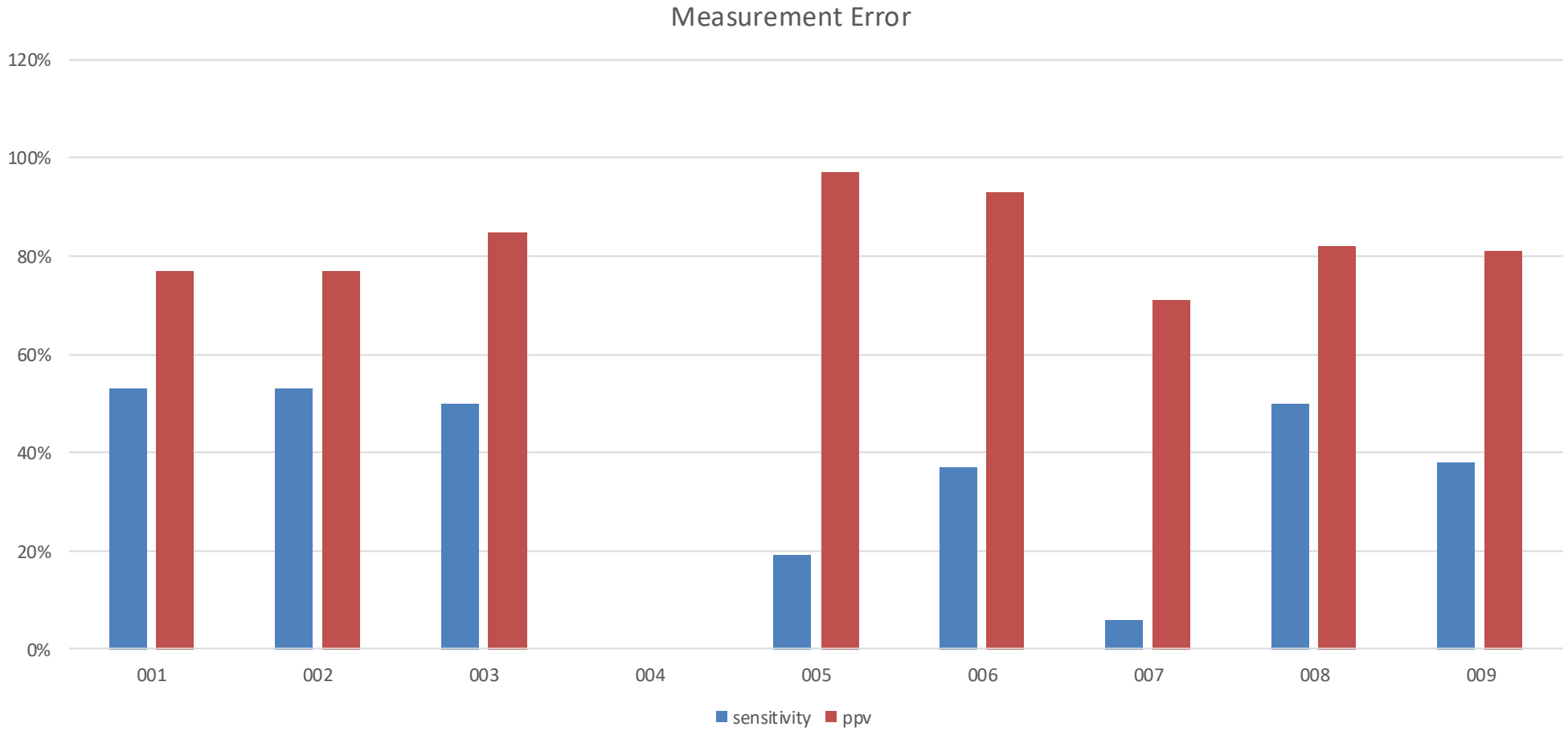
False-Positive



AI generated

False-Negatives




Measurement Error
120%
100%
80%
60%
40%
20%
0%
001
002
003
004
005
006
007
008
009
sensitivity
ppv

Clinical elements associated with disease status

- **Diagnosis of interest:** 'Acute myocardial infarction'
- **Symptoms:** Chest pain, Difficulty breathing, Sweating, Nausea, …
- **Diagnostics:**
  - Procedures: Electrocardiography, angiocardiography, …
  - Measurements: Troponin, creatine kinase, …
- **Therapeutic interventions:**
  - Drugs: beta blocker, aspirin, heparin, clopidogrel, …
  - Procedures: percutaneous coronary intervention, coronary artery bypass grafting, insertion of cardiac pacemaker…
- **Complications:** heart failure, cerebral hemorrhage, acute kidney injury, acute pulmonary edema, hepatic failure…
- **Alternative diagnoses:** Aortic aneurysm, panic attack, esophageal reflux…

ATLAS

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation
- Prediction
- Reusables
- Jobs
- Configuration
- Feedback
- Tools

[PhenotypeApril] persons with acute myocardial infarction

Definition | Concept Sets | Generation | Samples | Reporting | Export | Versions | Messages 22

Enter a cohort definition description here

Cohort Entry Events

Events having any of the following criteria:

- a condition occurrence of Diagnosis of interest
- a condition occurrence of Symptoms
- a procedure occurrence of diagnostic procedures and mea...
- a measurement of diagnostic procedures and mea...
- a drug exposure of therapeutic interventions - drug...
- a procedure occurrence of therapeutic interventions - drug...
- a condition occurrence of complications

Inclusion Criteria

New inclusion criteria

1. has diagnosis of interest
2. has symptom
3. has diagnostic procedure or measurment
4. has therapeutic intervention - drug or procedure
5. has follow-up care or complication
6. has no alternative diagnoses
7. has 2+ categories
8. has 3+ categories
9. has 4+ categories
10. has 5+ categories

has diagnosis of interest

Copy Delete

enter an inclusion rule description

having all of the following criteria:

+ Add criteria to group...

Delete Criteria

with at least 1 using all occurrences of:

a condition occurrence of Diagnosis of interest

+ Add attribute...

where event starts between

0 days Before and All days After index start date *add additional constraint*

The index date refers to the event from the Cohort Entry criteria.

☐ restrict to the same visit occurrence

☐ allow events from outside observation period

Inclusion Report for **Optum Extended DoD (v3787)** using 1 event per person

	Match Rate	Matches	Total Events
Summary Statistics:	0.18%	123,234	68,218,480

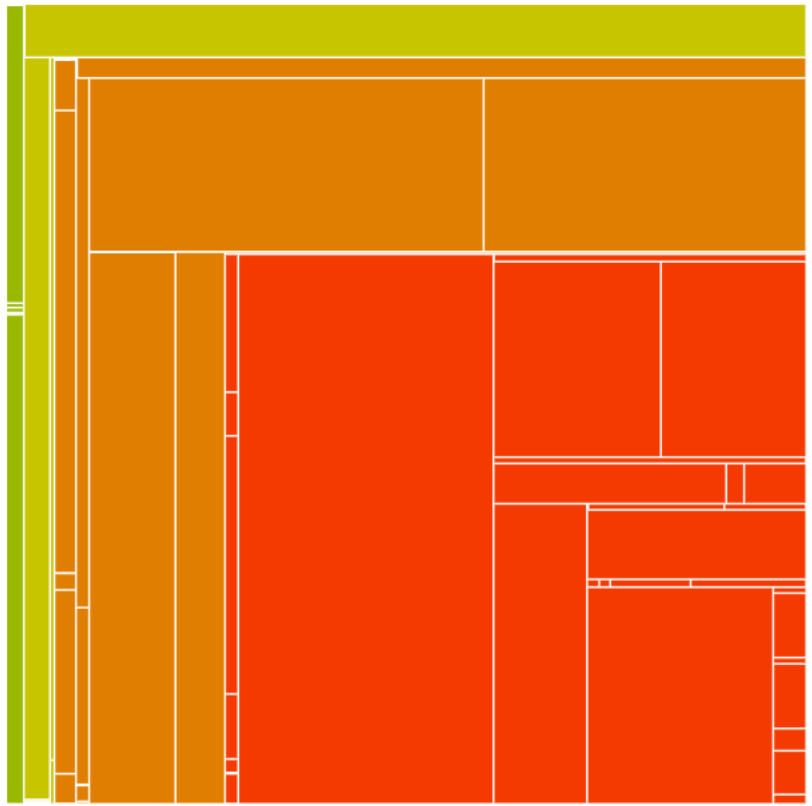
Having any of selected criteria passed

	Inclusion Rule	N	% Satisfied	% To-Gain
✓	1. has diagnosis of interest	1,529,357	2.24%	0.83%
✓	2. has symptom	59,083,628	86.61%	0.01%
✓	3. has diagnostic procedure or measurment	39,491,240	57.89%	0.00%
✓	4. has therapeutic intervention - drug or procedure	32,715,153	47.96%	0.01%
✓	5. has follow-up care or complication	17,155,854	25.15%	0.01%
✓	6. has no alternative diagnoses	41,217,790	60.42%	1.35%
✓	7. has 2+ categories	67,909,815	99.55%	0.00%
✓	8. has 3+ categories	61,289,210	89.84%	0.00%
✓	9. has 4+ categories	25,766,487	37.77%	0.00%
✓	10. has 5+ categories	6,106,186	8.95%	0.00%

Summary: 68,218,480 events (100.00%)

Population Visualization

Switch to attrition view



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	Match Rate	Matches	Total Events
Summary Statistics:	0.18%	123,234	68,218,480

	Inclusion Rule	N	% Remain	% Diff
1.	has diagnosis of interest	1,529,357	2.24%	97.76%
2.	has symptom	1,509,415	2.21%	0.03%
3.	has diagnostic procedure or measurment	1,490,217	2.18%	0.03%
4.	has therapeutic intervention - drug or procedure	1,408,301	2.06%	0.12%
5.	has follow-up care or complication	1,378,310	2.02%	0.04%
6.	has no alternative diagnoses	123,234	0.18%	1.84%

Attrition Visualization

Switch to intersect view