Outline

◆ Introduction to biomedical terminologies through an example
◆ “High-Impact” Biomedical Ontologies
  ● Structural perspective
◆ Biomedical Ontologies “in Action”
  ● Functional perspective
◆ Terminology research at NLM
Biomedical ontology in action
Part 1

Introduction to biomedical terminologies through an example
Addison's disease is a rare endocrine disorder. Addison's disease occurs when the adrenal glands do not produce enough of the hormone cortisol. For this reason, the disease is sometimes called chronic adrenal insufficiency, or hypocortisolism.
Adrenal insufficiency Clinical variants

- **Primary / Secondary**
  - Primary: lesion of the adrenal glands themselves
  - Secondary: inadequate secretion of ACTH by the pituitary gland
- **Acute / Chronic**
- **Isolated / Polyendocrine deficiency syndrome**
Addison’s disease: Symptoms

◆ Fatigue
◆ Weakness
◆ Low blood pressure
◆ Pigmentation of the skin (exposed and non-exposed parts of the body)
◆ …
AD in medical vocabularies

**Synonyms: different terms**
- Addisonian syndrome
- Bronzed disease
- Addison melanoderma
- Asthenia pigmentosa
- Primary adrenal deficiency
- Primary adrenal insufficiency
- Primary adrenocortical insufficiency
- Chronic adrenocortical insufficiency

**Contexts: different hierarchies**
- eponym
- symptoms
- clinical
- variants
Medical Subject Headings

**MeSH Tree Structures**

**Endocrine System Diseases [C19]**
- **Adrenal Gland Diseases [C19.053]**
  - **Adrenal Insufficiency [C19.053.500]**
    - ► **Addison Disease [C19.053.500.263]**
    - **Adrenoleukodystrophy [C19.053.500.270]**
    - **Hypoaldosteronism [C19.053.500.480]**
    - **Waterhouse-Friderichsen Syndrome [C19.053.500.740]**

**Immune System Diseases [C20]**
- **Autoimmune Diseases [C20.111]**
  - ► **Addison Disease [C20.111.163]**
    - **Anemia, Hemolytic, Autoimmune [C20.111.175]**
    - **Anti-Glomerular Basement Membrane Disease [C20.111.190]**
    - **Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis [C20.111.193]** +
    - **Antiphospholipid Syndrome [C20.111.197]**
    - **Arthritis, Juvenile [C20.111.198]**
    - **Arthritis, Rheumatoid [C20.111.199]** +
    - **Autoimmune Diseases of the Nervous System [C20.111.258]** +

[...]

Lister Hill National Center for Biomedical Communications
SNOMED CT

Concept Details

Summary

Parents
- Abdominal organ finding (finding)
- Disorder of abdomen (disorder)
- Disorder of endocrine system (disorder)
- Disorder of adrenal gland (disorder)
- Hypoadrenalism (disorder)
- Adrenal hypofunction (disorder)
- Disorder of adrenal gland (disorder)
- Disorder of adrenal cortex (disorder)
- Adrenal cortical hypofunction (disorder)

Addison’s disease (disorder)  ⭐
SCTID: 363732003
363732003 | Addison’s disease (disorder) |
Addison disease
Addison’s disease
Addison’s disease (disorder)

Children (4)
- Addison’s disease due to autoimmunity (disorder)
- Addison’s disease with adrenoleucodystrophy (disorder)
- Polyglandular autoimmune syndrome, type 1 (disorder)
- Tuberculous Addison’s disease (disorder)
“High-Impact” Biomedical Ontologies

A Structural Perspective
Overview

◆ Structural perspective
  ● What are they (vs. what are they for)?

◆ “High-impact” biomedical ontologies [J. Cimino, YBMI 2006]
  ● International Classification of Diseases (ICD)
  ● Logical Observation Identifiers, Names and Codes (LOINC)
  ● SNOMED Clinical Terms
  ● Foundational Model of Anatomy
  ● Gene Ontology
  ● RxNorm
  ● Medical Subject Headings (MeSH)
  ● NCI Thesaurus
  ● Unified Medical Language System (UMLS)
International Classification of Diseases
ICD Characteristics (1)

- Current version: ICD-10 (2017)
  - Annual updates
- Type: Classification
- Domain: Disorders
- Developer: World Health Organization (WHO)
- Funding: WHO
- Publicly available: Yes
- Used for: Mortality and morbidity statistics worldwide
- URL: http://www.who.int/classifications/icd/en/
ICD Characteristics (2)

◆ Number of
  ● Concepts: 12,320 (ICD-10, 2004)
  ● Terms: 1 per concept (tabular)

◆ Major organizing principles:
  ● Tree (single inheritance hierarchy)
  ● No explicit classification criteria
    - Idiosyncratic inclusion/exclusion mechanism
  ● .8 slots for Not elsewhere classified (NEC)
  ● .9 slots for Not otherwise specified (NOS)

◆ Specific coding rules

◆ Distribution: Proprietary format
ICD Top level

ICD-10 Version: 2016

- I Certain infectious and parasitic diseases
- II Neoplasms
- III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
- IV Endocrine, nutritional and metabolic diseases
- V Mental and behavioural disorders
- VI Diseases of the nervous system
- VII Diseases of the eye and adnexa
- VIII Diseases of the ear and mastoid process
- IX Diseases of the circulatory system
- X Diseases of the respiratory system
- XI Diseases of the digestive system
- XII Diseases of the skin and subcutaneous tissue
- XIII Diseases of the musculoskeletal system and connective tissue
- XIV Diseases of the genitourinary system
- XV Pregnancy, childbirth and the puerperium
- XVI Certain conditions originating in the perinatal period
- XVII Congenital malformations, deformations and chromosomal abnormalities
- XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
- XIX Injury, poisoning and certain other consequences of external causes
- XX External causes of morbidity and mortality
- XXI Factors influencing health status and contact with health services
- XXII Codes for special purposes

http://apps.who.int/classifications/icd10/browse/
ICD Example

- Idiosyncratic inclusion/exclusion criteria

![ICD Example Diagram](image-url)

*Type 1 diabetes mellitus*

**Incl.:** diabetes mellitus:
- brittle
- juvenile-onset
- ketosis-prone

**Excl.:** diabetes mellitus (in):
- malnutrition-related ([E12.-](#))
- neonatal ([P70.2](#))
- pregnancy, childbirth and the puerperium ([O24.-](#))

glycosuria:
- NOS ([R81](#))
- renal ([E74.8](#))

impaired glucose tolerance ([R73.0](#))

postsurgical hypoinsulinaemia ([E89.1](#))
ICD Example

- *Not elsewhere classified* (NEC)
- *Not otherwise specified* (NOS)

**Example: Cystic Fibrosis**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E84</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>E84.0</td>
<td>Cystic fibrosis with pulmonary manifestations</td>
</tr>
<tr>
<td>E84.1</td>
<td>Cystic fibrosis with intestinal manifestations</td>
</tr>
<tr>
<td></td>
<td>Distal intestinal obstruction syndrome</td>
</tr>
<tr>
<td></td>
<td>Meconium ileus in cystic fibrosis† (P75*)</td>
</tr>
<tr>
<td>E84.8</td>
<td>Cystic fibrosis with other manifestations</td>
</tr>
<tr>
<td>E84.9</td>
<td>Cystic fibrosis, unspecified</td>
</tr>
</tbody>
</table>

*Incl.:* mucoviscidosis

*Excl.:* meconium obstruction (ileus) in cases where cystic fibrosis is known not to be present (P76.0)
ICD-10-CM

- Derived from: ICD-10
  - Finer-grained (both clinically and administratively)
- Type: Classification
  - 92,042 codes (2015)
  - Terms: 1.2 per concept
- Domain: Disorders
- Developer: National Center for Health Statistics (CDC/NCHS)
- Funding: U.S. Government
- Publicly available: Yes
- Used for: Billing
- URL: http://www.cdc.gov/nchs/icd/icd10cm.htm
ICD-10 vs. ICD-10-CM

**E72** Other disorders of amino-acid metabolism

**Excl.** abnormal findings without manifest disease (R29.0)
- disorders of:
  - aromatic amino-acid metabolism (E70.-)
  - branched-chain amino-acid metabolism (E71.-)
  - fatty-acid metabolism (E71.3)
  - purine and pyrimidine metabolism (E79.-)
  - gout (M10.-)

**E72.0** Disorders of amino-acid transport

- Cystine storage disease† (N29.8*)
- Cystinosis
- Cystinuria
- Fanconi(-de Toni)(-Debré) syndrome
- Hartnup disease
- Lowe syndrome

**Excl.** disorders of tryptophan metabolism (E70.8)

**E72.00** Disorders of amino-acid transport, unspecified

**E72.01** Cystinuria

**E72.02** Hartnup's disease

**E72.03** Lowe's syndrome
  - Use additional code for associated glaucoma (H42)

**E72.04** Cystinosis
  - Fanconi (-de Toni) (-Debré) syndrome with cystinosis
  - Excludes: Fanconi (-de Toni) (-Debré) syndrome without cystinosis

**E72.09** Other disorders of amino-acid transport
  - Fanconi (-de Toni) (-Debré) syndrome, unspecified
ICD-10 vs. ICD-10-CM

**W58** Bitten or struck by crocodile or alligator

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>W58</td>
<td>Contact with crocodile or alligator</td>
</tr>
<tr>
<td>W58.0</td>
<td>Contact with alligator</td>
</tr>
<tr>
<td>W58.01</td>
<td>Bitten by alligator</td>
</tr>
<tr>
<td>W58.02</td>
<td>Struck by alligator</td>
</tr>
<tr>
<td>W58.03</td>
<td>Crushed by alligator</td>
</tr>
<tr>
<td>W58.09</td>
<td>Other contact with alligator</td>
</tr>
<tr>
<td>W58.1</td>
<td>Contact with crocodile</td>
</tr>
<tr>
<td>W58.11</td>
<td>Bitten by crocodile</td>
</tr>
<tr>
<td>W58.12</td>
<td>Struck by crocodile</td>
</tr>
<tr>
<td>W58.13</td>
<td>Crushed by crocodile</td>
</tr>
<tr>
<td>W58.19</td>
<td>Other contact with crocodile</td>
</tr>
</tbody>
</table>

- W58.01A Bitten by alligator, initial encounter
- W58.01D Bitten by alligator, subsequent encounter
- W58.01S Bitten by alligator, sequela
Logical Observation Identifiers, Names and Codes (LOINC)
LOINC Characteristics (1)

- **Current version:** 2.61 (June 2017)
  - 2 annual releases
- **Type:** Controlled terminology*
- **Domain:** Laboratory and clinical observations
- **Developer:** Regenstrief Institute
- **Funding:** NLM and other sources
- **Publicly available:** Yes
- **Used for:** information exchange
- **URL:** [https://loinc.org/](https://loinc.org/)
LOINC Characteristics (2)

◆ Number of
  ● Concepts: 73,958 active codes (2.52, June 2015)
  ● Terms: 1 per concept (“long name”)

◆ Major organizing principles:
  ● No hierarchical structure among the main codes
  ● 6 axes
    ■ Component (analyte [+ challenge] [+ adjustments])
    ■ Property
    ■ Timing
    ■ System
    ■ Scale
    ■ [Method]

◆ Distribution: proprietary database format
**LOINC Example**

- *Sodium [Moles/volume] in Serum or Plasma*
  [the molar concentration of sodium is measured in the plasma (or serum), with quantitative result]

<table>
<thead>
<tr>
<th>Axis</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component</td>
<td>Sodium</td>
</tr>
<tr>
<td>Property</td>
<td>SCnc – Substance Concentration (per volume)</td>
</tr>
<tr>
<td>Timing</td>
<td>Pt – Point in time (Random)</td>
</tr>
<tr>
<td>System</td>
<td>Ser/Plas – Serum or Plasma</td>
</tr>
<tr>
<td>Scale</td>
<td>Qn – Quantitative</td>
</tr>
<tr>
<td>Method</td>
<td>--</td>
</tr>
</tbody>
</table>
2951-2  Sodium [Moles/volume] in Serum or Plasma

NAME

Fully-Specified Name:              Sodium

Component      Property | Time  | System     | Scale | Method

PART DEFINITION/DESCRIPTION(S)

Sodium is an essential nutrient that regulates blood volume, blood pressure, osmotic equilibrium and electrolyte balance. Sodium chloride is the principal source of sodium in the diet, and is used for seasoning and as a preservative. Increased levels of sodium intake can cause hypertension and reportedly leads to 7.6 million premature deaths worldwide. Sodium is also important in neuron function and osmoregulation between cells and the extracellular fluid.

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BASIC ATTRIBUTES

Class/Type: CHEM/Lab
CDISC Lab Test: Y
Common Lab Results Rank: #5
Common SI Lab Results Rank: #5
Common Orders Rank: #107
Last Updated in Version: 2.34
Order vs. Obs.: Both
Status: Active

EXAMPLE UNITS

Unit  Source Type
mmol/L  EXAMPLE UCUM UNITS
mmol/L  REGENSTrief
mmol/L  eCHN

UNITS AND RANGE

Range  Units Type
mmol/L [136,145]
SNOMED Clinical Terms
SNOMED CT Characteristics (1)

- Current version: July 31, 2017
  - 2 annual releases
- Type: Reference terminology / ontology
- Domain: Clinical medicine
- Developer: IHTSDO
- Funding: IHTSDO member countries
- Publicly available: Yes*
- Used for: clinical documentation, information exchange, analytics
- URL: http://www.ihtsdo.org/
SNOMED CT Characteristics (2)

◆ Number of
  - Concepts: 320,912 active concepts (Sept. 2016)
  - Terms: 2.6 per concept (“descriptions”)

◆ Major organizing principles:
  - Polyhierarchy
  - Rich set of associative relationships
  - Logical definitions (incomplete: many primitives)
  - Built using description logics (EL++)

◆ Distribution: RF2 (proprietary)
SNOMED CT Top level

- SNOMED CT Concept
  - Body structure (body structure)
  - Clinical finding (finding)
  - Environment or geographical location (environment / location)
  - Event (event)
  - Observable entity (observable entity)
  - Organism (organism)
  - Pharmaceutical / biologic product (product)
  - Physical force (physical force)
  - Physical object (physical object)
  - Procedure (procedure)
  - Qualifier value (qualifier value)
  - Record artifact (record artifact)
  - Situation with explicit context (situation)
  - SNOMED CT Model Component (metadata)
  - Social context (social concept)
  - Special concept (special concept)
  - Specimen (specimen)
  - Staging and scales (staging scale)
  - Substance (substance)
SNOMED CT Example

Parents

- Operation on appendix (procedure)
- Partial excision of large intestine (procedure)

Appendectomy (procedure)

SCTID: 80146002

- Appendectomy
- Excision of appendix
- Appendicectomy
- Appendectomy (procedure)

Procedure site - Direct → Appendix structure
Method → Excision - action

Children (8)

- Appendectomy with drainage (procedure)
- Emergency appendectomy (procedure)
- Excision of appendiceal stump (procedure)
- Excision of ruptured appendix by open approach (procedure)
- Incidental appendectomy (procedure)
- Interval appendectomy (procedure)
- Laparoscopic appendectomy (procedure)
- Non-emergency appendectomy (procedure)
SNOMED CT Example

80146002
Appendectomy (procedure)

27010001
Partial excision of large intestine (procedure)

8613002
Operation on appendix (procedure)

405813007
Procedure site - Direct (attribute)

66754008
Appendix structure (body structure)

260686004
Method (attribute)

129304002
Excision - action (qualifier value)
RxNorm Characteristics (1)

- Current version: August 2017
  - Monthly releases (+weekly updates)
- Type: Controlled terminology
- Domain: Drug names
- Developer: NLM
- Funding: NLM
- Publicly available: Yes*
- Used for: e-prescribing, information exchange, analytics
- URL: http://www.nlm.nih.gov/research/umls/rxnorm/
RxNorm Characteristics (2)

- **Number of**
  - Concepts: 117,774 (March 2016)
  - Terms: 1.5 per concept

- **Major organizing principles:**
  - Generic vs. brand
  - Ingredient + Strength + Dose form
  - No hierarchical structure; rich graph of associative relations
  - Integrates all major US drug information sources
  - No clinical information

- **Distribution:** similar to UMLS RRF format
RxNorm Normalized form

- **Strength**: 4mg/ml
- **Ingredient**: Fluoxetine
- **Dose form**: Oral Solution

Semantic clinical drug component

Semantic clinical drug form

Semantic clinical drug
RxNorm Example

- **Ingredient**: Azithromycin
- **C. Drug Comp.**: Azithromycin 250 MG
- **C. Drug Form**: Azithromycin Oral Tablet
- **C. Drug**: Azithromycin 250 MG Oral Tablet
- **B. Drug Comp.**: Azithromycin 250 MG
- **B. Drug Form**: Azithromycin Oral Tablet [Zithromax]
- **B. Drug**: Zithromax 250 MG Oral Tablet
- **B. Pack**: Z-PAK
- **G. Pack**: {6 (Azithromycin 250 MG Oral Tablet) } Pack

*Example for Azithromycin 250 MG Oral Tablet*
Overview

- Functional perspective
  - What are they for (vs. what are they)?

- “High-impact” biomedical ontologies

- 3 major categories of use
  - Knowledge management
    - Annotating data and resources
    - Mapping across biomedical ontologies
  - Decision support and analytics
    - Value sets and clinical quality measures
  - Data integration, exchange and semantic interoperability
    - Common data models
    - Fast Healthcare Interoperability Resources (FHIR)

[Bodenreider, YBMI 2008]
Knowledge management

Mapping across biomedical ontologies
Terminology integration systems

- Terminology integration systems (UMLS, RxNorm) help bridge across vocabularies

- Uses
  - Information integration
  - Ontology alignment
  - Medication reconciliation
Integrating subdomains

- Clinical repositories
- Genetic knowledge bases
  - Genetic annotations
  - Genome annotations
  - Biomedical literature
- Model organisms
- Other subdomains
  - SNOMED CT
  - OMIM
  - MeSH
  - GO
  - FMA
  - Anatomy
  - NCBI Taxonomy
  - UMLS
Integrating subdomains

- Clinical repositories
- Genetic knowledge bases
- Biomedical literature
- Genome annotations
- Anatomy
- Model organisms
- Other subdomains
Trans-namespace integration

Clinical repositories

Genetic knowledge bases

Biomedical literature

Addison Disease (D000224)

NCBI Taxonomy

Model organisms

Anatomy

FMA

GO

OMIM

SNOMED CT

UMLS C0001403

Addison's disease (363732003)

Other subdomains
UMLS Source Vocabularies

- 153 families of source vocabularies
  - Not counting translations
- 25 languages
- Broad coverage of biomedicine
  - 9.8M names (normalized)
  - 3.2M concepts
  - ~13M relations among concepts
- Common presentation
Metathesaurus Basic organization

◆ Concepts
  ● Synonymous terms are clustered into a concept
  ● Properties are attached to concepts, e.g.,
    ▪ Unique identifier
    ▪ Definition

◆ Relations
  ● Concepts are related to other concepts
  ● Properties are attached to relations, e.g.,
    ▪ Type of relationship
    ▪ Source
Data integration, exchange and semantic interoperability

Common data models
Clinical data models

- Used in clinical data warehouses
  - Oriented towards analytics
  - Different from the transactional data models of EHR systems
  - Used to normalize data across EHR systems
- Multiple “common” data models
  - OMOP
  - i2b2
  - PCORnet
  - Sentinel
  - CDISC
OMOP

- OMOP – Observational Medical Outcomes Partnership

Diagram showing data transformation from multiple sources to a common data model and analysis.
OMOP Common Data Model

Standardized clinical data:
- Person
  - Observation_period
  - Specimen
  - Death
  - Visit_occurrence
  - Procedure_occurrence
  - Drug_exposure
  - Device_exposure
  - Condition_occurrence
  - Measurement
  - Note
  - Observation

Standardized health system data:
- Location
- Care_site
- Provider
- Payer_plan_period
- Visit_cost
- Procedure_cost
- Drug_cost
- Device_cost

Standardized meta-data:
- CDM_source

Standardized vocabulary:
- Concept
- Vocabulary
- Concept_relationship
- Relationship
- Concept_synonym
- Concept_ancestor
- Source_to_concept_map
- Drug_strength
- Cohort_definition

Standardized derived elements:
- Cohort
- Drug_era
- Dose_era
- Condition_era

Courtesy of Christian Reich
• Standardized Clinical Data Tables
  • PERSON
  • OBSERVATION_PERIOD
  • SPECIMEN
  • DEATH
  • VISIT_OCCURRENCE
  • PROCEDURE_OCCURRENCE
  • DRUG_EXPOSURE
  • DEVICE_EXPOSURE
  • CONDITION_OCCURRENCE
  • MEASUREMENT
  • NOTE
  • NOTE_NLP (V5.2)
  • OBSERVATION
  • FACT_RELATIONSHIP
• Standardized Health System Data Tables
  • LOCATION
  • CARE_SITE
  • PROVIDER
• Standardized Health Economics Data Tables
  • PAYER_PLAN_PERIOD
  • COST (V5.0.1)
  • VISIT_COST - removed
  • PROCEDURE_COST - removed
  • DRUG_COST - removed
  • DEVICE_COST - removed
• Standardized Derived Elements
  • COHORT
  • COHORT_ATTRIBUTE
  • DRUG_ERA
  • DOSE_ERA
  • CONDITION_ERA

• Standardized Vocabularies
  • CONCEPT
  • VOCABULARY
  • DOMAIN
  • CONCEPT_CLASS
  • CONCEPT_RELATIONSHIP
  • RELATIONSHIP
  • CONCEPT_SYNONYM
  • CONCEPT_ANCESTOR
  • SOURCE_TO_CONCEPT_MAP
  • DRUG_STRENGTH
  • COHORT_DEFINITION
  • ATTRIBUTE_DEFINITION
• Standardized meta-data
  • CDM_SOURCE
Common data models in action

Characterizing treatment pathways at scale using the OHDSI network

George Hripcsak, Patrick B. Ryan, Jon D. Duke, Nigam H. Shah, Rae Woong Park, Vojtech Huser, Marc A. Suchard, Martijn J. Schuemie, Frank J. DeFalco, Adler Perotte, Juan M. Banda, Christian G. Reich, Lisa M. Schilling, Michael E. Matheny, Daniella Meeker, Nicole Pratt, and David Madigan

www.pnas.org/cgi/doi/10.1073/pnas.1510502113

PNAS | July 5, 2016 | vol. 113 | no. 27 | 7329–7336
A Diabetes

- Metformin
- Pioglitazone
- Sitagliptin
- Glipizide
- Glimepiride
- Gliclazide
- Glyburide
- Rosiglitazone
- Insulin, Glargine, Human
- Exenatide
- Insulin, Aspart, Human
- Liraglutide
- Saxagliptin
- Insulin, Lispro, Human
- Glucose
- Insulin, Isophane, Human
Biomedical ontology in action
Part 4

Terminology research at NLM

Examples of terminology-related projects
Quality assurance in SNOMED CT

Non-lattice subgraph

Suggested remediation

Duodenal ulcer with perforation AND obstruction

Chronic duodenal ulcer with perforation AND obstruction
Coverage of phenotypes

- UMLS
- SNOMED CT
- Consumer Health Vocabulary
- MedDRA
- MeSH
- NCI thesaurus
- ICD-10-CM
- ICD-9-CM
- ICD-10
- OMIM
- MedlinePlus

% HPO concepts covered
% HPO concepts with Cross-references
Identifying terms for Fetal Medicine
Suitability of drug classification systems

Proportion of claims vs. Proportion of classes for different classification systems:
- VAC
- ATC
- EPC
- MoA
- Chem
- PE
Evolution of the UMLS Metathesaurus

- Physiology
- Phenomena
- Organizations
- Occupations
- Objects
- Geographic Areas
- Genes & Molecular Sequences
- Disorders
- Devices
- Concepts & Ideas
- Living Beings
- Chemicals & Drugs
- Procedures
- Anatomy
- Activities & Behaviors

Timeline from 2002 to 2015
References  Review articles


Additional references


Medical Ontology Research

Contact: olivier@nlm.nih.gov
Web: https://mor.nlm.nih.gov

Olivier Bodenreider
Lister Hill National Center for Biomedical Communications
Bethesda, Maryland - USA

U.S. National Library of Medicine