UNIVERSITÄT LEIPZIG

Medizinische Fakultät

ONTOLOGICAL MODELLING AND REASONING OF PHENOTYPES

JOWO/ODLS, September 2019, Graz

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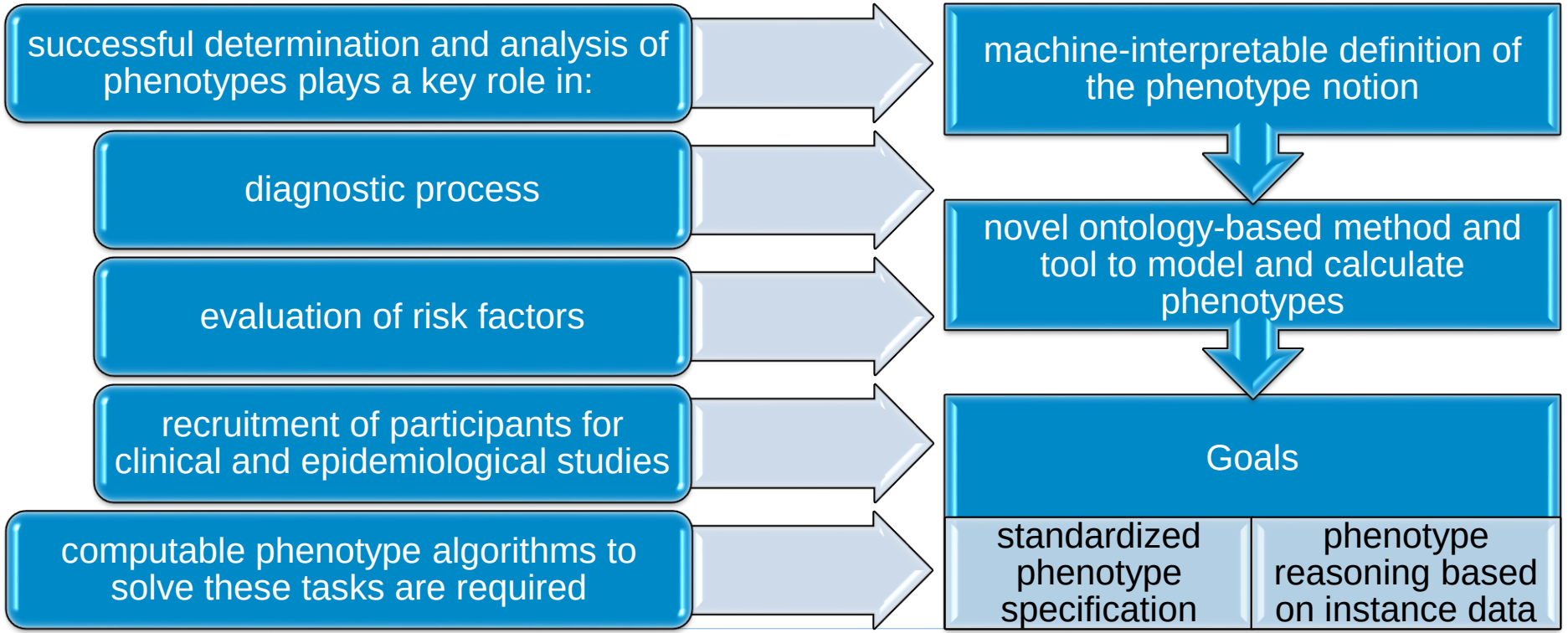
Agenda

1. Motivation
2. Smart Medical Information Technology for Healthcare (SMITH)
3. PhenoMan Integration in SMITH
4. Core Ontology of Phenotypes (COP)
5. Phenotype Algorithm Specification Ontologies (PASO)
6. Phenotype Manager (PhenoMan)
7. Conclusion

Motivation


successful determination and analysis of phenotypes plays a key role in:
diagnostic process
evaluation of risk factors
recruitment of participants for clinical and epidemiological studies
computable phenotype algorithms to solve these tasks are required
machine-interpretable definition of the phenotype notion
novel ontology-based method and tool to model and calculate phenotypes
Goals
standardized phenotype specification
phenotype reasoning based on instance data

Smart Medical Information Technology for Healthcare (SMITH)

- The main goal of the German Medical Informatics Initiative (MII) is making clinical data available for research
- SMITH is one of four funded consortia

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Smart Medical Information Technology for Healthcare (SMITH)

- The main goal of the German Medical Informatics Initiative (MII) is making clinical data available for research
- SMITH is one of four funded consortia
- A phenotyping pipeline (PheP) will be established to systematically develop, evaluate and execute validated algorithms and models for classifying and annotating patient data based on routine electronic health records (EHR)
  - triggering alerts and actions
  - data sharing and deep analyses of patient care and outcomes
  - phenotype engines and factories required to specify, set up and execute phenotype algorithms

SMITH
Smart Medical Information Technology for Healthcare

MEDIZIN INFORMATIK INITIATIVE

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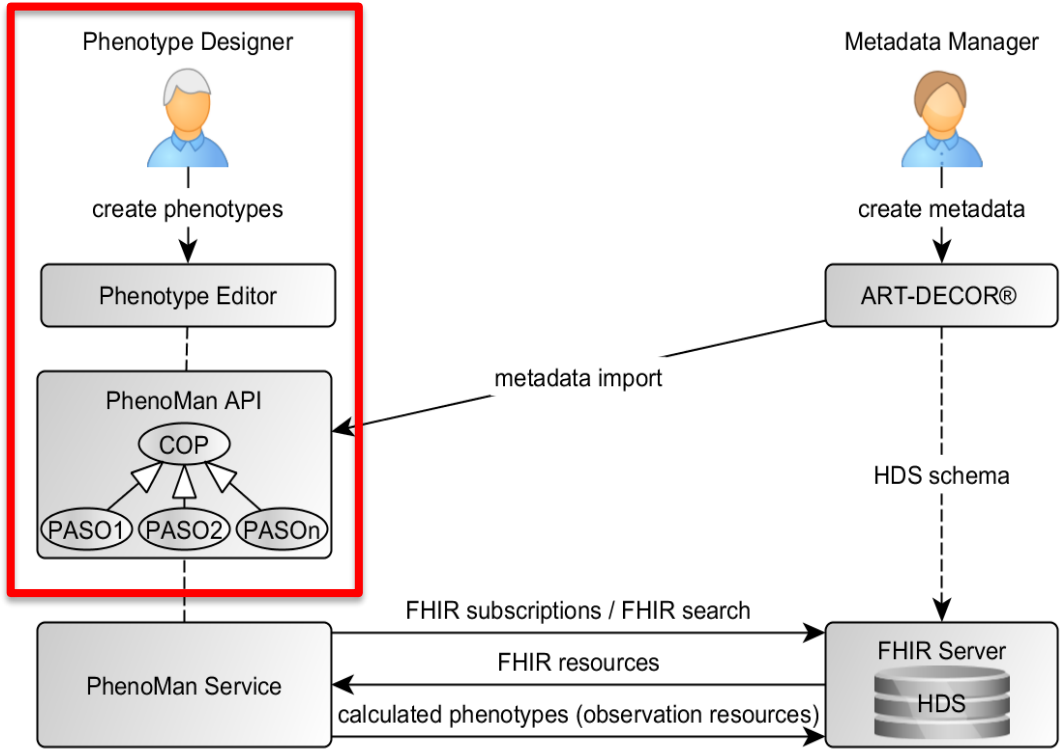
PhenoMan Integration in SMITH



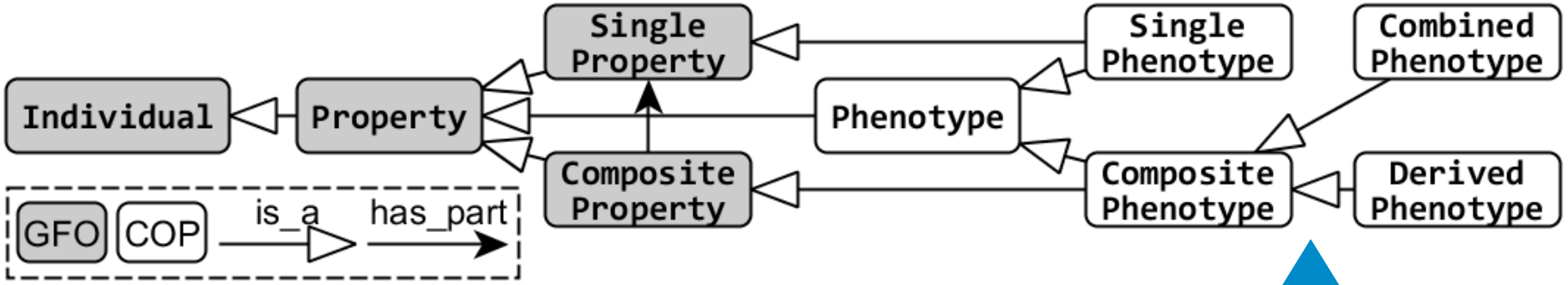
art-decor.org

HL7 FHIR

Sources (last access: 2019-09-16):
https://www.hl7.org/fhir/
https://art-decor.org

ONTOLOGICAL MODELLING OF PHENOTYPES

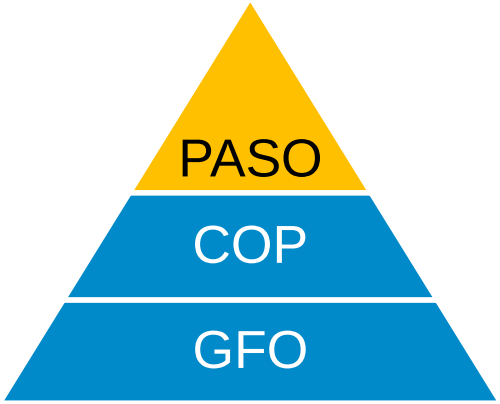
Core Ontology of Phenotypes (COP)



- Phenotype vs. Phenotype Class
- Single vs. Composite Phenotypes
- Restricted vs. non-Restricted Phenotype Classes

Phenotype Algorithm Specification Ontologies (PASO)

- Model specific phenotypes (algorithms) using the COP
- Are embedded in the COP
  - the classes of the PASO are subclasses of the COP classes
  - every PASO subclass of the COP classes cop:Single_Phenotype, cop:Combined_Phenotype or cop:Derived_Phenotype is a phenotype class and is instantiated by phenotypes
  - direct subclasses are non-restricted, while the subclasses of the non-restricted phenotype classes are restricted



Example: BMI-PASO

	Underweight	Normal weight	Overweight	Obese
Age: >=18; <34	BMI: <19	BMI: >=19; <25	BMI: >=25; <30	BMI: >=30
Age: >=34	BMI: <19	BMI: >=19; <27	BMI: >=27; <30	BMI: >=30

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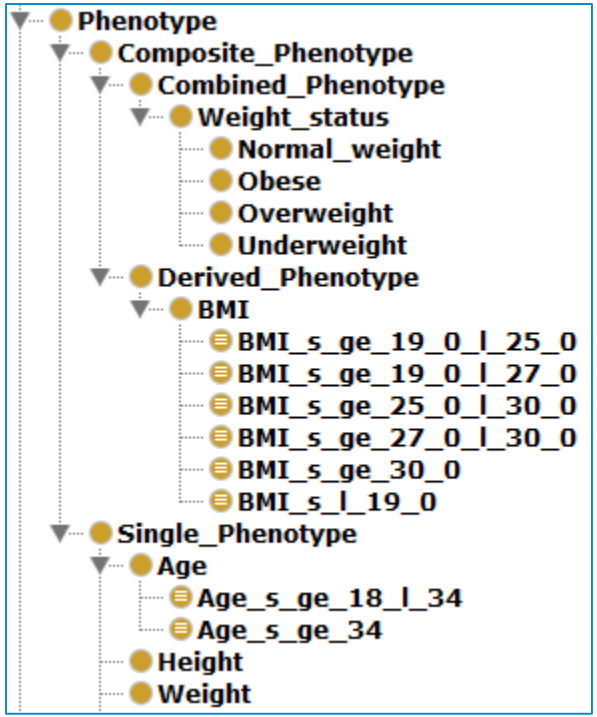

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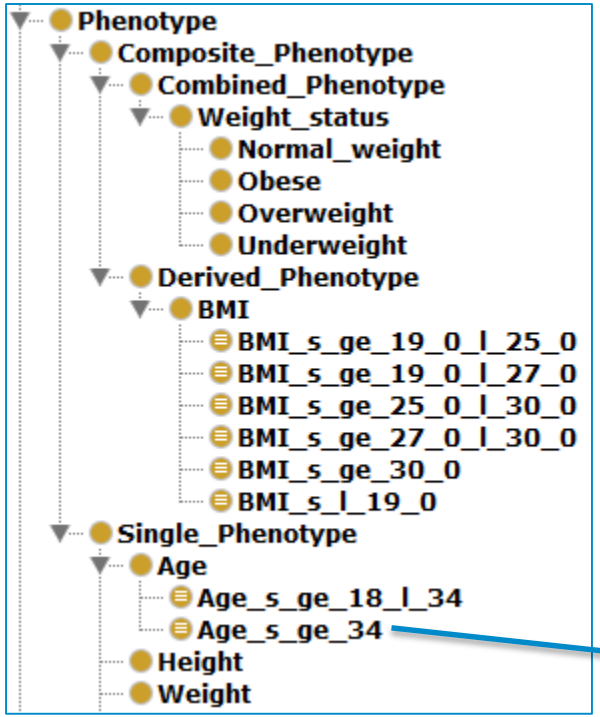

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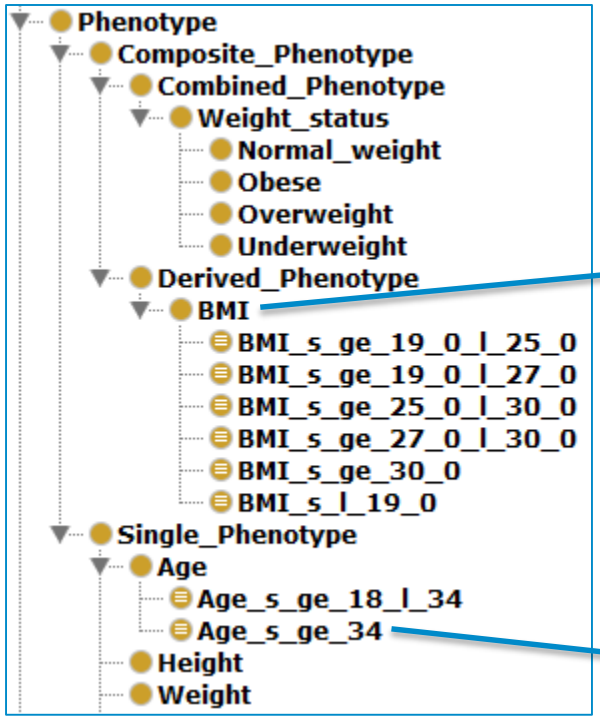

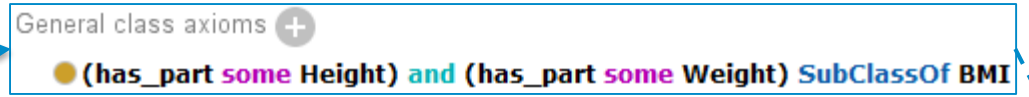

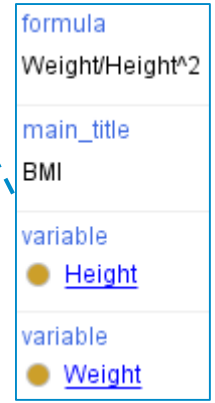

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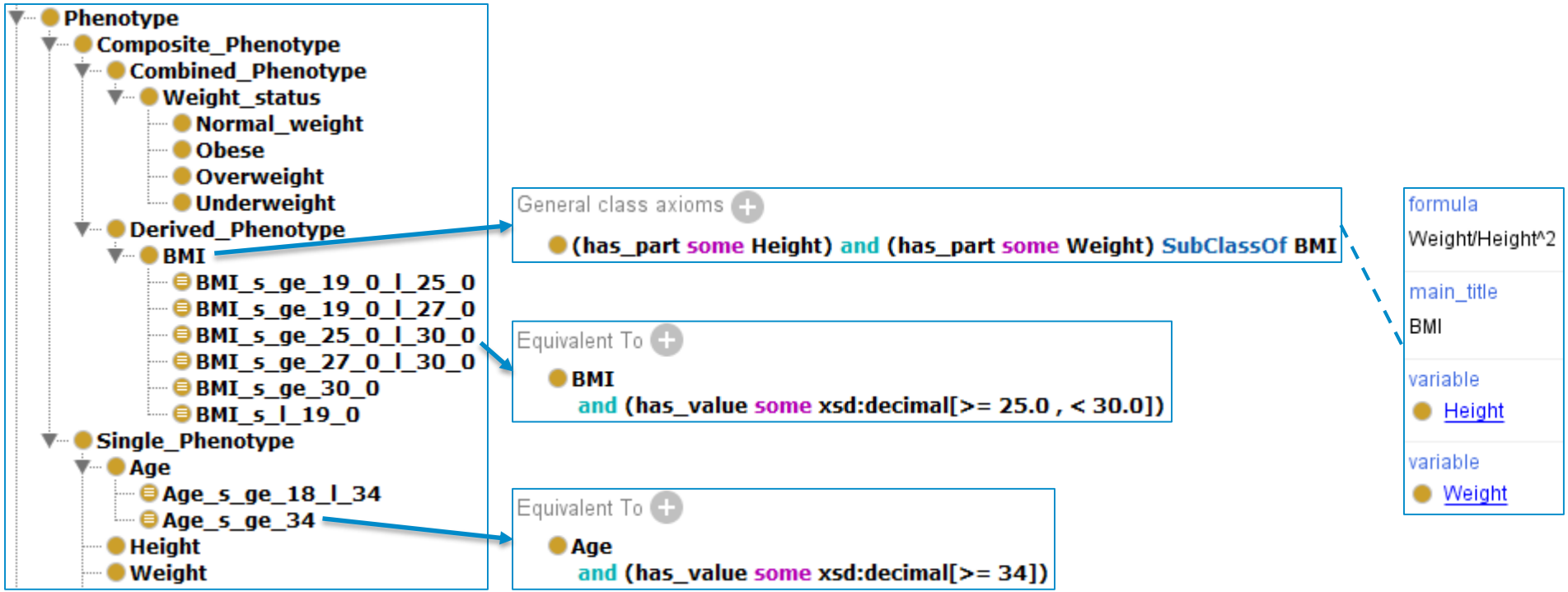

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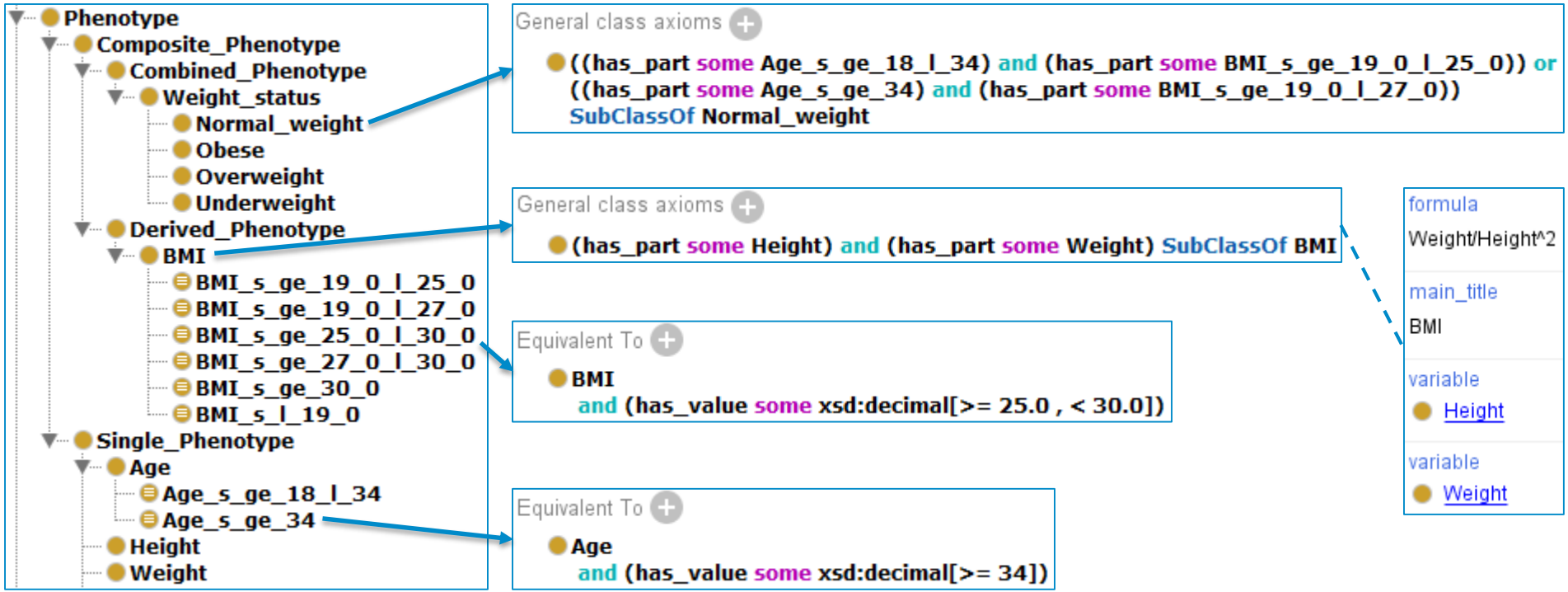

TECHNICAL ASPECTS OF THE PHENOTYPE MANAGER (PHENOMAN)

Phenotype Manager (PhenoMan)

Phenotype Manager (PhenoMan)


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      "code": "3141-9",
      "display": "Body weight"
    },
    {
      "system": "http://snomed.info/sct",
      "code": "27113001",
      "display": "Body weight (observable entity)"
    }
  ]
},
"subject": {
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},
"effectiveDateTime": "2019-08-26T13:09:58+02:00",
"valueQuantity": {
  "value": 75.0,
  "unit": "kg",
  "system": "http://unitsofmeasure.org",
  "code": "kg"
},
```


HL7 FHIR Resource of weight observation as JSON

Phenotype Manager (PhenoMan)

- Implements a multistage reasoning approach combining standard reasoners (e.g., Pellet or HermiT) and mathematical calculations
- Receives instance data set from a FHIR Server as FHIR resources, interprets and inserts it into the ontology


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- Implements a multistage reasoning approach combining standard reasoners (e.g., Pellet or HermiT) and mathematical calculations
- Receives instance data set from a FHIR Server as FHIR resources, interprets and inserts it into the ontology
  - individual properties (single phenotypes) as instances of the direct subclasses of cop:Single_Phenotype (e.g., Weight, Height) with property assertions (e.g., “has_value 75” for Weight)
  - a composite phenotype as instance of the class cop:Composite_Phenotype, which combines all the single phenotype instances using has_part property assertions


```
"resourceType": "Observation",
"id": "162209",
"meta": {
  "versionId": "1",
  "lastUpdated": "2019-08-26T11:10:19.353+00:00"
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"code": {
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HL7 FHIR Resource of weight observation as JSON

PhenoMan Execution Example (BMI) - I

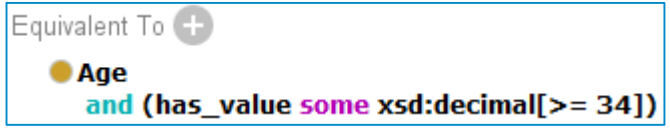
Composite Phenotype

Age = 40 years

Height = 1.7 m

Weight = 75 kg

1. Classification step
   - the single phenotype instances are classified in restricted classes (age ranges)



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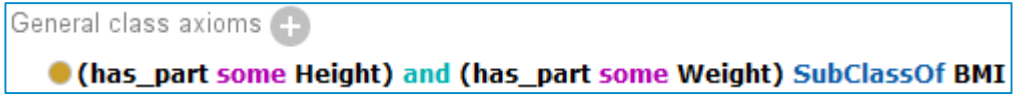

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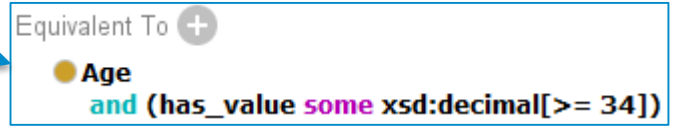

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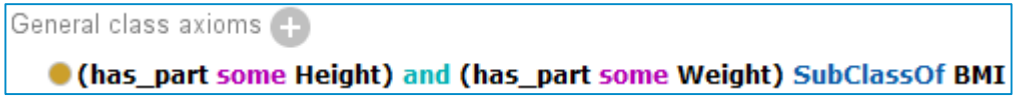

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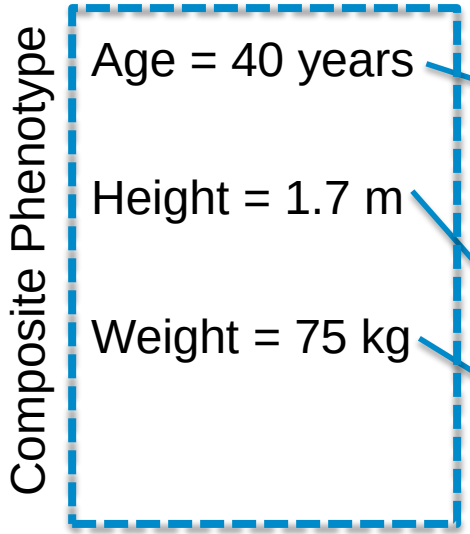

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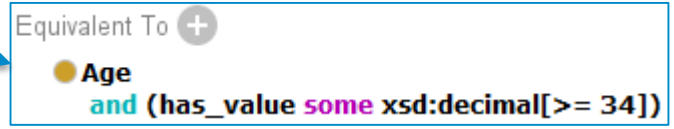

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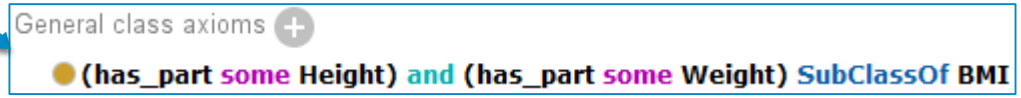


PhenoMan Execution Example (BMI) - II

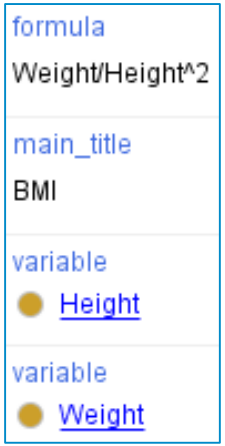
Composite Phenotype

Age = 40 years

Height = 1.7 m

Weight = 75 kg

2. Calculation step
   - the formula of the derived phenotypes is calculated (BMI)
   - a BMI instance with the calculated value (≈ 26) is added to the composite phenotype instance



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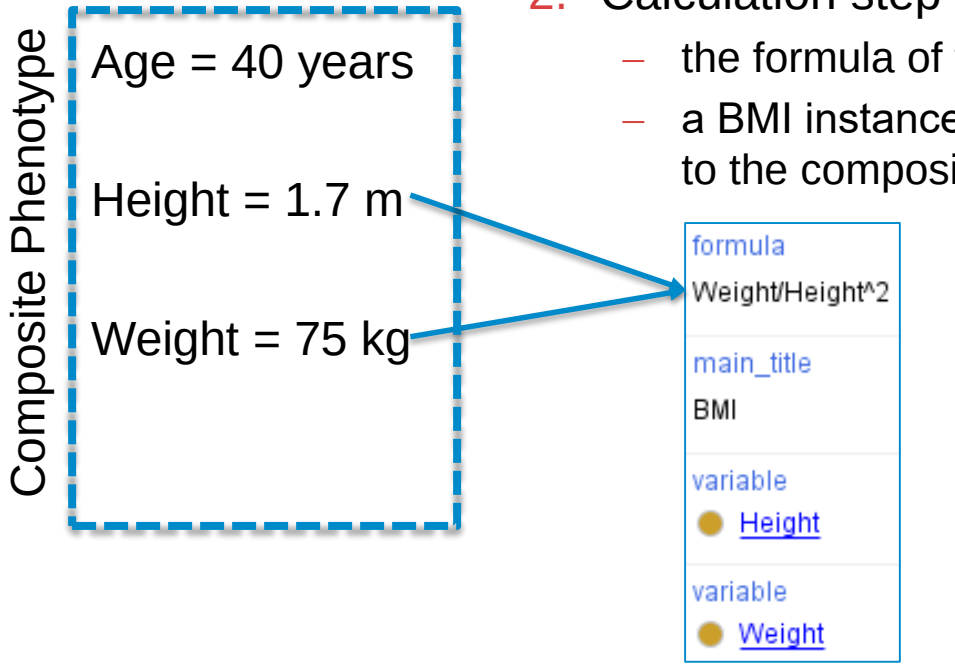

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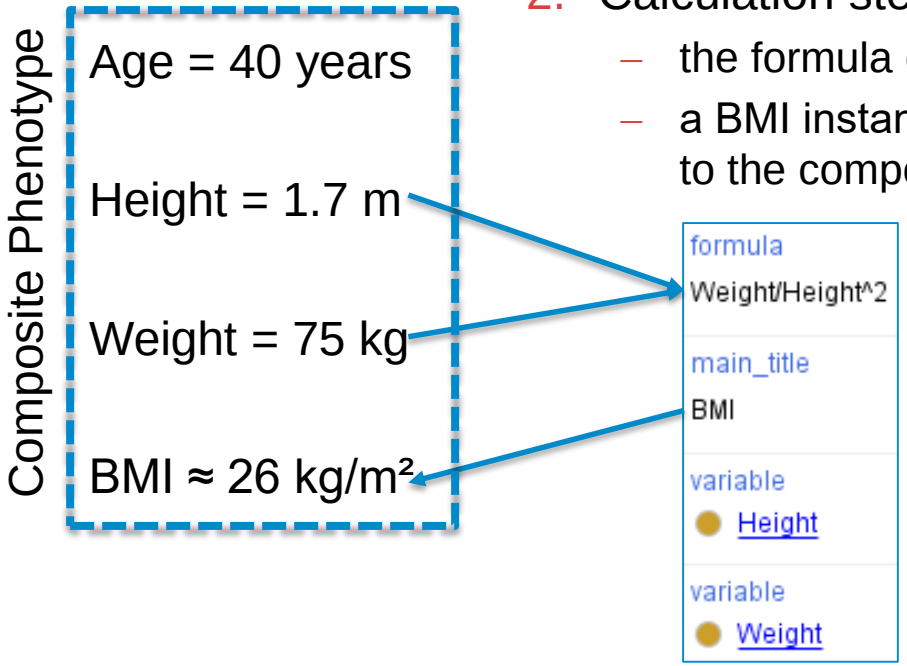
PhenoMan Execution Example (BMI) - II



2. Calculation step
   - the formula of the derived phenotypes is calculated (BMI)
   - a BMI instance with the calculated value (≈ 26) is added to the composite phenotype instance

PhenoMan Execution Example (BMI) - III

Composite Phenotype

Age = 40 years

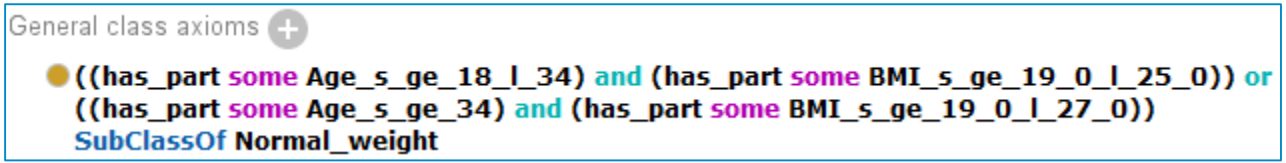
Height = 1.7 m

Weight = 75 kg

BMI ≈ 26 kg/m²

3. Classification step
   - the BMI instance is classified in restricted classes (BMI ranges)

   - the weight status is derived based on age und BMI range



PhenoMan Execution Example (BMI) - III

Composite Phenotype

Age = 40 years

Height = 1.7 m

Weight = 75 kg

BMI ≈ 26 kg/m²

3. Classification step
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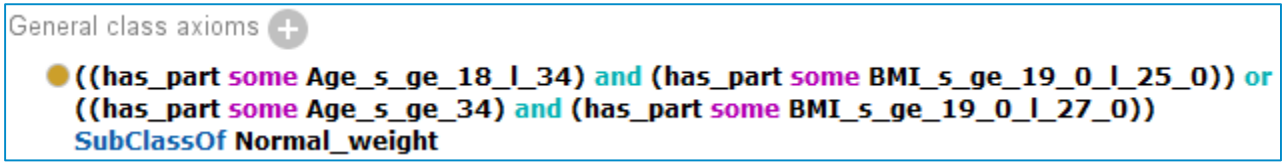
   - the weight status is derived based on age und BMI range



PhenoMan Execution Example (BMI) - III

Composite Phenotype

Age = 40 years

Height = 1.7 m

Weight = 75 kg

BMI ≈ 26 kg/m²

Normal Weight

3. Classification step
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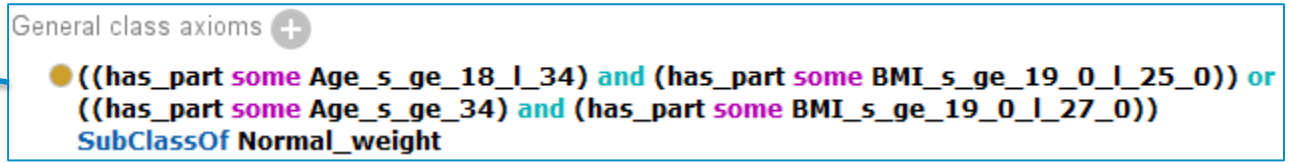
   - the weight status is derived based on age und BMI range



PhenoMan Execution Example (BMI) - IV

- Classification and calculation steps can be repeated several times until all formulas are calculated and all phenotypes are classified
  - if a non-restricted phenotype class has subclasses, which are in turn used in combined phenotypes

PhenoMan Execution Example (BMI) - IV

- Classification and calculation steps can be repeated several times until all formulas are calculated and all phenotypes are classified
  - if a non-restricted phenotype class has subclasses, which are in turn used in combined phenotypes
- PhenoMan writes the results (calculated or derived phenotypes) as observations back to the FHIR server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  ]
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  "reference": "Patient/157411"
},
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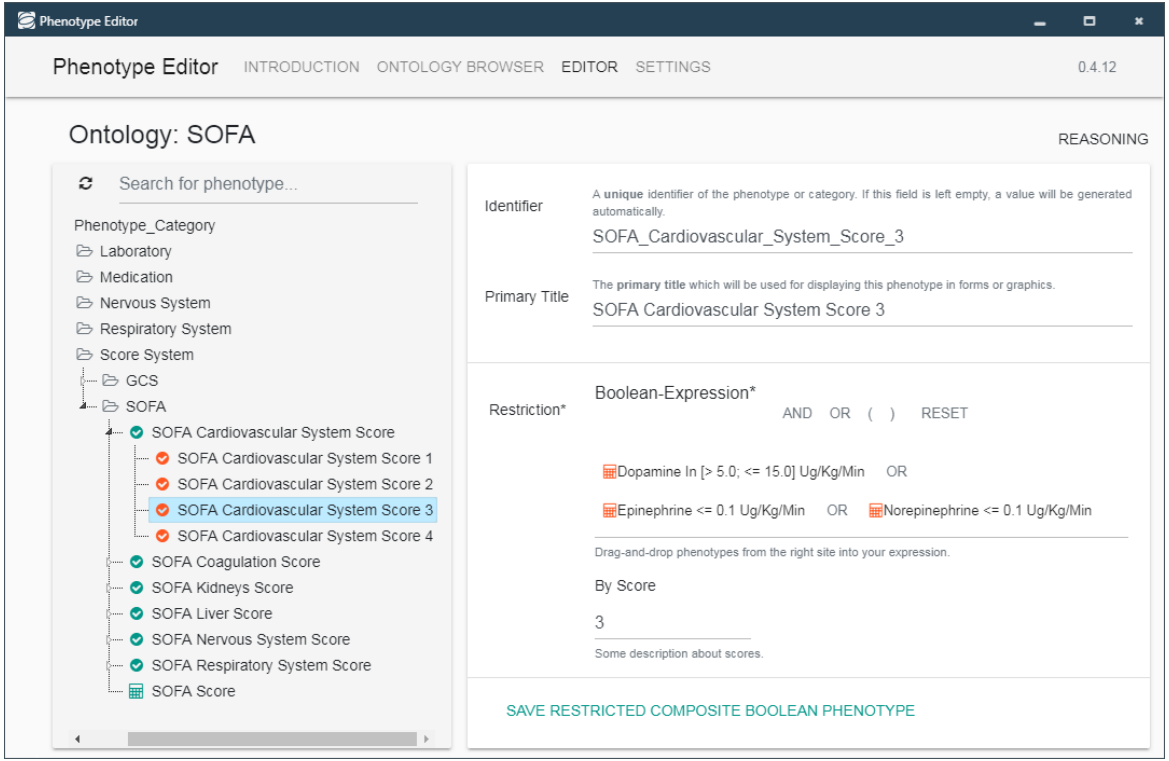
    }
  ]
}
```


HL7 FHIR Resource of BMI observation as JSON

Creating PASOs with the Phenotype Editor



Conclusion

- Novel ontology-based method to model phenotypes for **automated phenotype reasoning based on instance data** (e.g., patient data)
- Iterative reasoning approach, which **combines classification tasks with mathematical calculations** at runtime
- Can be used in **clinical context**, e.g., for supporting the diagnostic process or recruiting appropriate participants for studies
- Successfully evaluated
  - some algorithms (such as socio-economic status) were evaluated in comparison with the corresponding SPSS derivatives based on the research database of the LIFE study

UNIVERSITÄT LEIPZIG

Medizinische Fakultät

THANK YOU FOR YOUR ATTENTION!

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Alexandr.Uciteli@imise.uni-Leipzig.de

Christoph Beger
www.imise.uni-leipzig.de/Mitarbeiter/Christoph_Beger
Christoph.Beger@imise.uni-Leipzig.de

imise.

Implementation

PhenoMan:

- OWL API, HermiT, Openllet
- For calculations: Java Expression Evaluator (EvalEx)
  - enables evaluating mathematical and Boolean (e.g., Boolean operators and IF-THEN-ELSE structures) expressions
  - supports defining custom functions and operators.

Phenotype Editor:

- Desktop app designed with JavaScript and shipped as cross platform Electron app with an integrated lightweight web browser (Chromium)
- Backend service provides information and management functionalities of a PASO via REST interface (DropWizard), serves as a mediator to the PhenoMan API

Prototype available on GitHub (GPL-3.0):
https://github.com/ChristophB/ontology_service
https://github.com/ChristophB/phenotype_editor