The Disease Ontology Consortium (DOC) seeks to create a defined, logically structured vocabulary representing the domain of human disease. This unifying structure will provide a common basis for describing disease manifestation and etiology. DO will enable the integration of disease knowledge with datasets from human and model organisms.
Overview

- Recapitulate the R01 specific aims
- Current status of DO
  - Source/external vocabularies
- DO R01 specific aims
- DO resources

The specific aims of this project are to:

(i) Develop the core Disease Ontology (DO), organized by etiological disease category: disease of anatomical entity, disease of behavior, biological process, environmental origin, infectious agent and syndromes;

(ii) Develop community engagement activities and hold annual DO design and annotation workshops;

(iii) Build evidence-based mappings between phenotype (symptoms and findings available in the Human Phenotype Ontology and Symptom Ontology) and disease;

(iv) Define and validate mappings between DO and other disease relevant vocabularies including UMLS, MeSH, ICD, the NCI thesaurus, OMIM entries and SNOMED;

(v) Institute a formalized validation process involving an ongoing measure of DO integration metrics to assess the DO degree of integration, DO impact factor, and to identify novel terms to add to DO in an ongoing basis;

(vi) Develop additional scientific use cases to further drive design and validation of DO based on community input and engagement of physician scientists.
Disease Ontology Version 3, r21

- Is an OBO Foundry ontology for the Integration of Biomedical Data
- Is inclusive of genetic, environmental and infectious diseases
- Is semantically organized and computable
- Has 12,564 terms and 21,024 branches
- Has a maximum depth of 13 and is ‘node heavy in the middle’, meaning many nodes are in the 6-10 node deep range

DO Mappings

<table>
<thead>
<tr>
<th>External Reference</th>
<th>Unique xref:DOID Mappings</th>
<th>Unique xrefs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-9</td>
<td>186278</td>
<td>10109</td>
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<td>UMLS_SNOM DCT_2005_01_31_AUI</td>
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<tr>
<td>UMLS_ST</td>
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<tr>
<td>SNOMEDCT_2005_01_31</td>
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<tr>
<td>NCI2004_11_17</td>
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</tr>
<tr>
<td>UMLS_CSP2004_AUI</td>
<td>2269</td>
<td>2269</td>
</tr>
</tbody>
</table>

Unique mappings in DO to ICD-9, SNOMED CT, NCI metathesaurus (EVS), MESH, UMLS and MESH terms. The compound reference names, such as UMLS_SNOMEDCT_2005_01_31_AUI show the release of UMLS used to perform the SNOMED CT mappings. All existing mappings are to exact or closest concept match between a DO term and the external reference source.
Medical Vocabularies in DO

- UMLS Metathesaurus and Semantic Network
  - 5 million concepts and a million terms
- MeSH (Medical Subject Headings)
  - Shallow graph with no direct disease mapping
- NCI Thesaurus (National Cancer Institute)
  - Broad coverage, not deep outside cancer domain
  - No direct mapping to ICD9
- SNOMED (Systemized Nomenclature of Medicine)
  - Large, broad but duplicate concepts in different contexts
  - Restrictive, only free for research in the US
- ICD9/ICD10 (International Classification of Disease)
  - Poor coverage, few high level terms, confused terms

DO Subversion Repository
How to obtain DO - Guidance from the DO Wiki

Downloading DO - latest version, ongoing development

To get the latest version, choose one of the following methods:

- To download the Disease Ontology using the subversion command line:
  
  ```
  svn checkout https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/diseaseontology
  ```

- If you download it from the command line, you can look at the full commit history:
  
  ```
  svn log HumanDO.obo
  ```

- If you download it from the command line, you can also compare changes between the current version and any previous version. Depending on how far back in time you look and the number of changes, this command can take several minutes to return a result:
  
  ```
  svn diff -r 213 HumanDO.obo
  ```

- Get it from the disease ontology subversion web interface
  
  https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/

- Download it from the OBO Foundry. This version may lag from the current sourceforge release.
  
  http://www.obofoundry.org/go/bo/1/0/19/82/disease_ontology.rdf

- The current focus of the Disease Ontology is to improve the ontological soundness of the ontology, such as removal of plural terms and removal of upper case terms. Additionally, we will be working to add a significant number of definitions to the Disease Ontology.
Also see: https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/HumanDO.obo

DO Subversion Repository

Revision 235 - Directory Listing
Modified Thu Jan 14 22:23:47 2010 UTC (6 hours, 49 minutes ago) by snadendla
 Made some modifications in the definitions

Revision 234 - Directory Listing
Modified Thu Jan 14 22:18:03 2010 UTC (6 hours, 55 minutes ago) by laronhughes
 merged, edited, or rearranged terms that mention "unspecified"

Revision 233 - Directory Listing
Modified Thu Jan 14 20:53:39 2010 UTC (8 hours, 19 minutes ago) by snadendla
 Made central nervous system parasitic infection a child of parasitic infection

Rev $ log
r235 | snadendla | 2010-01-14 16:23:47 -0600 (Thu, 14 Jan 2010) | 1 line
 Made some modifications in the definitions

r234 | laronhughes | 2010-01-14 16:18:03 -0600 (Thu, 14 Jan 2010) | 1 line
 merged, edited, or rearranged terms that mention "unspecified"

r233 | snadendla | 2010-01-14 14:53:39 -0600 (Thu, 14 Jan 2010) | 1 line
 Made central nervous system parasitic infection a child of parasitic infection

r232 | laronhughes | 2010-01-14 14:50:11 -0600 (Thu, 14 Jan 2010) | 1 line
 merged, edited, or rearranged terms that mention "other/Other"

r231 | snadendla | 2010-01-14 10:28:10 -0600 (Thu, 14 Jan 2010) | 1 line
 Merged obstructive chronic bronchitis with acute bronchitis-with obstructive chronic bronchitis

r230 | snadendla | 2010-01-13 15:56:53 -0600 (Wed, 13 Jan 2010) | 1 line
 Merged Tuberculosis+pregnancy with tuberculosis

r229 | snadendla | 2010-01-13 14:54:14 -0600 (Wed, 13 Jan 2010) | 1 line
 Merged cystic fibrosis with combined manifestations with cystic fibrosis
DO Subversion Repository

$ svn log
r228 | laronhughes | 2010-01-13 11:57:05 -0600 (Wed, 13 Jan 2010) | 1 line
merged more terms that mention "with"

r227 | mchibuco | 2010-01-13 11:35:27 -0600 (Wed, 13 Jan 2010) | 1 line
cleaned up viral exanthem terms including cowpox and paravaccinia et cetera

r226 | mchibuco | 2010-01-13 11:26:30 -0600 (Wed, 13 Jan 2010) | 1 line
cleaned up chickenpos (varicella) with unspecified and other complications terms

r225 | mchibuco | 2010-01-13 11:21:19 -0600 (Wed, 13 Jan 2010) | 1 line
measles and rubella cleanup of unnecessary terms, i.e. without or other

r224 | mchibuco | 2010-01-13 11:00:48 -0600 (Wed, 13 Jan 2010) | 1 line
more herpes (simplex and zoster) cleanup

r223 | mchibuco | 2010-01-13 10:27:48 -0600 (Wed, 13 Jan 2010) | 1 line
ocular herpes simplex

r222 | snadendla | 2010-01-13 10:05:09 -0600 (Wed, 13 Jan 2010) | 1 line
Merged herpes simplex without mention of complication

Also see https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/HumanDO.obo

DO Subversion Repository

$ svn log
r221 | jynn_schriml | 2010-01-12 18:24:24 -0600 (Tue, 12 Jan 2010) | 1 line
updating DO removing obsolete connections, fixing definitions

r220 | laronhughes | 2010-01-12 14:51:56 -0600 (Tue, 12 Jan 2010) | 1 line
merged more terms that mention "with"

r219 | snadendla | 2010-01-12 13:30:47 -0600 (Tue, 12 Jan 2010) | 1 line
Modified some definitions

r218 | snadendla | 2010-01-12 09:16:27 -0600 (Tue, 12 Jan 2010) | 1 line
Deleted an obsolete term as a parent of extrinsic allergic alveolitis

r217 | snadendla | 2010-01-11 15:33:36 -0600 (Mon, 11 Jan 2010) | 1 line
Merged non-neoplastic lung disorder with lung disease

r216 | snadendla | 2010-01-11 09:31:28 -0600 (Mon, 11 Jan 2010) | 1 line
Modified the definition of pertussis

r215 | laronhughes | 2010-01-08 14:57:36 -0600 (Fri, 08 Jan 2010) | 1 line
merge terms that mention "without" and "within", along with some terms that mention "with"

Also see https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/HumanDO.obo
DO Subversion Repository

$ svn log

r214 | snadendla | 2010-01-08 14:45:19 -0600 (Fri, 08 Jan 2010) | 1 line
Trying to empty non-neoplastic lung disorder node to merge it with its parent later
r213 | snadendla | 2010-01-08 13:28:07 -0600 (Fri, 08 Jan 2010) | 1 line
Corrected bronchiolitis obliterans organizing pneumonia parentage
r212 | snadendla | 2010-01-07 14:39:47 -0600 (Thu, 07 Jan 2010) | 1 line
Corrected bronchiolitis obliterans parentage
r211 | laronhughes | 2010-01-07 14:11:55 -0600 (Thu, 07 Jan 2010) | 1 line
merge terms with "without mention of" to their respective parent terms
r210 | snadendla | 2010-01-06 15:46:34 -0600 (Wed, 06 Jan 2010) | 1 line
Merged abscess of lung and mediastinum with mediastinum disease
r209 | snadendla | 2010-01-06 14:27:57 -0600 (Wed, 06 Jan 2010) | 1 line
Merged lung abscess with lung disease
r208 | snadendla | 2010-01-06 11:57:00 -0600 (Wed, 06 Jan 2010) | 1 line
Merged axillary abscess with axillary disease

Also see https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/HumanDO.obo
DO Subversion Repository

$ svn diff -r 202 HumanDO.obo | wc
  16602  51532  572399
$ svn diff -r 213 HumanDO.obo | wc
  14120  43552  483380
$ svn diff -r 230 HumanDO.obo | wc
  3750  14013  141747

Also see https://diseaseontology.svn.sourceforge.net/svnroot/diseaseontology/trunk/HumanDO.obo

Disease Ontology Tracker

http://sourceforge.net/tracker/?group_id=79168&atid=555739
Ontology Viewer at the EBI

http://www.ebi.ac.uk/ontology-lookup/
Past and Current Applications

- The primary driver for the creation of the Disease Ontology is the ability to integrate disparate datasets that contain disease concepts or concepts that can be mapped to disease.
- The Disease Ontology provides a unifying structure to map disease knowledge between datasets such as patient records and large scale genome, sequencing and microbiome projects.

**GeneRIF and NUgene studies**: DO fulfills that role in an unbiased and granular fashion by providing the key component in the arsenal of tools by providing computable relationships between disease and concepts that can be mapped to disease such as genetic associations to disease, symptoms and biological process.

**Gemina project**: DO has been utilized to annotate incidents of infectious pathogens and to provide a query and retrieval vocabulary linking disease to hosts and transmissions and outbreaks of disease. (http://gemina.igs.umaryland.edu)

**eMERGE Consortium's electronic medical records (EMR)** will be validated by the Disease Ontology so that we can more easily map participants to specific disease cohorts and map data coming from each EMR system to common standards.

FunDO, GeneAnswers, CASIMIR, VPH, Human Microbiome Project

DO and PATO

- A critical aspect in applying DO to medical literature and medical records is that ability to walk between "Signs and Symptoms" attached to a patient record or the medical literature and the disease
- PATO will describe the phenotype, possibly with a 'Signs and Symptoms' view, and DO will describe the disease concept(s) linked with those signs and symptoms
- When we map from ICD-9 to DO, for instance, we find that collections of signs and diagnoses are associated with disease, and that it is the collection, rather than a single association, that enables the inference of disease from a set of observables
DO and model systems for disease

- DO is human-centric
- Is DO sufficient to link disease concepts between organisms?
- What happens when the underlying mechanisms appear to have changed between the organisms?
  - Epilepsy in Dogs and Human
  - Viral Diseases
  - Rat and Mouse models and Cancer in Humans

Curation Goals

**Year 1:** NW & IGS: establishment of weekly conference calls
- Coordinate weekly tasks, exchange development ideas and share plans, identify and solve ongoing curatorial issues, to continue dialog and to plan for future curation goal

**First Curation Steps: IGS/UMB**
(1) Infectious Disease Ontology
   - Reviewed and updated with breadth of infectious disease terms present in Medical Microbiology textbook (summer ’09)
   - ID branch has been re-organized by: [in progress]
     1st: dominant body system
     2nd: etiological agent (virus, bacteria, fungus)
     3rd: vector

The goal: two major tasks:
(1) Entire node reorganization, orphan terms cleanup
(2) Body system approach: deep annotation, definitions, addition of terms, dbXrefs, synonyms, division of body system and ID terms

- Reorganizing the entire node, identifying correct placement of unplaced terms, coordinating body systems with anatomy branch, separating out diseases and infectious diseases to correct and preserve true path rule
Overview of goals & strategies

- Wholesale high-level term rearrangement
- Merging terms upward
  - Maintain dbxrefs
  - Selective removal of terms (e.g.) ‘laboratory infection’
- Fixing clear lineage errors
  - Bacterial child of viral
- Plurals, capitals, word order, adding synonyms
- Reasoner issues cleanup
- Obsolete – non-obsolete term connections evaluated and fixed (temp holding cases)

General cleanup

Deeper curation
Cleaning up respiratory system infection node

- Viruses
- Bacteria
- Fungi
- Parasites

Infectious disease node

Getting rid of redundancies

Note: Ongoing curation discussion: forms of disease: acute, chronic, subacute
    further cleanup as DO will only retain distinct diseases, not alternative forms of the same diseases

Disease Ontology Definition

Here is a breakdown of the format of the Disease Ontology definition formation

A disease which is
A disease which involves
A disease which is manifested in

The first sentence should describe:
    the disease involves .... "these conditions, signs, symptoms".
    headache, severe joint pain and a rash.

The second sentence: additional symptoms, if needed.

The third sentence: the etiology: the cause of the disease
    e.g. dengue viruses [NCBITaxon:12637]
    transmission, e.g. vector: transmitted by mosquitoes of the genus Aedes [NCBITaxon:7158]
Barry Smith, Richard Scheuermann, Chris Mungall, Saul Lozano

On Aug 18, 2009, at 3:45 PM, Richard M. Scheuermann, Ph.D. wrote:

This DHF definition seems to imply that anyone experiencing a second infection with a different serotype would have DIF, even if they were asymptomatic. Is that what you intend?

I would not include the monophasic vector in the definition of the disease. I would expect that one fever from a blood transfusion. I would abandon the use of dengue by itself. It is both ambiguous and confusing, especially to (anticipate) who are not immunologists.

Some of these definitions have a lot of superfluous tidbits that, while interesting facts, are not the disease.

The policy is O2 (which is still not uniformly applied) is to put the superfluous tidbits (which are very useful after the first period. The part before the full-stop is the formal definition, the part after is the additional descriptive text. Ideally these would go in separate controlled fields but that’s not really how it evolved.

Richard makes a good point for the vector going in the descriptive text.

Barry Smith, Richard Scheuermann, Chris Mungall, Saul Lozano
Adding definitions to “respiratory system infection” terms

Before

- Disease of respiratory system
- Disease of pulmonary infection
- Disease of respiratory tract infection
- Disease of upper respiratory tract
- Disease of lower respiratory tract
- Disease of respiratory system caused by infection
- Disease of respiratory system caused by inflammation

After

- Disease
- Disease by environmental factor
- Disease by infectious agent
- Disease of pulmonary system
- Disease of respiratory system
- Disease of upper respiratory system
- Disease of lower respiratory system
- Disease of respiratory system caused by infection
- Disease of respiratory system caused by inflammation
Organization of “respiratory system disease”

**Before**
- Respiratory system disease
  - Croup
  - Essential Brown injection of lung
  - Non-respiratory tract disorder
  - Non-respiratory tract disease
  - Fever and infection
  - Upper respiratory tract disease
  - Lower respiratory tract disease
  - Lower respiratory tract disease
  - Pulmonary fibrosis
  - Pulmonary edema
  - Pulmonary edema
  - Pulmonary edema
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**After**
- Respiratory system disease
  - Croup
  - Essential Brown injection of lung
  - Non-respiratory tract disorder
  - Non-respiratory tract disease
  - Fever and infection
  - Upper respiratory tract disease
  - Lower respiratory tract disease
  - Lower respiratory tract disease
  - Pulmonary fibrosis
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**Pneumonia**
- Respiratory system infection
  - Croup
  - Lower respiratory tract disease
  - Lower respiratory tract disease
  - Pulmonary fibrosis
  - Pulmonary edema
  - Pulmonary edema
  - Pulmonary edema
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  - Pulmonary edema

Only the infectious pneumonias
# Summary of UMB group progress

- A total of 129 (as of November 20th) revisions committed to SourceForge
- Adding comments, dbxrefs, definitions periodically during process
  - Not yet concentrated effort
- Removing is_a relationships to incorrect parents
  - More needed
- Made decision to link terms out to anatomy
  - Follow FMA
- Created high-level terms (or renamed them) for major taxonomic groups
  - bacterial, fungal, protozoan, viral, parasitic
- Deleted ‘anatomy site specific infection’ after addressing numerous child terms
- Moved many terms to child of ‘zoonotic infection’ from main ID
  - ‘arthropod borne infection’ for example
- Curators keeping Google Docs files
- Auditory system infection, moving respiratory infection terms under respiratory diseases
- Removal of redundancies in anatomy (e.g. thoracic diseases)
- FMA dbxrefs (94): (01-15-2008)

## Started reworking Cancer

Pulled neoplasms out of cancer
Merging carcinomas and cancer
May need to organize cancer by tumor forming (‘solid’ tumors) and non-tumor forming (heme malignancies or leukemias)
Reorganizing cancer system and tissue type of origin
(from [http://www.oncologychannel.com/staging.shtml](http://www.oncologychannel.com/staging.shtml))

Site of origin/ tissue type classification describes the type of tissue in which the cancer cells begin to develop.

Here are some common examples of site of origin classification:
- Adenocarcinoma - originates in glandular tissue
- Blastoma - originates in embryonic tissue of organs
- Carcinoma - originates in epithelial tissue (i.e., tissue that lines organs and tubes)
- Leukemia - originates in tissues that form blood cells
- Lymphoma - originates in lymphatic tissue
- Myeloma - originates in bone marrow
- Sarcoma - originates in connective or supportive tissue (e.g., bone, cartilage, muscle)
Cancer: new organization plan by cancer type
Sample hierarchy:

- neoplasm
- benign neoplasm
- tumor forming
  - papilloma
- pre-malignant neoplasm
- malignant neoplasm
  - tumor forming malignant neoplasm
    - sarcoma (mesodermal cancer)
    - carcinoma (epithelial cancer)
      - ductal carcinoma
      - ductal carcinoma of breast
      - adenocarcinoma (glandular epithelial cancer)
      - adenocarcinoma of breast
    - non-tumor forming (hematologic malignancy)
      - leukemia
      - lymphoma

So that 'sarcoma' is a 'tumor forming malignant neoplasm' and 'ductal carcinoma of breast' is a 'ductal carcinoma' is 'carcinoma'.

---

First Curation Steps: NW

- Cancer: new organization plan by cancer type
- Sample hierarchy:
  - neoplasm
  - benign neoplasm
  - tumor forming
    - papilloma
  - pre-malignant neoplasm
  - malignant neoplasm
    - tumor forming malignant neoplasm
      - sarcoma (mesodermal cancer)
      - carcinoma (epithelial cancer)
        - ductal carcinoma
        - ductal carcinoma of breast
        - adenocarcinoma (glandular epithelial cancer)
        - adenocarcinoma of breast
      - non-tumor forming (hematologic malignancy)
        - leukemia
        - lymphoma
  - So that 'sarcoma' is a 'tumor forming malignant neoplasm' and 'ductal carcinoma of breast' is a 'ductal carcinoma' is 'carcinoma'.

---

Spring/Summer/Fall 2009 Curation work

- Remove terms containing: NOS [Not otherwise specified], plurals, ‘other’, commas, terms with odd characters, e.g. ‘/’
- Removed terms containing “EC” [Disease classified elsewhere: e.g.: DOID: 10313]
- Removed terms containing OS [other specified organisms]
- Removed terms with “unspecified”
- Merge non-disease terms up to parent terms, to retain dbXrefs
- Standardize microbial-caused diseases to “pathogen infection”
- Split terms with many pathogens as possible causative agents

Example:

- Disease due to Genus species
  - ancylostomiasis
  - ancylostomiasis due to *Ancylostoma braziliense*
  - ancylostomiasis due to *Ancylostoma ceylanicum*

- Synonym cleanup in DO:
  - Removed all instances of [D|M|X] in DO - 676 changes, all but one were synonyms (part of revision 59)
  - Disease “involving” or “of the” anatomic part – merging these into parent nodes (e.g. tuberculosis)
Six Month Milestones

- Add DO Definitions
- General Clean up of Terms Task
- Identify Types of Terms to Clean: ‘other’, terms with brackets, also check synonyms
- Review SNOMED Terms
  - This task will involve going back to UMLS mappings, as SNOMED has removed some synonyms that we still have in DO
- DO Disease Focusing Task
  - Clean Out DO of the nodes that are non-leaf nodes, mine temp holding

Nine Month Milestones

- DO First Annual Advisory Board/DO Use Case Meeting
  - Slated for early 2010
- Groups: FMA, HPO, GO Biological Process, OMIM, PATO
  - Focus: discuss cross products and driving Use Cases
- Release DO v4

DO V3… to V4 To Dos [in progress]

DO Improvements:
- Ontological structure: FMA anatomy based and coordinated between nodes
- Definitions: OBO foundry structured, coordinated, approved, deep annotation of infectious diseases
- dbxrefs: FMA
- Synonyms

DO CLEANUP:
- Remove top-node, non-specific DO categories
- DO syntactic cleanup
DO Terms/Branches for Discussion:

disease of environmental origin branch

Notes for discussion: (05/22/2009)
• areas of this branch that need review
• specifically the review of whether these branches should remain in the DO. Such as the injury and poisoning branch.
• Additionally, the substance-related disorders, fall more into the gray area of disorders, rather than diseases. Perhaps this may be an area of branching for DO.

DO Plans Northwestern and UMB

6 months: Project launch (July 16th, 2009)
  Curation Driven Development:
  Review, term cleanup, term additions, and term definitions
  1st DO workshop (Chicago – January 2010)

1st year: Complete cleanup, major review and updates. Use Review direction of Use Case development

2nd year: Initiate grant for further development, integrate neurological ontology, integrate use case driven development

DO User Community Workshop Fall 2010 at UMB
DO Resources

<table>
<thead>
<tr>
<th>Ontology Tools</th>
<th>URLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiki</td>
<td><a href="http://diseaseontology.sourceforge.net">http://diseaseontology.sourceforge.net</a></td>
</tr>
<tr>
<td>DO Listserv</td>
<td><a href="http://sourceforge.net/mailarchive/forum.php?forum_name=diseaseontology-discussion">http://sourceforge.net/mailarchive/forum.php?forum_name=diseaseontology-discussion</a></td>
</tr>
<tr>
<td>DO Sourceforge Tracker for term submission/definitions</td>
<td><a href="https://sourceforge.net/tracker/?group_id=79168&amp;atid=555739">https://sourceforge.net/tracker/?group_id=79168&amp;atid=555739</a></td>
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<tr>
<td>Subversion</td>
<td><a href="https://diseaseontology.svn.sourceforge.net/viewvc/diseaseontology/trunk/HumanDO.obo?view=log">https://diseaseontology.svn.sourceforge.net/viewvc/diseaseontology/trunk/HumanDO.obo?view=log</a></td>
</tr>
</tbody>
</table>

Curation Reference and Resources

Merck Manuals: Online Medical Library:
   http://www.merck.com/mmhe/index.html

Medline Plus Medical Dictionary:

Glossary of Public Health Terms:
   http://www.hls.gov.bc.ca/phact/glossary.html

ICD-9-CM codes: