Requirements and Strategy for the Development of a Pediatric Drug Ontology

Rachel Richesson, PhD
Jyoti Pathak, PhD
Wendy McLeod
Ginger Blackmon
Kendra Vehik, PhD

3rd International Conference On Biomedical Ontology
Graz, Austria
July 21 – 25, 2012

Duke University School of Nursing
Outline

• Introduction and setting
• TEDDY investigations
• Approach to collection
• Ontological approach to analysis
• Discussion
• Future Directions
Pediatric Epidemiology Center

The Division of Bioinformatics and Biostatistics Pediatric Epidemiology Center is comprised of a diverse team with expertise in biostatistics, epidemiology, health informatics, computer science, genetics, nutrition, public health, clinical trials, and health services research. With funding from the NIH, DoD, and other sources, we are able to provide the technical means to facilitate interaction and contributions in knowledge between physicians and patients throughout the US and International communities. By strengthening this vital network, we can work to improve research on many different types of diseases.

**OUR MISSION**

- Provide guidance on research study design, statistical methodology, data analysis, and data interpretation
- Establish an infrastructure to implement and coordinate new

**What We Do**

We provide the services and technology to enable clinical studies to recruit, gather and analyze data, and facilitate
Research Background

- Research looks at characteristics between groups
- Groups are assembled by aggregating data
  - rules for membership
  - comparable representations
- Research is all about explicit, reproducible methods
Research Data

- Always collect data at most granular level possible
- Bigger groups can be created by aggregating data as needed for analytic problem
  - Chemical properties
  - Physiological effects
  - Clinical context (e.g., indications)

- Observational studies include some *unknown* analyses (and hence unknown groupings/classifications)
Medication Data

Supports many uses:
- Clinical
- Quality & safety monitoring
- Business operations
- Clinical research
  - Epidemiology

Use of medication data requires:
1. Appropriate representation and coding of medications prescribed or reported
2. Well-defined classes/groups of drugs for analysis
3. Linkage between 1&2
Biomedical Research Problem

• The classification of medications is time-consuming, prone to error, and not easily reportable or reproducible without programming code.

• The TEDDY study
  – 8 Principal Investigators
  – >60 investigators from 4 nations
  – 9 subcommittees
  – 12 primary research questions + many ancillary questions

• Ad-hoc classification has already led to multiple duplicative and error-prone efforts by TEDDY working groups.
Finding diabetes early can prevent serious illness and complications.

Most of the new cases of type 1 diabetes occur in children who have no family history of the disease.

Clinical Centers:
- Finland
- Germany
- Sweden
- United States
  - Colorado
  - Georgia/Florida
  - Washington

Data & Coordinating Center:
- USF (Tampa, FL)

What is Type-1 Diabetes?
Type 1 diabetes is one of the most common and serious long-term diseases in children. It is a disease where the body's immune system attacks the cells that make insulin. Insulin helps sugar (glucose) get into your cells so it can be used as energy.

Children with type 1 diabetes must take insulin several times a day to stay alive and healthy. Right now, there is no cure for type 1 diabetes.

- T1D is a serious disease affecting 1 out of every 300 (1/300) children in the United States.
- T1D occurs when special cells in the pancreas, called beta cells, are destroyed by the body's own immune system. When the beta cells are destroyed, the body can no longer make insulin.
- Insulin is needed to keep blood sugar levels normal. If there is no insulin, your body can't use the sugars from the food you eat, causing serious illness or even death.
- A child with T1D must take insulin shots or use an insulin pump every day to stay well. Insulin has to be taken every day for the rest of the life of a child with diabetes.

What is the TEDDY Study?
Every child in TEDDY helps us come closer to preventing this disease.

The TEDDY study - The Environmental Determinants of Diabetes in the Young - is looking for the causes of type 1 diabetes mellitus (T1DM). T1DM used to be called childhood diabetes or insulin-dependent diabetes.

Research tells us that children who get diabetes have certain kind of genes. Other children who have these genes are at higher risk for getting diabetes. However, not all children who are higher risk get diabetes. We think that something happens that "triggers" or causes a child with higher risk genes to actually get diabetes. It is the purpose of this study to try and find out what are the triggers that cause children to get diabetes.

Learn about the TEDDY Study >>>

http://teddy.epi.usf.edu/
TEDDY Follow-up Visits

- **Clinic visits every 3 months**
- **Blood for:** GADA, IAA, IA-2A, DNA, mRNA, infectious agents, storage plasma/serum, erythrocytes, PBMC, HbA1c
- **Nasal swabs, tap water, toenail clippings and salivary cortisol**
TEDDY Publications and Presentations

Publications:


As of July 10, 2012:

>25 published papers
>5 in press
>50 scientific presentations
Committees:

- Steering Committee
- Executive Committee
- Ancillary Studies Committee
- Celiac Disease Committee
- Clinical Implementation Committee
- Diet Committee
- Environmental Exposures Committee
- Genetics Committee
- Human Subjects/Publicity Committee
- Immune Markers Committee
- Infectious Agents Committee
- Laboratory Implementation Committee
- Maternal Study Committee
- Psychosocial Committee
- Quality Assurance Committee
- Study Coordinators Committee
TEDDY Data

- >8,600 high-risk infants and children; mostly “healthy”
  - >2 million data points
  - >200,000 instances of reported medications
  - 846 unique medications
  - 745 unique ingredients

- How can these data be used to formulate new hypotheses?
  - Antibiotic medications $\rightarrow$ T1D outcomes?
  - Drug products that treat fever $\rightarrow$ T1D outcomes?
  - Acetaminophen? $\rightarrow$ T1D outcomes?
Outline

• Introduction and setting
• TEDDY investigations
• **Approach to collection**
• **Ontological approach to analysis**
• Discussion
• Future Directions
Medications coded granularly: RxNorm
Need to **group** for analysis:

**VA NDF-RT**

Drug Classification

- Developed and Maintained by U.S. Dept. of Veterans Affairs to organize VA drug formulary

~43,000 orderable clinical drugs & ingredients, & classes

- Freely available via UMLS and NCBO Bioportal
Early evaluation....
# High-Frequency TEDDY Medications

<table>
<thead>
<tr>
<th>TEDDY_CODE</th>
<th>Medication</th>
<th>Frequency Reported as of Nov 30, 2009</th>
<th>% of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED00010</td>
<td>ACETAMINOPHEN</td>
<td>34479</td>
<td>31%</td>
</tr>
<tr>
<td>MED00001</td>
<td>IBUPROFEN</td>
<td>7202</td>
<td>7%</td>
</tr>
<tr>
<td>MED00002</td>
<td>AMOXICILLIN</td>
<td>5666</td>
<td>5%</td>
</tr>
<tr>
<td>MED00079</td>
<td>OXYMETAZOLINE</td>
<td>5357</td>
<td>5%</td>
</tr>
<tr>
<td>MED00051</td>
<td>ALBUTEROL</td>
<td>4319</td>
<td>4%</td>
</tr>
<tr>
<td>MED00227</td>
<td>HOMEOPATHIC PREPARATION</td>
<td>2827</td>
<td>3%</td>
</tr>
<tr>
<td>MED00008</td>
<td>SIMETHICONE</td>
<td>2344</td>
<td>2%</td>
</tr>
<tr>
<td>MED00106</td>
<td>PENICILLIN V</td>
<td>2012</td>
<td>2%</td>
</tr>
<tr>
<td>MED00200</td>
<td>NAPROXEN</td>
<td>1984</td>
<td>2%</td>
</tr>
<tr>
<td>MED00003</td>
<td>AMOXICILLIN + CLAVULANIC ACID</td>
<td>1684</td>
<td>2%</td>
</tr>
<tr>
<td>MED00158</td>
<td>XYLOMETAZOLINE</td>
<td>1512</td>
<td>1%</td>
</tr>
<tr>
<td>MED00041</td>
<td>AZITHROMYCIN</td>
<td>1401</td>
<td>1%</td>
</tr>
<tr>
<td>MED00058</td>
<td>Budesonide</td>
<td>1396</td>
<td>1%</td>
</tr>
<tr>
<td>MED00013</td>
<td>DIPHENHYDRAMINE</td>
<td>1285</td>
<td>1%</td>
</tr>
<tr>
<td>MED00054</td>
<td>UNKNOWN ANTIBIOTIC</td>
<td>1223</td>
<td>1%</td>
</tr>
<tr>
<td>MED00111</td>
<td>BROMHEXINE HYDROCHLORIDE + EPHEDRINE HYDROCHLORIDE</td>
<td>1065</td>
<td>1%</td>
</tr>
<tr>
<td>MED00080</td>
<td>CHLORAMPHENICOL</td>
<td>1021</td>
<td>1%</td>
</tr>
<tr>
<td>MED00207</td>
<td>DIMETHICONE + SIMETHICONE</td>
<td>867</td>
<td>1%</td>
</tr>
<tr>
<td>MED00118</td>
<td>HYDROCORTISONE</td>
<td>861</td>
<td>1%</td>
</tr>
</tbody>
</table>
“.... Please examine the spreadsheet, row by row. For each row, in Column D, please answers ‘yes’ or ‘no’ to the accuracy of the drug ingredient (Column B) and Class (Column C) pair. In other words, tell us whether you agree that the [INGREDIENT] is part of the named [CLASS]? There are 203 records to review. Each record is a unique Ingredient-Class PAIR.”
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Class</th>
<th>Domain Expert Review - yes or no</th>
</tr>
</thead>
<tbody>
<tr>
<td>(please ignore the numbers in [brackets] and consider)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIMICROBIALS:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 ACYCLOVIR</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>2 FAMCICLOVIR</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>3 FOSCARNET</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>4 LAMIVUDINE</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>5 OSELTAMIVIR</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>6 PALIVIZUMAB</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>7 RIBAVIRIN</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>8 RIMANTADINE</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>9 VALACYCLOVIR</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>10 ZANAMIVIR</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td>11 ZIDOVUDINE</td>
<td>[AM800] ANTIVIRALS</td>
<td></td>
</tr>
<tr>
<td><strong>STEROIDS:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 BETAMETHASONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>14 BUDESONIDE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>15 DEXAMETHASONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>16 HYDROCORTISONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>17 METHYLПREDNISOLONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>18 PREDNISOLONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>19 PREDNISONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>20 TRIAMCINOLONE</td>
<td>[HS051] GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>21 TESTOSTERONE</td>
<td>[HS100] ANDROGENS/ANABOLICS</td>
<td></td>
</tr>
<tr>
<td>22 LEVONORGESTREL</td>
<td>[HS200] CONTRACEPTIVES,SYSTEMIC</td>
<td></td>
</tr>
<tr>
<td>23 ESTRADIOL</td>
<td>[HS300] ESTROGENS</td>
<td></td>
</tr>
<tr>
<td>24 ESTRADIOL, CONJUGAT</td>
<td>[HS300] ESTROGENS</td>
<td></td>
</tr>
<tr>
<td>25 ETHINYL ESTRADIOL</td>
<td>[HS300] ESTROGENS</td>
<td></td>
</tr>
<tr>
<td>26 CHORIONIC GONADOTROPINS</td>
<td>[HS400] GONADOTROPINS</td>
<td></td>
</tr>
<tr>
<td>Page No.</td>
<td>Term</td>
<td>Pathology/Drug Class</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>107</td>
<td>ACETAMINOPHEN [RE506] ANTIHISTAMINE/DECONGESTANT/ANTITUSSIVE/ANALGESIC</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ACETAMINOPHEN is a ANTIHISTAMINE <em>OR</em> DECONGESTANT <em>OR</em> ANTITUSSIVE <em>OR</em> an ANALGESIC?</td>
</tr>
<tr>
<td>108</td>
<td>ACETAMINOPHEN [RE509] ANTIHISTAMINE/ANTITUSSIVE/ANALGESIC</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ACETAMINOPHEN is a ANTIHISTAMINE <em>OR</em> ANTITUSSIVE <em>OR</em> an ANALGESIC?</td>
</tr>
<tr>
<td>109</td>
<td>ACETAMINOPHEN [RE514] DECONGESTANT/ANTITUSSIVE/EXPECTORANT/ANALGESIC</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ACETAMINOPHEN is a DECONGESTANT <em>OR</em> ANTITUSSIVE <em>OR</em> an <em>OR</em> and EXPECTORANT <em>OR</em> an ANALGESIC?</td>
</tr>
<tr>
<td>110</td>
<td>ACETAMINOPHEN [RE515] DECONGESTANT/ANTITUSSIVE/ANALGESIC</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ACETAMINOPHEN is a DECONGESTANT <em>OR</em> ANTITUSSIVE <em>OR</em> an ANALGESIC?</td>
</tr>
<tr>
<td>111</td>
<td>ACETAMINOPHEN [RE599] COLD REMEDIES,OTHER</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ACETAMINOPHEN is a type of cold remedy?</td>
</tr>
<tr>
<td>112</td>
<td>ALUMINUM ACETATE [RE599] COLD REMEDIES,OTHER</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ALUMINUM ACETATE is a type of cold remedy?</td>
</tr>
<tr>
<td>113</td>
<td>AMMONIUM CHLORIDE [RE599] COLD REMEDIES,OTHER</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that AMMONIUM CHLORIDE is a type of cold remedy?</td>
</tr>
<tr>
<td>114</td>
<td>ASCORBIC ACID [RE501] ANTIHISTAMINE/DECONGESTANT</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ASCORBIC ACID is an ANTIHISTAMINE <em>OR</em> a DECONGESTANT?</td>
</tr>
<tr>
<td>115</td>
<td>ASPIRIN [RE599] COLD REMEDIES,OTHER</td>
<td>Regardless of whether there is a better or more precise classification, would it be accurate to say that ASPIRIN is a type of cold remedy?</td>
</tr>
</tbody>
</table>
“Starter” Classes for TEDDY

- Antimicrobials
- NSAI
- Antivirals
- Anti-fungals
- Opiod & non-opiod analgesics
- Cold remedies, combinations
- Anti-asthma/Bronchodilators
- Antihypertensives
- Beta-blockers
- Gastric Medications
- Minerals
- Hormones
- Sedatives
- Diuretics
- Antiemetics
- Anesthetics
- Antihistamines
- …
- Sleep agents
- Psychotropics
- Antibiotics
- Allergy Meds

Duke University School of Nursing
Obvious Findings from Assessment of NDF-RT

- NDF-RT has many, many classes irrelevant to TEDDY
- NDF-RT has the ‘knowledge’ pediatric epidemiology researchers need
- NDF-RT does not always match views of our pediatric epidemiological researchers
- NDF-RT navigation can be daunting for a study-specific aggregation need
  - Need the ability to define “views” to create subsets
Approach for Evaluating Drug Ontology

1) Explicitly defined ancillary research question:
   “Is early exposure to antibiotics related to the presence and taxa of intestinal bacteria?”

2) Specific TEDDY dataset generated

3) Re-code medication (RxNorm → NDF-RT meds.)

4) Identify relevant NDF-RT classes (top-down)

5) Identify relevant NDF-RT sub-classes (bottom-up)

6) Create analysis variable

7) Validate classification

Duke University School of Nursing
Analysis Data Set
(“Is early exposure to antibiotics related to the presence and taxa of intestinal bacteria?”)

- 90 subjects
  - In highest HLA risk group
  - Complete data (w/ stool samples).
  - 339 reported medications

- Medication data
  - 203 unique medications; 143 w/ RxNorm codes
  - Classified using NDF-RT hierarchical relationships

- Validation data for current case study
  - 143 medication ingredients
  - 60 underspecified medications

Duke University School of Nursing
“Antibiotic” Classes in NDF-RT

<table>
<thead>
<tr>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTIBACTERIAL, TOPICAL</td>
</tr>
<tr>
<td>ANTIBACTERIALS, TOPICAL OPHTHALMIC</td>
</tr>
<tr>
<td>ANTI-INFECTIVES, OTHER</td>
</tr>
<tr>
<td>AMINOGLYCOSIDES</td>
</tr>
<tr>
<td>PENICILLINS, AMINO DERIVATIVES</td>
</tr>
<tr>
<td>NITROFURANS ANTIMICROBIALS</td>
</tr>
<tr>
<td>ERYTHROMYCINS/MACROLIDES</td>
</tr>
<tr>
<td>ANTIVIRALS</td>
</tr>
<tr>
<td>CEPHALOSPORIN 2ND GENERATION</td>
</tr>
<tr>
<td>CEPHALOSPORIN 1ST GENERATION</td>
</tr>
<tr>
<td>CEPHALOSPORIN 3RD GENERATION</td>
</tr>
<tr>
<td>CHLORAMPHENICOL</td>
</tr>
<tr>
<td>PENICILLIN-G RELATED PENICILLINS</td>
</tr>
<tr>
<td>NITROFURANS ANTIMICROBIALS</td>
</tr>
<tr>
<td>SULFONAMIDE/RELATED ANTIMICROBIALS</td>
</tr>
<tr>
<td>TETRACYCLINES</td>
</tr>
</tbody>
</table>
Specifics

• Used MS Excel to document the expert review.
• Used the NCBO BioPortal interface to traverse the hierarchy to determine if data-driven classes are descendants of classes defined as ‘antibiotics’.
  – The appropriateness of these classes was verified by TEDDY investigators.
• Created a new dichotomous variable in the spreadsheet called “Antibiotic” (yes/no)
• Validated the resulting relationships by having a domain expert verify asserted relationships.
<table>
<thead>
<tr>
<th>Row ID</th>
<th>Ingredient</th>
<th>Antibiotic (determined by JP/RR)</th>
<th>Reviewer - Do you agree that Ingredient in Column E is correctly classified as an Antibiotic in Column I?</th>
<th>Comments (questions, clarifications, etc.) optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>194</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>253</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>290</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>338</td>
<td>Acetaminophen</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>Acetylcysteine</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>316</td>
<td>Activated Charcoal</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Acyclovir</td>
<td>yes</td>
<td></td>
<td>antiviral</td>
</tr>
</tbody>
</table>

Results – Expert Review

- One reviewer (practicing pharmacist)
- Agreed w/ 141/143 values of ‘Antibiotic’ (y/n) variable
  - 44 +
- Disagreed in 2 cases:
  - Acyclovir (an antiviral)
  - Triclosan (topical antibiotic rather than systemic)

- Of 60 “under-specified” medications (e.g., “unknown steroid”)
  - 5 antibiotics
  - 2 exhibited “antibiotic properties”
Benefits

• Data-driven approach limited the number of NDF-RT classes that need to be considered as having antibiotic properties.

• Analysis context drove the selection of parent classes in a particular hierarchy (i.e., the VA legacy class hierarchy which is clinically-oriented).
Limitations

• One domain expert
• One analysis data set / question
• Mechanism for changing NDF-RT remains uncertain
Conclusions

• In our sample,
  – The classification of reported medications as antibiotics was correct
    • Expert noted mistakes in author selection of
  – NDF-RT relationships tested by our sample appear correct
  – Refinements and additions possible
  – NDF-RT has some benefit for research coding
  – NDF-RT + RxNorm supports data needs for TEDDY study
  – Future validation needed for other axes, classes, and pediatric medications
  – Approach is simple and effective

Duke University School of Nursing
Future Plans.....
# Department of Health and Human Services

## Part 1. Overview Information

<table>
<thead>
<tr>
<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
</tr>
</thead>
</table>
| **Components of Participating Organizations** | National Institute of General Medical Sciences (NIGMS)  
National Cancer Institute (NCI)  
National Heart, Lung, and Blood Institute (NHLBI)  
National Human Genome Research Institute (NHGRI)  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)  
National Institute of Biomedical Imaging and Bioengineering (NIBIB)  
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)  
National Institute of Environmental Health Sciences (NIEHS)  
National Institute of Mental Health (NIMH)  
Common Fund (Roadmap) |

<table>
<thead>
<tr>
<th>Funding Opportunity Title</th>
<th>Collaborations with National Centers for Biomedical Computing (R01)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity Code</strong></td>
<td>R01 Research Project Grant</td>
</tr>
<tr>
<td><strong>Announcement Type</strong></td>
<td>Reissue of PAR-06-184</td>
</tr>
<tr>
<td><strong>Related Notices</strong></td>
<td></td>
</tr>
</tbody>
</table>
  - November 29, 2011 - See Notice NOT-MH-11-115. This Notice is intended to clarify the role of the Common Fund in this FOA. |
| **Funding Opportunity Announcement (FOA) Number** | PAR-12-001 |
| **Companion FOA** | None |
| **Number of Applications** | See Section III.3. Additional Information on Eligibility |
| **Catalog of Federal Domestic Assistance (CFDA) Number(s)** | 93.113, 93.172, 93.233, 93.837, 93.838, 93.839, 93.242, 93.273, 93.286, 93.392, 93.303, 93.394, 93.395, 93.396, 93.307, 93.398, 93.300, 93.847, 93.859 |
| **FOA Purpose** | This funding opportunity announcement (FOA) is for proposals from individual investigators or small groups to collaborate with the NIH Common Fund for Medical Research National Centers for Biomedical Computing (NCBCs). For a description of the NCBCs see [http://www.ncbc.gov](http://www.ncbc.gov). The intent of the collaborating projects is to engage researchers across the nation in building an excellent biomedical computing environment using the computational tools and biological and behavioral application drivers of the funded NCBCs as foundation stones. |

## Key Dates

<table>
<thead>
<tr>
<th><strong>Posted Date</strong></th>
<th>October 7, 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open Date (Earliest Submission Date)</strong></td>
<td>January 5, 2012</td>
</tr>
<tr>
<td><strong>Letter of Intent Due Date</strong></td>
<td>Not Applicable</td>
</tr>
<tr>
<td><strong>Application Due Date(s)</strong></td>
<td>Standard dates apply, by 5:00 PM local time of applicant organization.</td>
</tr>
<tr>
<td><strong>AIDS Application Due Date(s)</strong></td>
<td>Standard dates apply, by 5:00 PM local time of applicant organization.</td>
</tr>
<tr>
<td><strong>Scientific Merit Review</strong></td>
<td>Standard dates apply</td>
</tr>
<tr>
<td><strong>Advisory Council Review</strong></td>
<td>Standard dates apply</td>
</tr>
<tr>
<td><strong>Earliest Start Date(s)</strong></td>
<td>Standard dates apply</td>
</tr>
<tr>
<td><strong>Expiration Date</strong></td>
<td>January 8, 2015</td>
</tr>
</tbody>
</table>

---

![The National Center for Biomedical Ontology](image-url)
“Pediatric Drug Ontology for Research (P-DOR)”

1) Identify and validate a pediatric subset of NDF-RT
2) Demonstrate P-DOR to support TEDDY
   – hypotheses testing
   – new associations and hypotheses for the relationships between medications and T1DM risk & development
3) Evaluate P-DOR as a data analysis tool
4) Implement P-DOR in other pediatric data sets
5) Share it!
   1) NCBO community
   2) Diabetes-related scientific and professional audiences
   3) Biomedical researchers

Duke University School of Nursing
### Existing datasets

- [List of datasets]

### Instances of pediatric medications

- [Table: pediatric medications]

### NDF-RT

- [List of categories]

### Medication-level data

#### TEDDY Investigators

- [Photo of investigators]

#### Methods:

- Explicit
- Standardized
- Reproducible
- Validated

#### Data Analysis

- [Diagram: data analysis]

#### Class-level data

- [Diagram: class-level data]

#### Classes of interest

- [List of classes]

#### 4. Publication

- [Diagram: publication process]

#### 2. Review & validate

- [Diagram: review and validation process]

#### 1. Query

- [Diagram: query process]

#### P-DOR

- [Diagram: P-DOR process]

- [List of categories]
Formulate research questions; identify relevant drug classes

Tools will be developed and used for 3 Data Tasks

Task 1: Recode medications in datasets using (analysis-specific) classes from P-DOR

Task 2: “Browse” P-DOR for classes, query/count instances, and generate descriptive reports of # data records by Drug Class.

Task 3: “Browse” P-DOR, select classes of interest, query data from data set or Warehouse.
Multi-Disciplinary Team

- Informatics
- Biomedical Investigators
- Domain Experts
  - Pharmacy
  - Biomedical research
  - Clinical
  - Data analysts
- Ontology Experts
Assumptions & Assertions

• A ontology relevant and validated for medications used in pediatric populations will facilitate efficient, consistent, and reproducible analyses.
  – NDF-RT useful starting point

• Standardized approaches to medication data grouping and analysis will support:
  – comparability across studies
  – interpretation and synthesis of research findings
  – meta-analysis

• Need methods and tools to re-use
  – Subsets of the reference terminology
  – Visualization
  – Validation
  – Analysis methods

Duke University School of Nursing
Acknowledgements

Co-authors & co-investigators:

- Jyotishman Pathak, PhD (Mayo)
- Kendra Vehik, PhD (U. of South Florida)
- Wendy McLeod (U. of South Florida)
- Ginger Blackmon (Wellhealth Pharmacy)

TEDDY project investigators and research staff (USF, UF)

Drs. Jeff Krischer, Mike Haller, and Helena Larsson; Lori Ballard, Susan Smith

TEDDY is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Disease (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC).

This work is also funded in part by the eMERGE grant.

Duke University School of Nursing
The Teddy Study Group

- **Colorado Clinical Center**: Marian Rewers, M.D., Ph.D., PI1,4,6,10,11, Katherine Barriga12, Kimberly Bautista12, Judith Baxter9,12,15, George Eisenbarth, M.D., Ph.D., Nicole Frank2, Patricia Gesualdo2,6,12,14,15, Michelle Hoffmann12,13,14, Lisa Ide, Rachel Karban12, Edwin Liu, M.D.13, Jill Norris, Ph.D.2,12, , Kathleen Waugh7,12,15 Adela Samper-Imaz, Andrea Steck, M.D., University of Colorado, Anschutz Medical Campus, Barbara Davis Center for Childhood Diabetes.

- **Georgia/Florida Clinical Centers**: Jin-Xiong She, Ph.D., PI1,3,4,11, Desmond Schatz, M.D.*4,5,7,8, Diane Hopkins12, Leigh Steed12,13,14,15, Jamie Thomas*6,12, Katherine Silvis2, Michael Haller, M.D.*14, Meena Shankar*2, Kim English, Richard McIndoe, Ph.D., Haitao Liu, M.D.†, John Nechtman†, Ashok Sharma, Joshua Williams, Gabriela Fohgis, Stephen W. Anderson, M.D.* Georgia Health Sciences University, *University of Florida, †Pediatric Endocrine Associates, Atlanta, GA.


- **Finland Clinical Centers**: Olli G. Simell, M.D., Ph.D., PI1,2,3,4,11,13, Heikki Hyöty, M.D., Ph.D.*6, Jorma Ionen, M.D., Ph.D.¶3, Mikael Knip, M.D., Ph.D.¶6, Maria Lonnrot, M.D., Ph.D.¶6, Elna Mantymaki¶6, Juha Mykkänen, Ph.D.¶3, Kirsti Nanto-Salonen, M.D., Ph.D.¶12, Tiina Niininen*, Mia Nyblom*, Anne Riikonen*‡2, Minna Rominen*, Barbara Simell¶6,12,15, Tuula Simell, Ph.D.¶6,9,12, Ville Simell¶6,13, Maija Sjöberg¶6,12,14, Aino Stenius*, Eeva Varjonen*, Ritva Veijola, M.D., Ph.D.¶6, Suvi M. Virtanen, M.D., Ph.D.*‡2, University of Turku, *University of Tampere, †University of Oulu, ‡Tampere University Hospital, §Oulu University Hospital, ¶National Institute for Health and Welfare, Finland, ¶University of Kuopio.

- **Sweden Clinical Centers**: Åke Lemmark, Ph.D., PI1,4,8,10,15, Daniel Agardh, M.D., Ph.D.13, Peter Almgren, Eva Andersson, Carin Andrén-Aronsson2,13, Maria Ask, Ulla-Marie Karlsson, Corrado Cillo, M.D., Ph.D., Jenny Bremer, Emilie Ericson-Hallström, Thomas Gard, Joanna Gerardsson, Gertie Hansson12,14, Monica Hansen, Susanne Hyberg, Rasmus Häkansson, Fredrik Johansen, Linda Jonsson, Helena Larsson M.D., Ph.D.14, Barbro Lemmark, Ph.D.9,12, Maria Markan, Theodosia Massadakis, Jessica Melin, Maria Månsson-Martinez, Anita Nilsson, Kobra Rahmati, Monica Sedig Järvirova, Sara Sibthorpe, Birgitta Sjöberg, Anna Skogberg, Carina Törn, Ph.D.3,15, Anne Wallin, Åsa Wiman, Sofie Åberg, Lund University.

- **Washington Clinical Centers**: William A. Hagopian, M.D., Ph.D., PI1,3,4,5,6,7,12,13, 14, Xiang Yan, M.D., Michael Killian6,7,12,13, Claire Cowen Crouch12,14,15, Kristen M. Hay2, Stephen Ayres, Carissa Adams, Brandi Bratrude, David Coughlin, Greer Fowler, Czarina Franco, Carla Hammor, Diana Heaney, Patrick Marcus, Arlene Meyer, Denise Mulenga, Elizabeth Scott, Jennifer Skidmore, Joshua Stabbert, Viktoria Stepetova, Nancy Williams. Pacific Northwest Diabetes Research Institute.

- **Pennsylvania Satellite Center**: Dorothy Becker, M.D., Margaret Franciscus12, MaryEllen Dalmago-Elias2, Ashi Daftary, M.D. Children’s Hospital of Pittsburgh of UPMC.

- **Data Coordinating Center**: Jeffrey P. Krischer, Ph.D., PI1,4,5,10,11, Michael Abbondondolo, Lori Ballard3,9,14,15, Rasheedah Brown12,15, Brant Burkhardt, Ph.D.5,6, David Cuthbertson, Christopher Eberhard, Steven Fiske, Veena Gowda, David Hadley, Ph.D.3,13, Hye-Seung Lee, Ph.D.3,6,13,15, Shu Liu, Kristian Lynch, Ph.D.9, Jamie Malloy, Cristina McCarthy12,15, Wendy McLeod2,5,6,13,15, Laura Smith, Ph.D.9, Susan Smith12,15, Ulla Uusitalo, Ph.D.2,15, Kendra Vehik, Ph.D. 4,5,9,14,15, Earnest Washington, Jimin Yang, Ph.D., R.D.2,15. University of South Florida.

- **Project scientist**: Beena Akolkar, Ph.D.1,3,4,5,7,10,11, National Institutes of Diabetes and Digestive and Kidney Diseases.

- **Other contributors**: Kasia Bourcier5, National Institutes of Allergy and Infectious Diseases, Ph.D. Thomas Briese, Ph.D.6,15, Columbia University, Henry Erlich, Ph.D.3, Children’s Hospital Oakland Research Institute, Suzanne Bennett Johnson, Ph.D.9,12, Florida State University, Steve Oberste, Ph.D.6, Centers for Disease Control and Prevention.
TEDDY Study Acknowledgements

• Funded by DK 63829, 63861, 63821, 63865, 63863, 63836, 63790 and UC4DK095300 and Contract No. HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC).