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Phenotypes in Standard Terminologies

Bridging the gap between clinical practice and research



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Outline

- ◆ Phenotype terms in the Human Phenotype Ontology (HPO)
- ◆ Biomedical terms in the Unified Medical Language System
- ◆ 3 approaches to mapping phenotype terms to SNOMED CT
 - Looking for equivalent terms
 - Pre-coordinated terms in UMLS
 - Post-coordinated terms in SNOMED CT
 - Looking for broader terms
- ◆ Challenges



Examples

HPO

- ◆ Multicystic kidney dysplasia
- ◆ Hypoplasia of the 3rd metatarsal
- ◆ **Recurrent** urinary tract infection

SNOMED CT

- ◆ Multicystic kidney
- ◆ Based on “Congenital hypoplasia of kidney”
- ◆ Urinary tract infection [partial match]



Loosely based on 3 papers

- ◆ Winnenburg R, Bodenreider O.
Coverage of phenotypes in standard terminologies.
Proceedings of the Joint Bio-Ontologies and BioLINK ISMB'2014
SIG session "Phenotype Day" 2014:41-44.
- ◆ Dhombres F, Winnenburg R, Case JT, Bodenreider O.
Extending the coverage of phenotypes in SNOMED CT through post-
coordination.
Stud Health Technol Inform (Proc Medinfo) 2015:(in press).
- ◆ Dhombres F, Bodenreider O.
Investigating the lexico-syntactic properties of phenotype terms –
Application to interoperability between HPO and SNOMED CT.
Proceedings of the Joint Bio-Ontologies and BioLINK ISMB'2015
SIG session "Phenotype Day" 2015:(in press).



Introduction

- ◆ Phenotyping is crucial to understanding how genetic variation relates to clinical manifestations
 - Precise phenotyping is required for the study of rare syndromes
 - Poor interoperability of phenotypic data
 - Across clinical data repositories
 - Between research and clinical data repositories



Phenotype terminologies

Human Phenotype Ontology

- ◆ Developed collaboratively
 - Coordination: Peter Robinson
- ◆ Nightly builds
- ◆ Distributed as an OWL file
- ◆ 10,589 classes (as of Jan. 21, 2015)
- ◆ 16,608 names for phenotype
 - One preferred term for each class
 - 6019 exact synonyms
- ◆ Cross-references to standard terminologies



Human Phenotype Ontology

Label

Name:

Multicystic kidney dysplasia

Synonyms:

Multicystic dysplastic kidney
Multicystic kidneys
Multicystic renal dysplasia

Identifier

Primary ID:

HP:0000003

Alternative IDs:

HP:0004715

Definition

Textual Definition:

Multicystic dysplasia of the kidney is characterized by multiple cysts of varying size in the kidney and the absence of a normal pelvocaliceal system. The condition is associated with ureteral or ureteropelvic atresia, and the affected kidney is nonfunctional.

Logical Definition:

intersection_of: PATO:0002089

intersection_of: inheres_in UBERON:0002113



Annotation of phenotypes in OMIM and OrphaNet

| | |
|---|---|
| #608836 CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LETHAL NEONATAL;;CARNITINE PALMITOYLTRANSFERAS... | CPT2 |
| #612513 CHROMOSOME 2P16.1-P15 DELETION SYNDROME | - |
| #614209 MECKEL SYNDROME, TYPE 9; MKS9 | B9D1 |
| #614527 CHROMOSOME 17Q12 DELETION SYNDROME | - |
| MOSAIC VARIEGATED ANEUPLOIDY SYNDROME | CEP57 ; BUB1B ; BUB1 ; BUB3 |
| BOR SYNDROME | SIX5 ; SIX1 ; EYA1 |
| BARDET-BIEDL SYNDROME | MKKS ; SDCCAG8 ; WDPCP ; BBS5 ; BBS1 ; TRIM32 ; BBS2 ; IFT27 ; ARL6 ; BBS4 ; CEP290 ; BBS12 ; LZTFL1 ; MKS1 ; BBS10 ; BBIP1 ; NPHP1 ; BBS7 ; IFT172 ; BBS9 ; TTC8 |
| SHORT RIB-POLYDACTYLY SYNDROME | - |
| CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY | - |
| NON-RHIZOMELIC CHONDRODYSPLASIA PUNCTATA | - |
| RENAL DYSPLASIA - MEGALOCYSTIS - SIRENOMELIA | - |
| INDOMETHACIN EMBRYOFETOPATHY | - |

Annotation of phenotypes in OrphaNet



| | | | |
|----------------------|--------------------------------------|----------------|--|
| ORPHA110 | | ICD-10: | Q87.8 |
| Synonym(s): | BBS | OMIM: | 209900 [↗] 600151 [↗] 605231 [↗] |
| Prevalence: | 1-9 / 1 000 000 | | 615981 [↗] 615982 [↗] 615983 [↗] |
| Inheritance: | Oligogenic or Autosomal recessive | | 615984 [↗] 615985 [↗] 615986 [↗] |
| Age of onset: | Infancy Neonatal Antenatal | | 615987 [↗] 615988 [↗] 615989 [↗] |
| | | UMLS: | 615990 [↗] 615991 [↗] 615992 [↗] |
| | | | 615993 [↗] 615994 [↗] 615995 [↗] |
| | | | 615996 [↗] |
| | | MeSH: | C0752166 |
| | | MedDRA: | D020788 |
| | | | 10056715 |

SUMMARY

Bardet-Biedl syndrome (BBS) is a ciliopathy with multisystem involvement. Its prevalence in Europe is estimated at between 1/125,000 and 1/175,000. This disorder is characterized by a combination of clinical signs: obesity, pigmentary retinopathy, post-axial polydactyly, polycystic kidneys, hypogenitalism, and learning disabilities, many of which appear several years after disease onset. Clinical expression is variable but most patients manifest the majority of clinical signs during the disease course. Pigmentary retinopathy is the only constant clinical sign after childhood. BBS may also be associated with several other manifestations including diabetes, hypertension, congenital cardiopathy and Hirschsprung disease (see this term). The wide clinical spectrum observed in BBS is associated with significant genetic heterogeneity. The disorder is transmitted mainly in an autosomal recessive manner but oligogenic inheritance has been reported in some cases. To date, mutations in 12 different genes (*BBS1* to *BBS12*) have been identified as being responsible for this phenotype. These genes code for proteins involved in the development and function of primary cilia. Absence or dysfunction of BBS proteins results in ciliary anomalies in organs such as the kidney or eye. However, the relationship between symptoms and ciliary dysfunction remains obscure for some of the clinical manifestations of BBS. Recognition of the clinical picture is important as the diagnosis can be confirmed by molecular analysis, allowing appropriate genetic counseling for family members and possible prenatal diagnosis. The differential diagnosis should include the Alström, McKusick-Kaufmann and Meckel-Gruber syndromes (see these terms). Patients with BBS will need multidisciplinary medical care. The renal abnormalities are the main life-threatening manifestations because they can lead to end-stage renal failure and require renal transplantation. Progressive vision loss due to retinal dystrophy, together with moderate intellectual deficit (when present), behavioral anomalies, hypomimia and obesity will affect the social life of these patients.

Additional information

Further information on this disease

- > Classification(s) (9)
- > Gene(s) (21)
- > Publications in PubMed [[↗](#)]
- > Other website(s) (9)

Health care resources for this disease

- > Expert centres (369)
- > Diagnostic tests (54)
- > Patient organisations (81)
- > Orphan drug(s) (1)

Research activities on this disease

- > Research projects (58)
- > Clinical trials (0)
- > Registries/biobanks (28)
- > Networks (20)

Orphanet Reports series

- > Prevalence



Biomedical terminologies

Unified Medical Language System (UMLS)

- ◆ Terminology integration system
- ◆ Developed by NLM
- ◆ Integrates many (140) standard biomedical terminologies
 - SNOMED CT
 - MeSH
 - International Classification of Diseases
 - MedDRA
- ◆ 3M concepts
- ◆ 8M normalized terms



UMLS Terminology Server

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Unified Medical Language System®

UMLS Terminology Services

Metathesaurus Browser

UTS Home Applications SNOMED CT Resources Downloads Documentation UMLS Home

Search Tree Recent Searches

Term CUI Code

multicystic renal dysplasia

Release: 2015AA

Search Type: Word

Source: All Sources
AIR
ALT
AOD
AOT

Search Results (2)

- [C1840451](#) MULTICYSTIC RENAL DYSPLASIA, BILAT
- [C3714581](#) Multicystic Dysplastic Kidney

Basic View Report View Raw View

Concept: [C3714581] Multicystic Dysplastic Kidney

Semantic Types

- [Congenital Abnormality](#) [T019]
- [Disease or Syndrome](#) [T047]

Definitions

MSH/MH | A nongenetic defect due to malformation of the KIDNEY which appears as a bunch of grapes with multiple renal cysts but lacking the normal renal bean shape, and the collection drainage system. This condition can be detected in-utero with ULTRASONOGRAPHY.

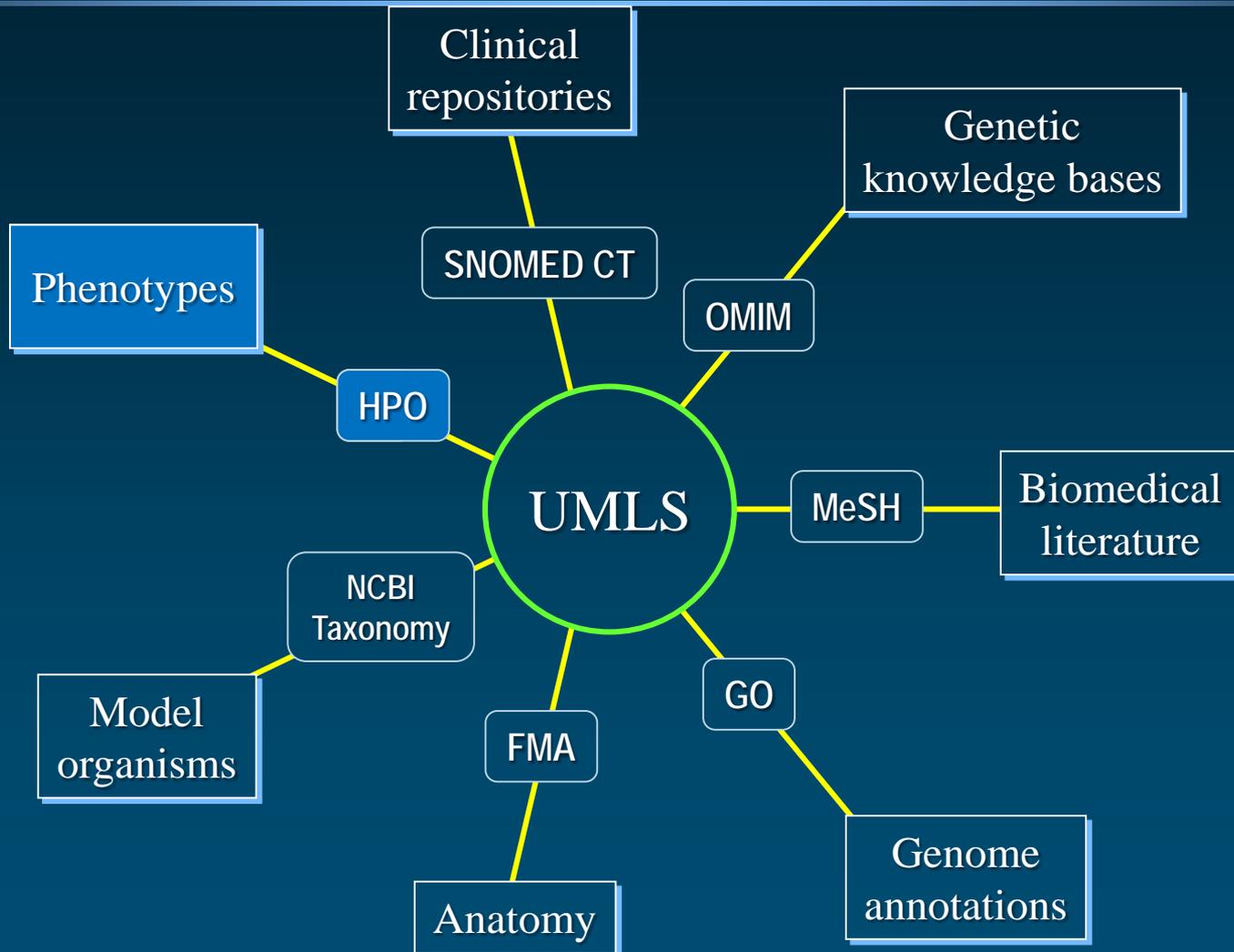
Atoms (78) string [AUI / RSAB / TTY / Code]

- [multicystic dysplastic kidney](#) [A18674881/CHV/SY/0000031000]
- [multicystic dysplastic kidneys](#) [A18637802/CHV/SY/0000031000]
- [multicystic kidney](#) [A18693263/CHV/PT/0000031000]
- [multicystic kidney dysplasia](#) [A18563499/CHV/SY/0000031000]
- [multicystic kidneys](#) [A18600533/CHV/SY/0000031000]
- [multicystic renal dysplasia](#) [A18656310/CHV/SY/0000031000]
- [Multicystic dysplastic kidney](#) [A17841572/ICD10CM/ET/Q61.4]
- [Multicystic renal dysplasia](#) [A17854225/ICD10CM/ET/Q61.4]
- [Dysplasia, Multicystic Kidney](#) [A1957002/MSH/PM/D021782]
- [Dysplasia, Multicystic Renal](#) [A8409910/MSH/PM/D021782]
- [Dysplasias, Multicystic Kidney](#) [A1957003/MSH/PM/D021782]
- [Dysplasias, Multicystic Renal](#) [A8409912/MSH/PM/D021782]
- [Kidney Dysplasia, Multicystic](#) [A1926033/MSH/PM/D021782]
- [Kidney Dysplasias, Multicystic](#) [A1926034/MSH/PM/D021782]
- [Multicystic Dysplastic Kidney](#) [A1927559/MSH/MH/D021782]
- [Multicystic Dysplastic Kidneys](#) [A1927560/MSH/PM/D021782]

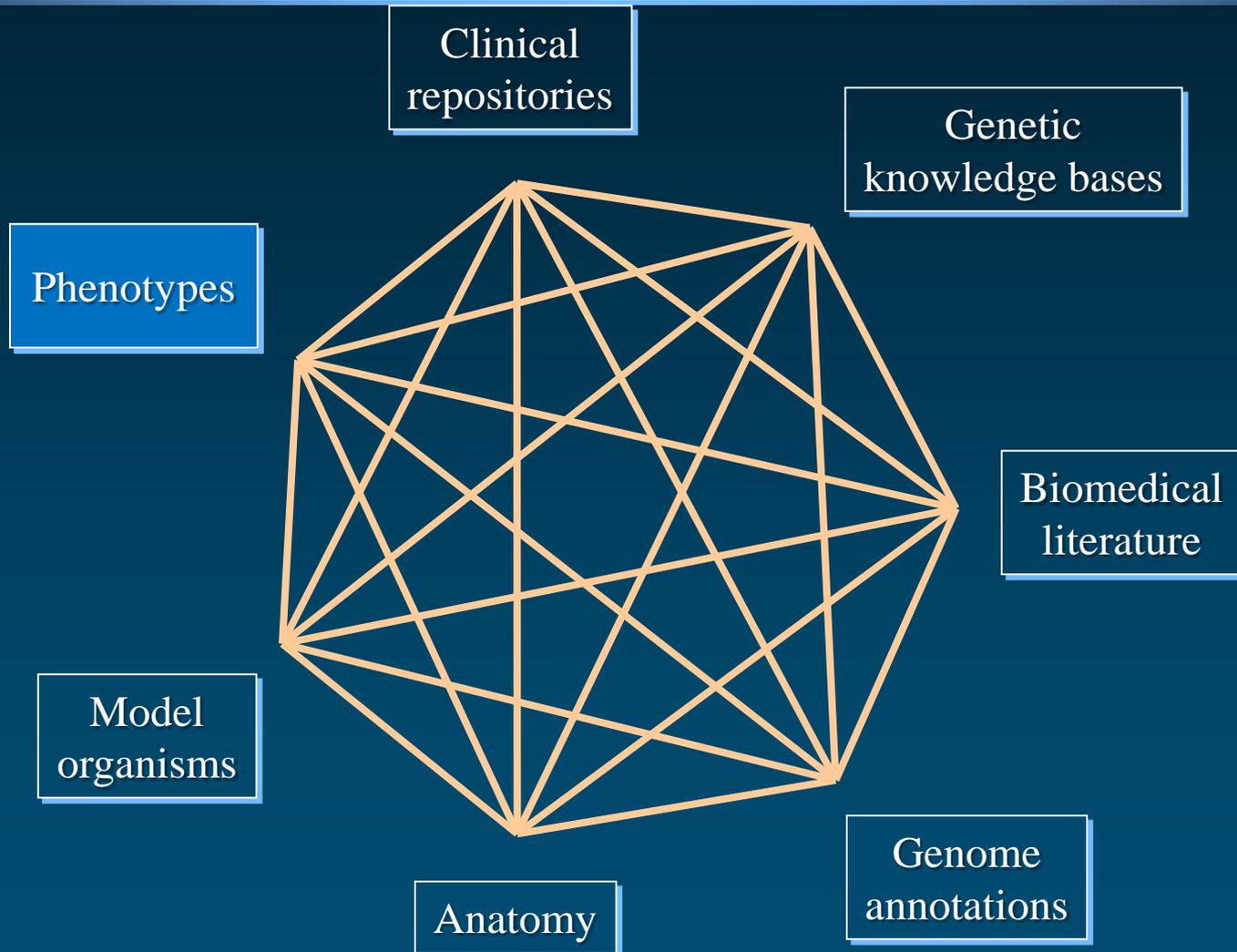
Copyright | Privacy | Accessibility | Freedom of Information Act | National Institutes of Health | Health & Human Services



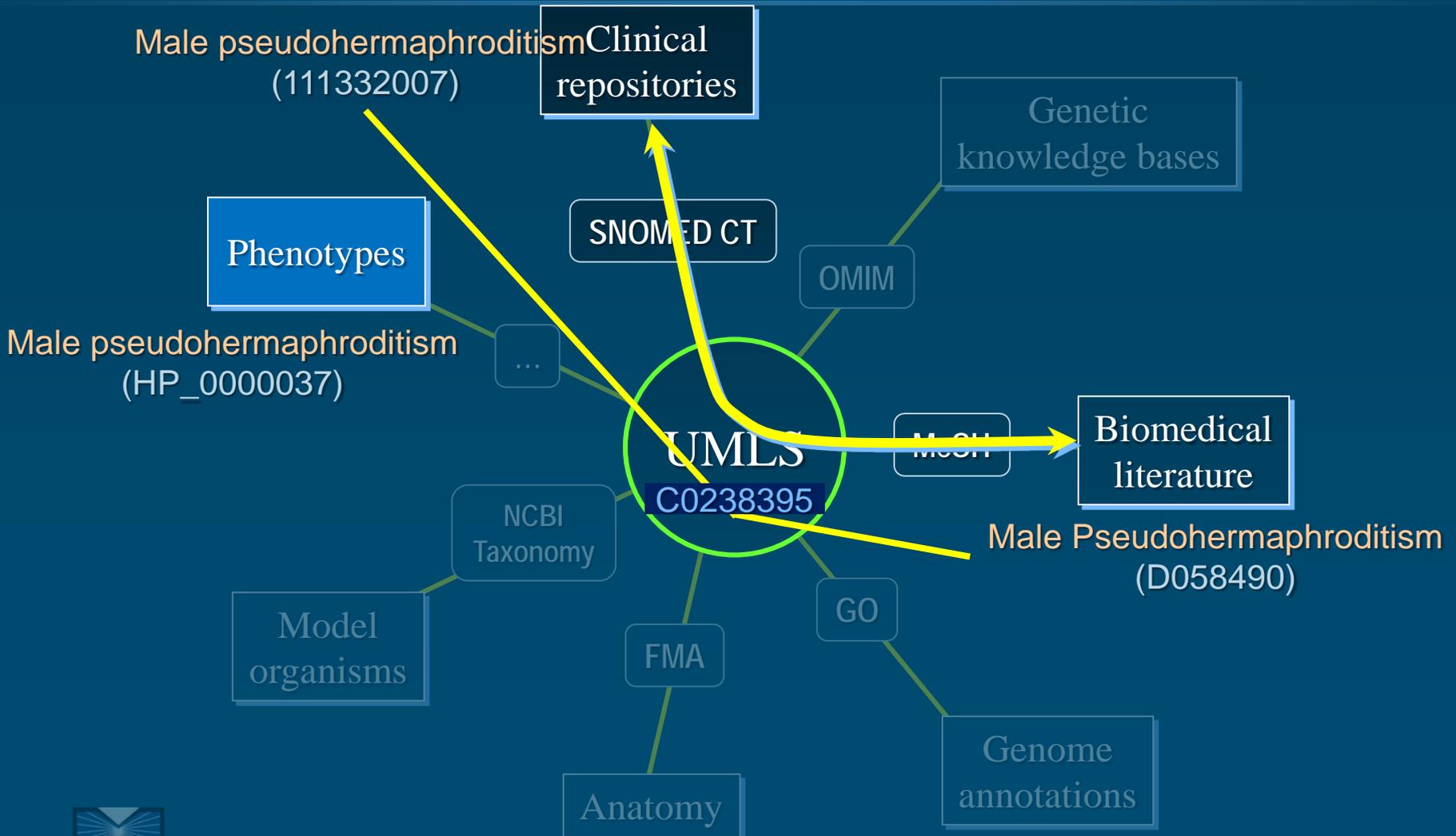
Integrating subdomains



Integrating subdomains



Terminology integration



SNOMED CT

- ◆ Developed by the International Health Terminology Standard Development Organization
- ◆ Description logics formalism
 - Supports post-coordination
- ◆ Broad coverage of clinical medicine
 - ~300,000 concepts
- ◆ Clinical findings
 - ~100,000 concepts
 - 169,000 names
- ◆ Integrated in the UMLS



SNOMED CT browser

IHTSDO SNOMED CT Browser Release: United States Edition 20150301 Perspective: Full Feedback About USA  Delivering SNOMED CT

Concept Details

Summary **Details** Diagram Refsets Members References

Parents Stated Inferred

-   Kidney disease (disorder)

 **Multicystic kidney (disorder)** 

SCTID: 204962002

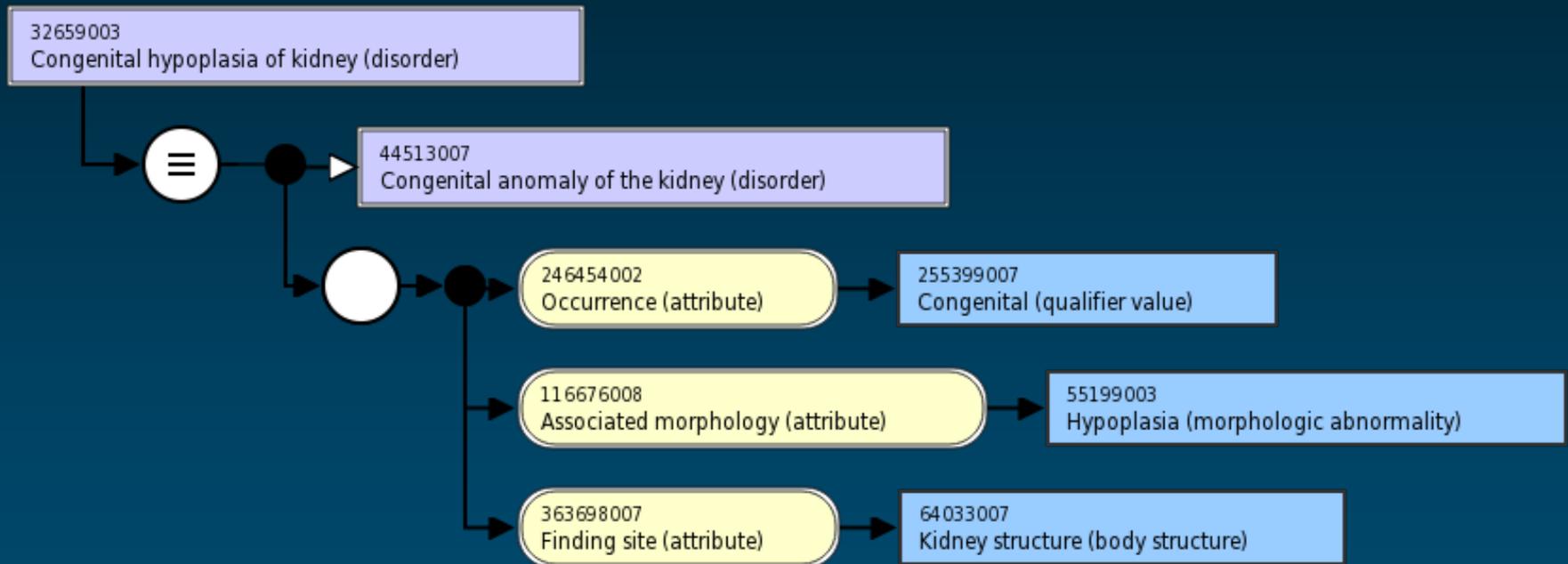
- Multicystic kidney (disorder)
- MCKD - Multicystic kidney disease
- Multicystic kidney
- Multicystic renal dysplasia

Finding site → Kidney structure

Children (0)
No children



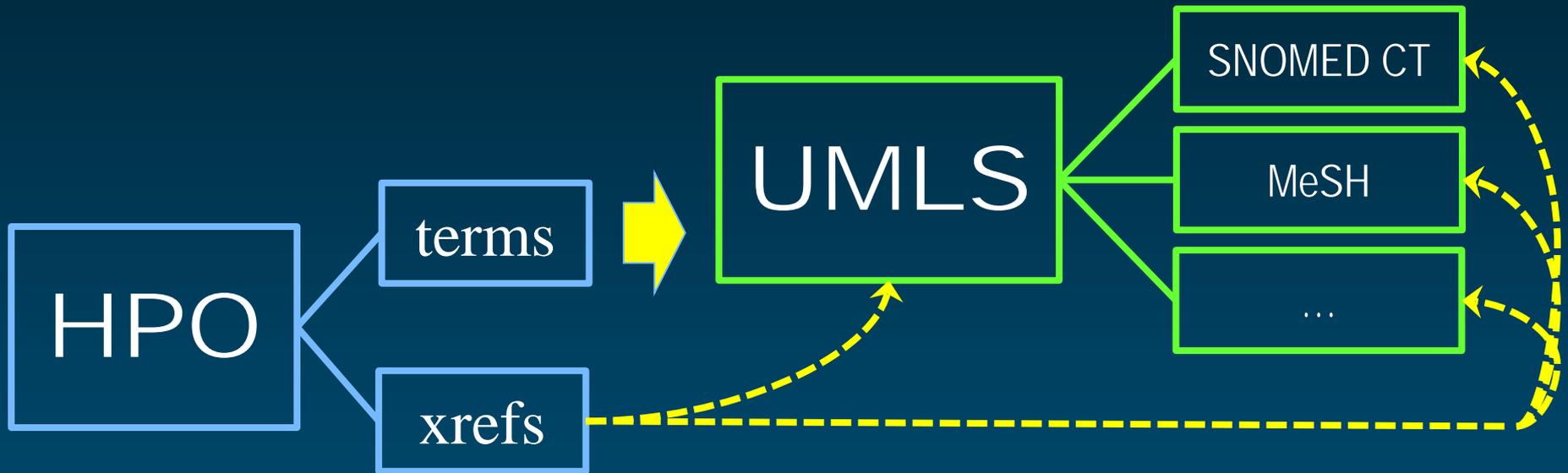
Post-coordinated expression



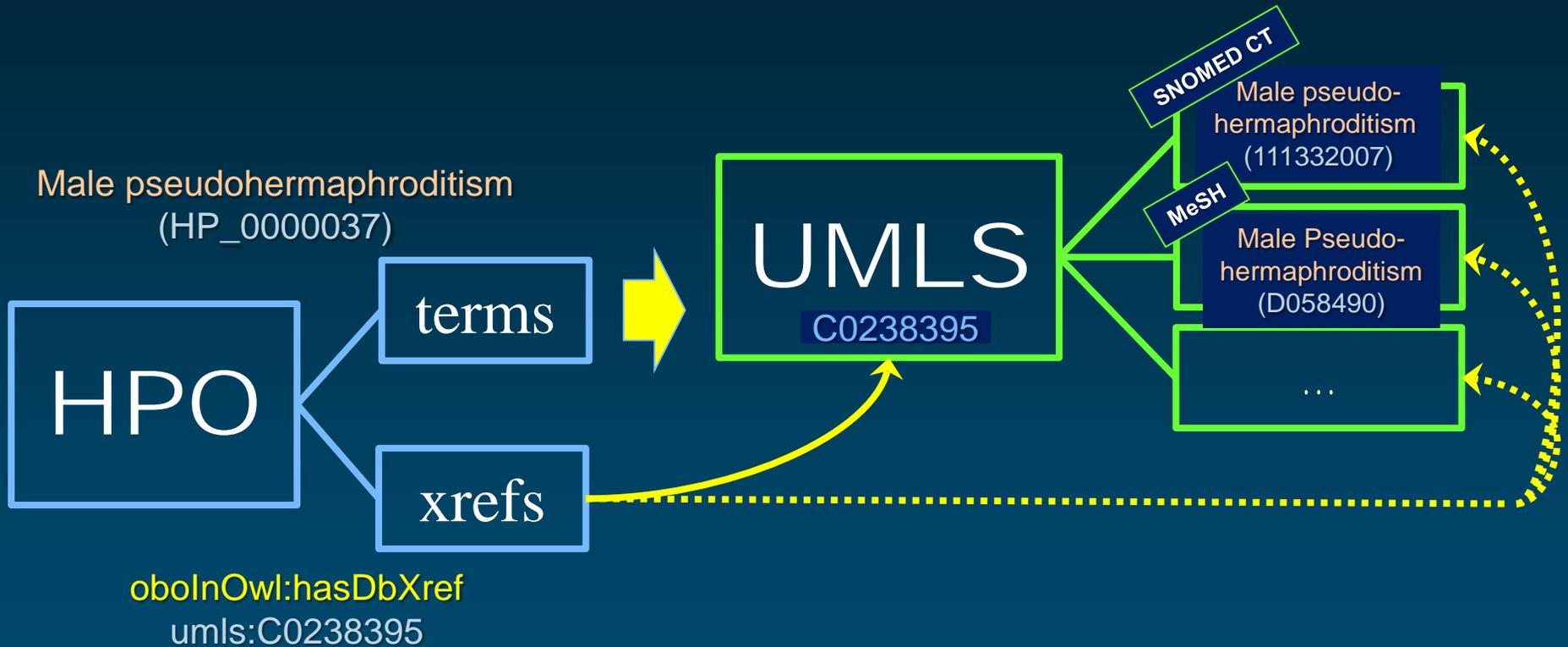
Coverage of human phenotypes in biomedical terminologies

(a) Finding equivalent concepts in biomedical terminologies (pre-coordinated terms)

Methods



Example



HPO terms covered by SNOMED CT (xref)

- ◆ Male pseudohermaphroditism (HP_0000037)
 - Lexical UMLS : C0238395
 - Xref UMLS: C0238395
 - Mapping to SNOMED CT: Male pseudohermaphroditism (111332007)
 - Xref SNOMED CT: Male pseudohermaphroditism (111332007)

- ◆ Spinal canal stenosis (HP_0003416)
 - Lexical UMLS : C0039144
 - Xref UMLS: C0039144
 - Mapping to SNOMED CT: Spinal stenosis (76107001)
 - Xref SNOMED CT: Spinal stenosis (76107001)

HPO terms covered by SNOMED CT (no xref)

- ◆ Atrial fibrillation (HP_0005110)
 - Lexical UMLS: C0004238
 - Xref UMLS: C0004238
 - Mapping to SNOMED CT: Atrial fibrillation (49436004)
 - Xref SNOMED CT: none
- ◆ Inlet ventricular septal defect (HP_0011622)
 - Lexical UMLS: C0221215
 - Through MeSH, SNOMED CT, ICD10-CM
 - Mapping to SNOMED CT: Common atrioventricular canal (360481003)
 - Xref UMLS: none
 - Xref SNOMED CT: none

HPO terms NOT covered by SNOMED CT

- ◆ Palmoplantar keratoderma (HP_0000982)
 - Lexical UMLS: C0022596
 - Through MeSH, MedDRA, ICD10-CM
 - Xref UMLS: none
 - Xref SNOMED CT: none

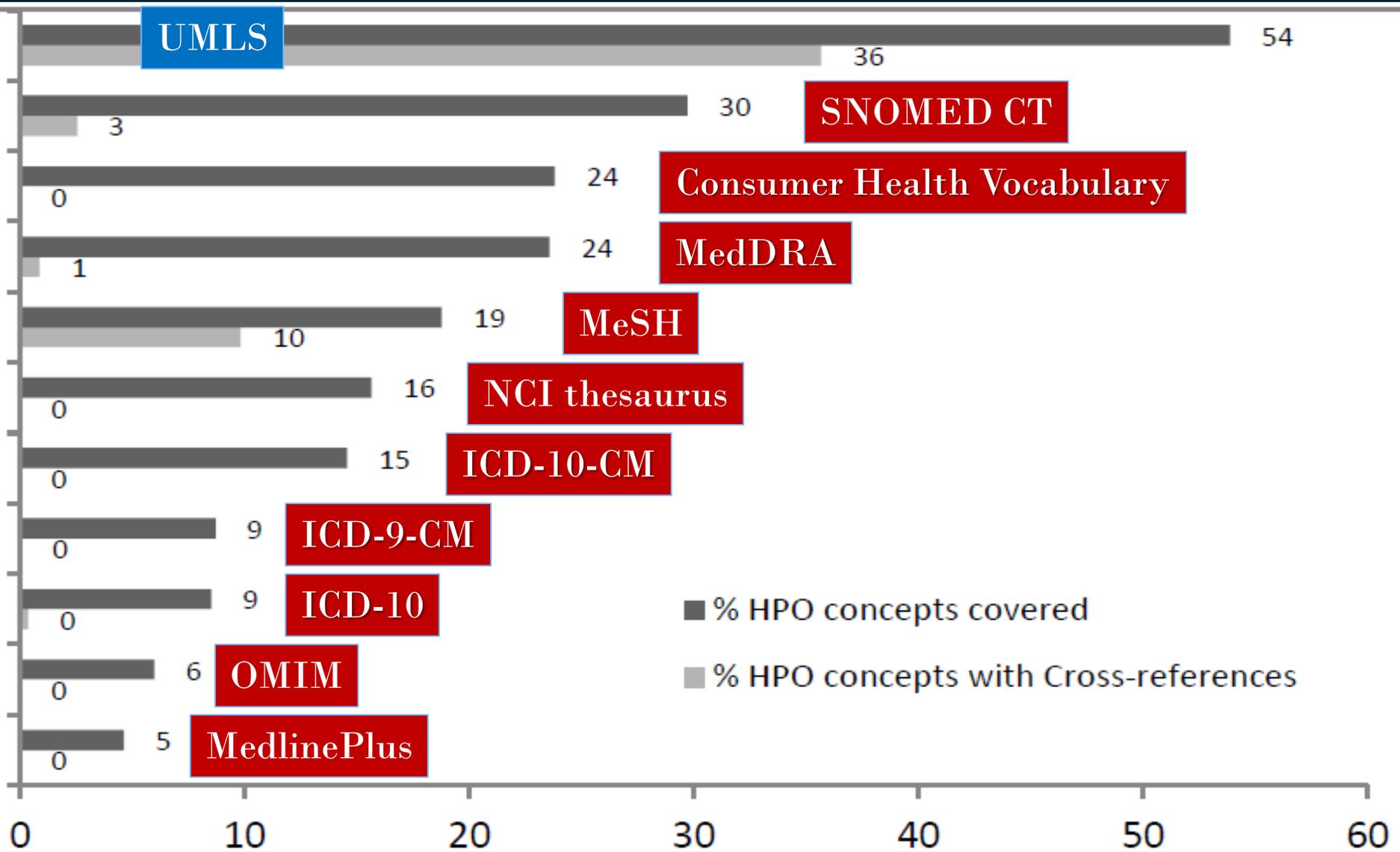
- ◆ Hypoplastic nasal septum (HP_0005104)
 - Lexical UMLS: C1861328
 - Through OMIM
 - Xref UMLS: C1861328
 - Mapping to SNOMEDCT: none
 - Xref SNOMED CT: none

HPO terms NOT covered by UMLS

- ◆ Oval transradiancy (humeral) (HP_0003877)
 - Lexical UMLS: none
 - Xref UMLS: none
 - Xref SNOMED CT: none

- ◆ Lower limb peromelia (HP_0009820)
 - Lexical UMLS: none
 - Xref UMLS: none
 - Xref SNOMED CT: none

Results



Summary

- ◆ Limited coverage of HPO phenotypes
 - In UMLS: 50%
 - In specific biomedical terminologies
 - Highest is SNOMED CT with 30%
- ◆ Insufficient for interoperability between research and healthcare datasets
- ◆ Integrating HPO into UMLS would benefit
 - UMLS by increasing its coverage of phenotypes
 - HPO by increasing/keeping up to date its set of cross-references



Coverage of human phenotypes in biomedical terminologies

(b) Expressing HPO concepts through post-coordinated expressions in SNOMED CT

Methods Intuition

- ◆ SNOMED CT already provides pre-coordinated concepts (and logical definitions) for some 3000 phenotypes
 - Which can be used as templates for other phenotypes
- ◆ Some phenotype concepts are more specialized than corresponding concepts in SNOMED CT
 - By removing modifiers in a controlled fashion, we map demodified phenotype terms to SNOMED CT
- ◆ Demodified HPO terms can be associated with SNOMED CT phenotype templates to create post-coordinated expressions



Methods Overview

- ◆ Transformation rules for phenotype terms
 - Replace
 - Split
 - Demodification to disorder (D0)
 - Demodification to anatomy, physiology or chemical substance (D1)
- ◆ Templates for phenotype concepts
- ◆ Mapping transformed HPO terms to SNOMED CT
- ◆ Creating post-coordinated expressions for HPO terms



1. Replace

- ◆ Replace the abbreviations for ordinals by their expanded form
- ◆ Example
 - “Aplasia of the phalanges of the *4th* toe”
 - → “Aplasia of the phalanges of the *fourth* toe”

2. Split

- ◆ Split expressions with words concatenated by “/” into two individual phrases
- ◆ Example
 - “aplasia/hypoplasia of the thymus”
 - → 2 phrases
 - “aplasia of the thymus”
 - “hypoplasia of the thymus”

3. Demodification to disorder (D0)

- ◆ HPO contains modifiers that specialize disorders
- ◆ By removing these modifiers, we create a more general disorder concept
- ◆ For example
 - “bilateral congenital cataract”
 - Modifier “congenital”
 - → “bilateral cataract”

4. Demodification to other types (D1)

- ◆ Modifiers denoting a disorder of a specific anatomical structure, physiological process or chemical substance
- ◆ By removing these modifiers, we extract the object of the disorder
- ◆ Examples
 - “Abnormality of the lip” → “lip”
 - “Abnormality of intracranial pressure” → “intracranial pressure”
 - “Abnormality of prothrombin” → “prothrombin”



Logical definitions for phenotype concepts in SNOMED CT

- ◆ “Congenital **hypoplasia** of **kidney**”
- ◆ *'Disease (disorder)'* and
 - *('Role group (attribute)'* some (
 - *('Associated morphology (attribute)'*
 - some **'Hypoplasia (morphologic abnormality)'**
 - *and ('Occurrence (attribute)'*
 - some *'Congenital (qualifier value)'*
 - *and ('Finding site (attribute)'*
 - some **'Kidney structure (body structure)'**)))

Template for phenotype concepts in SNOMED CT

- ◆ “Congenital **hypoplasia** of <ANATOMY>”
- ◆ *'Disease (disorder)'* and
 - (*'Role group (attribute)'* some (
 - (*'Associated morphology (attribute)'*
 - some **'Hypoplasia (morphologic abnormality)'**)
 - and (*'Occurrence (attribute)'*
 - some *'Congenital (qualifier value)'*)
 - and (*'Finding site (attribute)'*
 - some **'<ANATOMY> (body structure)'**)))

Templates for phenotype concepts in SNOMED CT

Template

{abnormal, abnormality of, abnormality of the, abnormality involving the }<ANATOMICAL STRUCTURE>
<ANATOMICAL STRUCTURE> {abnormal}

{aplastic, aplasia of, aplasia of the, aplasia involving the, absence of}<ANATOMICAL STRUCTURE>
<ANATOMICAL STRUCTURE> {agenesis, aplasia, absent}
{congenital absence of, congenital aplasia of }<ANATOMICAL STRUCTURE>

{hypoplastic, hypoplasia of, hypoplasia of the, hypoplasia involving, hypoplasia involving the, hypoplasia affecting the}<ANATOMICAL STRUCTURE>
<ANATOMICAL STRUCTURE> {hypoplasia}
{congenital hypoplasia of}<ANATOMICAL STRUCTURE>

{duplication of, duplication of the, duplication involving}<ANATOMICAL STRUCTURE>
<ANATOMICAL STRUCTURE> {duplication}
{complete duplication of, complete duplication of the}<ANATOMICAL STRUCTURE>

{bilateral, D1} <ANATOMICAL STRUCTURE>

examples :

{bilateral aplasia}<ANATOMICAL STRUCTURE>
{bilateral}<ANATOMICAL STRUCTURE> {aplasia}
{bilateral absence of}<ANATOMICAL STRUCTURE> ...

Logical definition

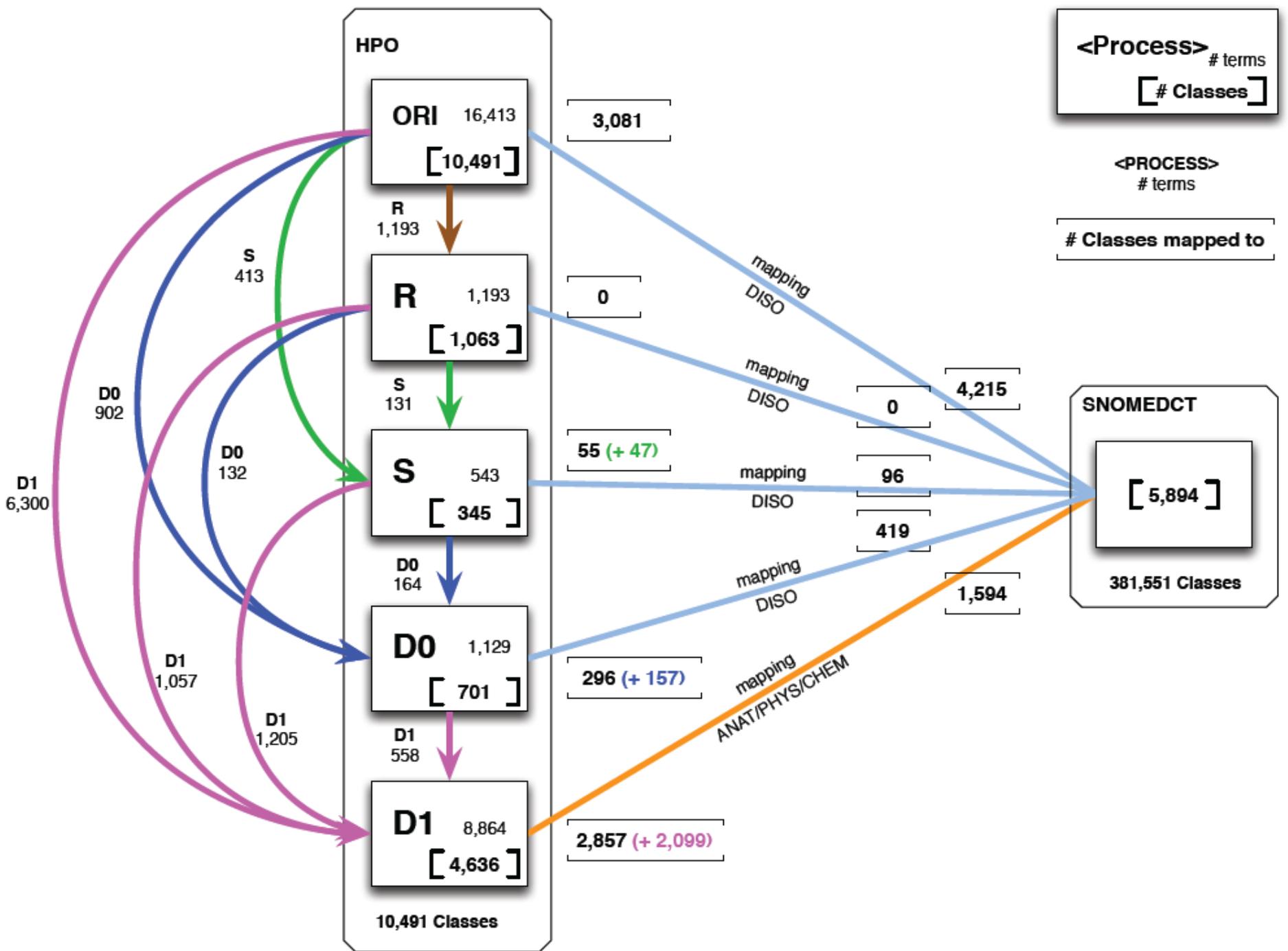
'Disease (disorder)' and ('Role group (attribute)' some ('Associated morphology (attribute)' some 'Developmental anomaly (morphologic abnormality)') and ('Occurrence (attribute)' some 'Congenital (qualifier value)') and ('Finding site (attribute)' some <ANATOMICAL STRUCTURE>)))

'Disease (disorder)' and ('Role group (attribute)' some ('Associated morphology (attribute)' some 'Congenital absence (morphologic abnormality)') and ('Occurrence (attribute)' some 'Congenital (qualifier value)') and ('Finding site (attribute)' some <ANATOMICAL STRUCTURE>)))

'Disease (disorder)' and ('Role group (attribute)' some ('Associated morphology (attribute)' some 'Hypoplasia (morphologic abnormality)') and ('Occurrence (attribute)' some 'Congenital (qualifier value)') and ('Finding site (attribute)' some <ANATOMICAL STRUCTURE>)))

'Disease (disorder)' and ('Role group (attribute)' some ('Associated morphology (attribute)' some 'Double structure (morphologic abnormality)') and ('Occurrence (attribute)' some 'Congenital (qualifier value)') and ('Finding site (attribute)' some <ANATOMICAL STRUCTURE>)))

'Disease (disorder)' and ('Role group (attribute)' some ... *D1 logical definition here* ... and ('Finding site (attribute)' some 'left <ANATOMICAL STRUCTURE>')) and ('Role group (attribute)' some ... *D1 logical definition here* ... and ('Finding site (attribute)' some 'right <ANATOMICAL STRUCTURE>'))



Post-coordinated expressions created

- ◆ 12 templates involving 10 *D1* modifiers
 - and 3 additional *D0* modifiers removed when necessary
- ◆ Post-coordinated expressions for 1,617 HPO classes
- ◆ HPO “Macular hypoplasia” [HPO:HP_0001104]
 - D1 modifier “hypoplasia”
 - template “Congenital hypoplasia of <ANATOMICAL STRUCTURE>”
 - Post-coordinated expression created by substituting “Macula lutea structure (body structure)”



Summary

- ◆ With 12 post-coordination templates, we generated post-coordinated mappings to SNOMED CT for 1617 HPO concepts
- ◆ In complement to the ~3000 HPO concepts for which there is a pre-coordinated mapping to SNOMED CT
- ◆ Template-based mappings are usually high-quality
- ◆ Additional templates could be investigated

Coverage of human phenotypes in biomedical terminologies

*(b) Finding more general concepts
in SNOMED CT*

Methods Intuition

- ◆ HPO phenotype concepts are often more specialized than corresponding concepts in SNOMED CT
 - By removing modifiers in a controlled fashion, we map demodified phenotype terms to SNOMED CT
- ◆ Demodified HPO terms can be associated with SNOMED CT pre-coordinated concepts
- ◆ Linguistically-motivated approach (shallow parsing)



Example

Lexico-syntactic analysis

◆ **Multicystic**_{mod} **kidney**_{mod} **dysplasia**_{head}

Remove modifiers

◆ 1 modifier: **Multicystic dysplasia**

◆ 1 modifier: **kidney dysplasia**

◆ 2 modifiers: **dysplasia**

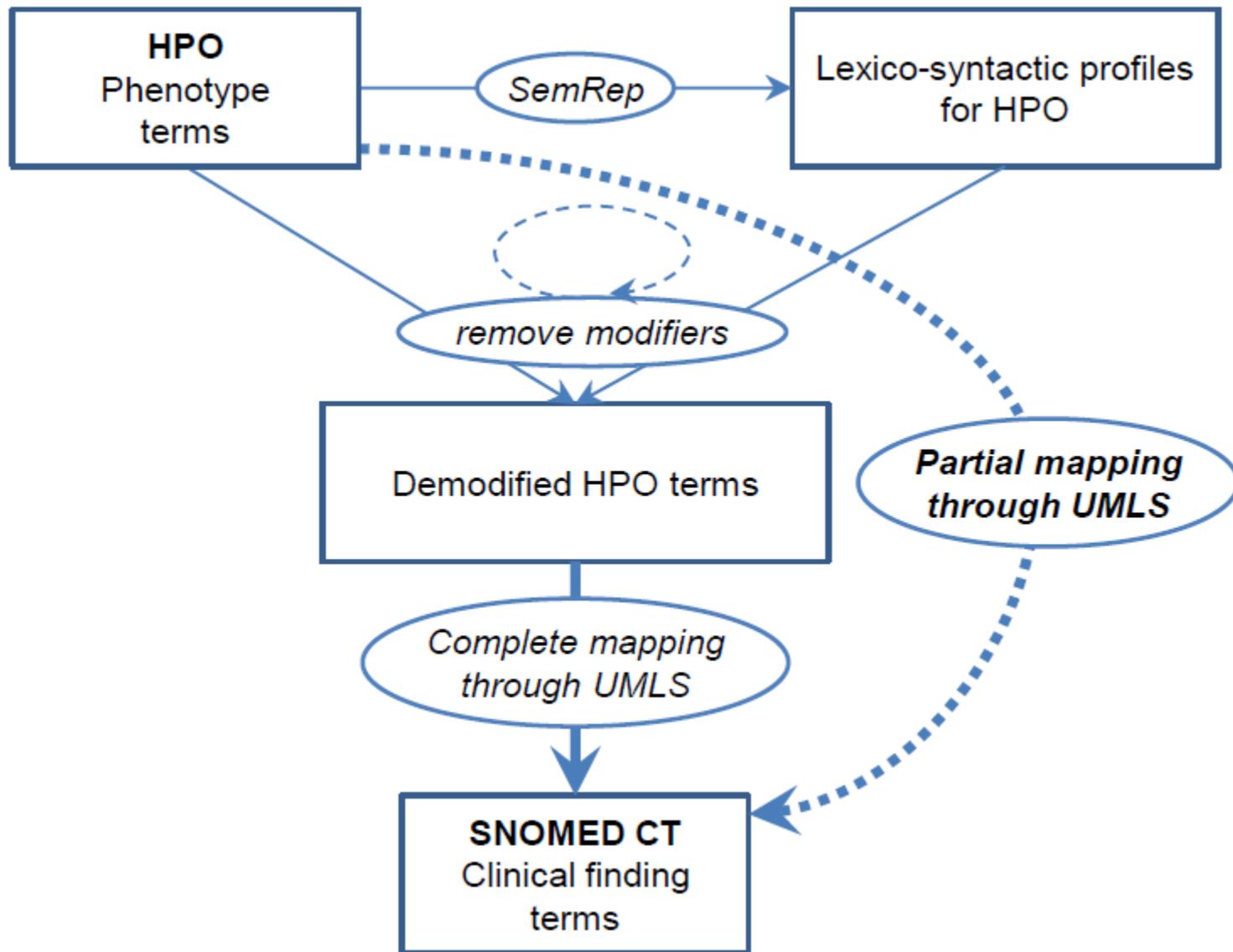
Map demodified terms to UMLS/SNOMED CT

◆ **Multicystic dysplasia** → no mapping

◆ **kidney dysplasia** → **Renal dysplasia**

◆ **dysplasia** → **[Dysplasia]**





Frequent lexico-syntactic profiles

| Lexico-syntactic profile | Freq. | % | Mapping | % |
|----------------------------|-------|----|---------|----|
| [MOD – HEAD] | 4722 | 28 | 2898 | 61 |
| [MOD – MOD – HEAD] | 2416 | 15 | 1095 | 45 |
| [HEAD] | 2294 | 14 | 1989 | 87 |
| [HEAD] [PREP – DET – HEAD] | 767 | 5 | 163 | 21 |
| [MOD – MOD – MOD – HEAD] | 549 | 3 | 149 | 27 |
| [HEAD] [PREP – MOD – HEAD] | 432 | 3 | 11 | 3 |
| [MOD – HEAD] [PREP – HEAD] | 392 | 2 | 151 | 39 |
| [HEAD] [PREP – HEAD] | 383 | 2 | 83 | 22 |

Frequent modifiers and head nouns

◆ Modifiers

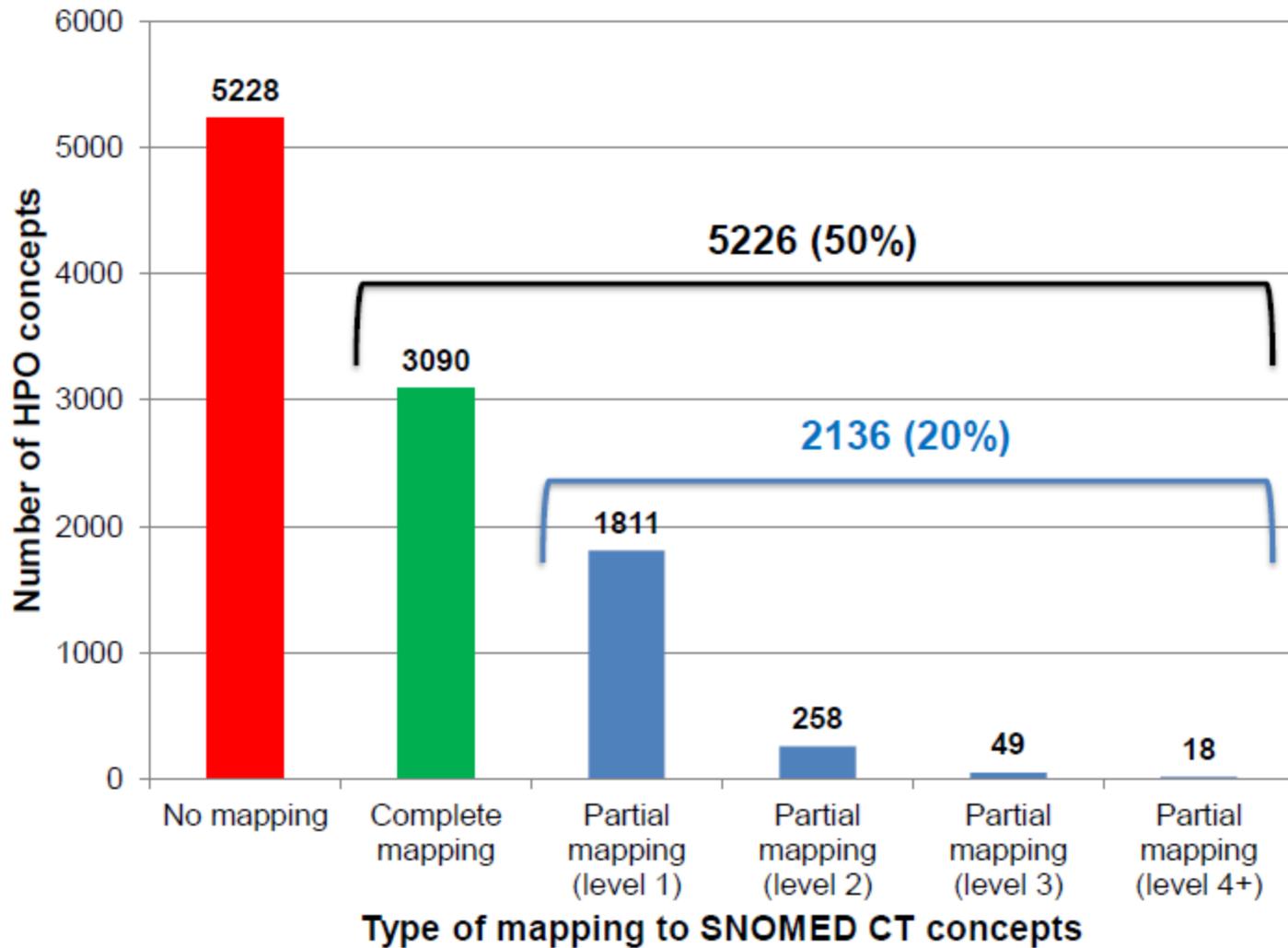
- *Abnormal*
- *Increased*
- *Decreased*
- *Absent*

◆ Head nouns

- *Hypoplasia*
- *Abnormality*
- *Atrophy*
- *Weakness*
- *Ossification*



Lexical mappings between HPO and SNOMED CT



Summary

- ◆ We found partial mappings for ~2000 HPO concepts for which no pre-coordinated mapping exists
- ◆ In complement to the ~3000 HPO concepts for which there is a pre-coordinated mapping to SNOMED CT

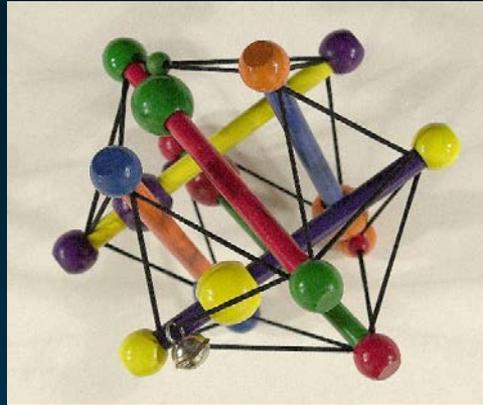
Ontological issues

- ◆ Anatomical structures as phenotypes
 - Small kidney vs. Hypoplasia of kidney
 - Small kidney isa Kidney (anatomical structure)
 - Hypoplasia of kidney isa Hypoplasia (clinical finding)
 - Ductus arteriosus
 - Syn. For Patent ductus arteriosus (condition)
 - Ductus arteriosus is a normal anatomical structure in the fetus
 - Its persistence after birth is abnormal

Conclusions

- ◆ Need for greater interoperability between terminologies used for research and for healthcare
- ◆ Need for greater collaboration between the developers of OBO-style ontologies and clinical terminologies
- ◆ HPO being integrated into the UMLS
 - Increase the coverage of phenotypes in UMLS
 - Facilitate the development and maintenance of cross-references in HPO





Medical Ontology Research

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