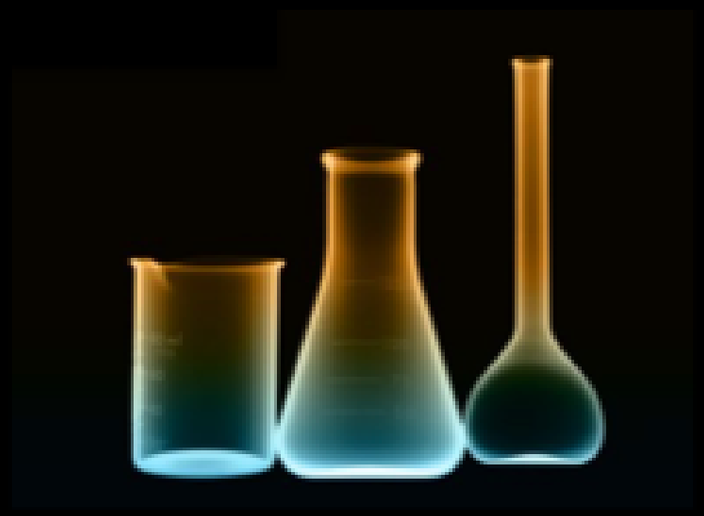
Integrating exposure data to evaluate risk: The Exposure Ontology (ExO)

Carolyn Mattingly, PhD
North Carolina State University

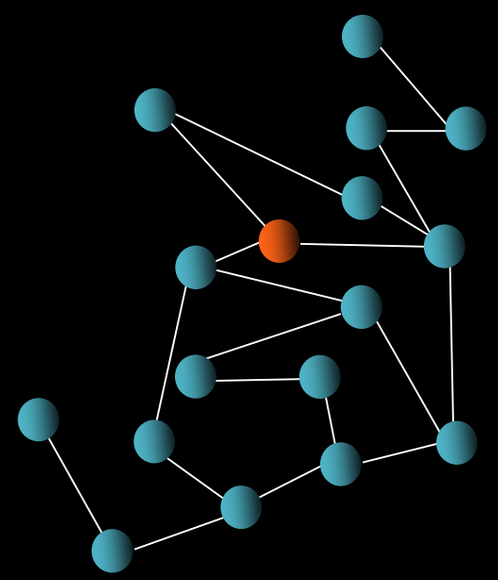
How does the environment affect our health?



Environment
(chemicals)

Genes

Disease



Giving insight into how chemicals affect our health.

Comparative Toxicogenomics Database

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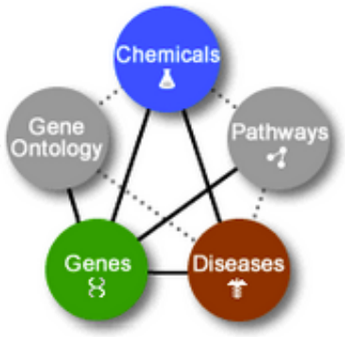
Connect. Compare.

CTD illuminates how environmental chemicals affect human health.
More...

Discover.

1. What human diseases are associated with a gene/protein? (Example)
2. What human diseases are associated with a chemical? (Example)
3. What genes/proteins interact with a chemical? (Example)
4. What chemicals interact with a gene/protein? (Example)
5. What references report a chemical–gene/protein interaction? (Example)
6. What cellular functions (GO terms) are affected by a chemical? (Example)



News

- *August 7, 2012*
  New data available!
- *July 19, 2012*
  You can now create custom similarity analyses for ChemComps and GeneComps!
- *May 8, 2012*
  Use our new Gene Set Enricher tool to find GO functional annotations or pathways that are enriched for a set of genes.
- *January 9, 2012*
  Use our new MyVenn tool to view relationships among your own data sets.
- *November 7, 2011*
  We have a new URL! http://ctdbase.org/
- *September 15, 2011*
  Exposure data is coming.
- *All changes...*

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Our Latest Publication

- Hirschman L, Burns GA, Krallinger M, Arighi C, Cohen KB, Valencia A, Wu CH, Chatr-Aryamontri A, Dowell KG, Huala E, Lourenço A, Nash R, Veuthey AL, Wiegers T, Winter AG.
  Text mining for the biocuration workflow.
  Database (Oxford). 2012 Apr 18;2012:bas020. Print 2012. [PMID:22513129]
- *All CTD publications...*

16,241,275 *TOXICOGENOMIC RELATIONSHIPS!*

Keyword Search

All

Name, ID, author...

Search | *Advanced searches*

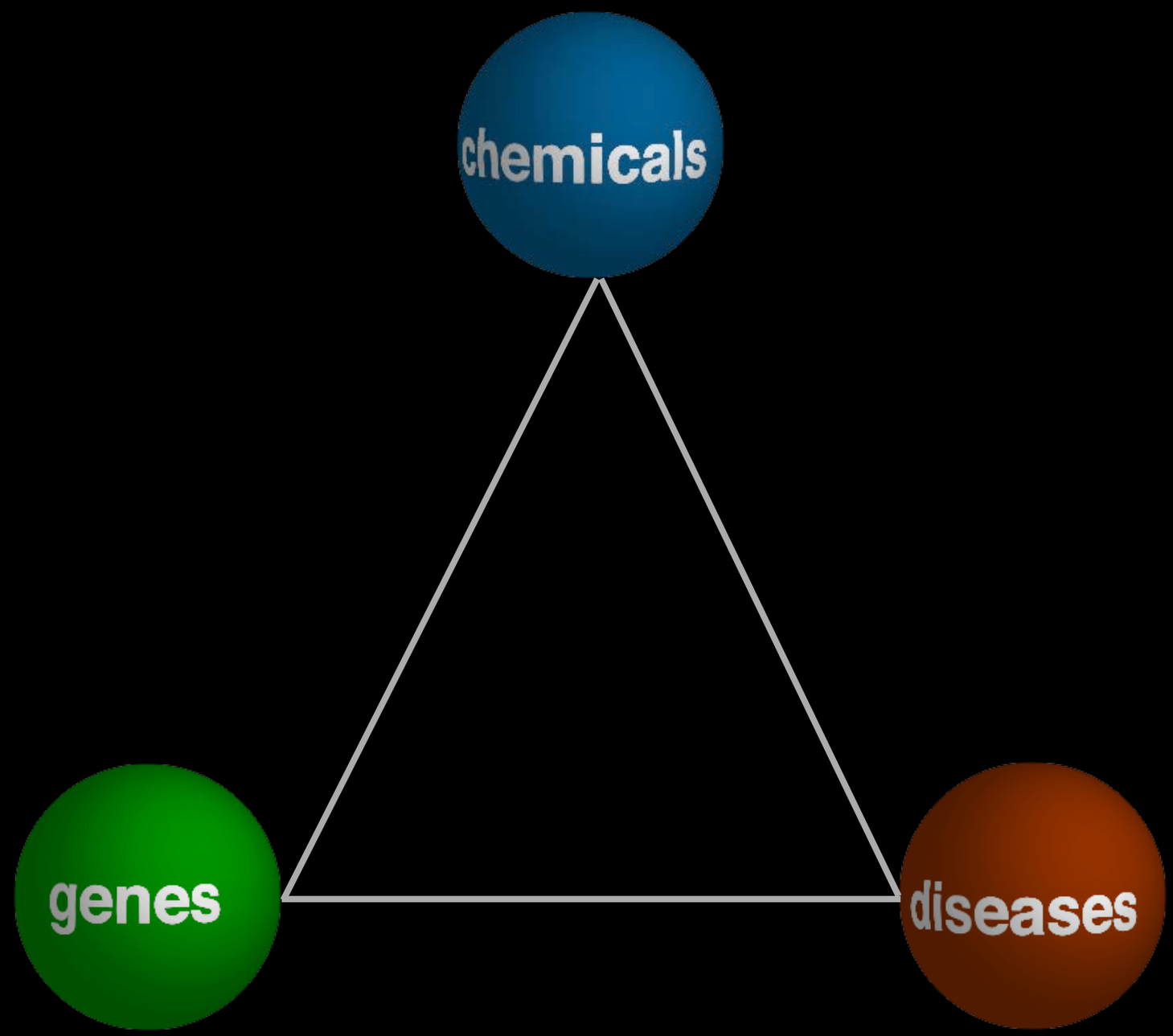
Updated Chemicals

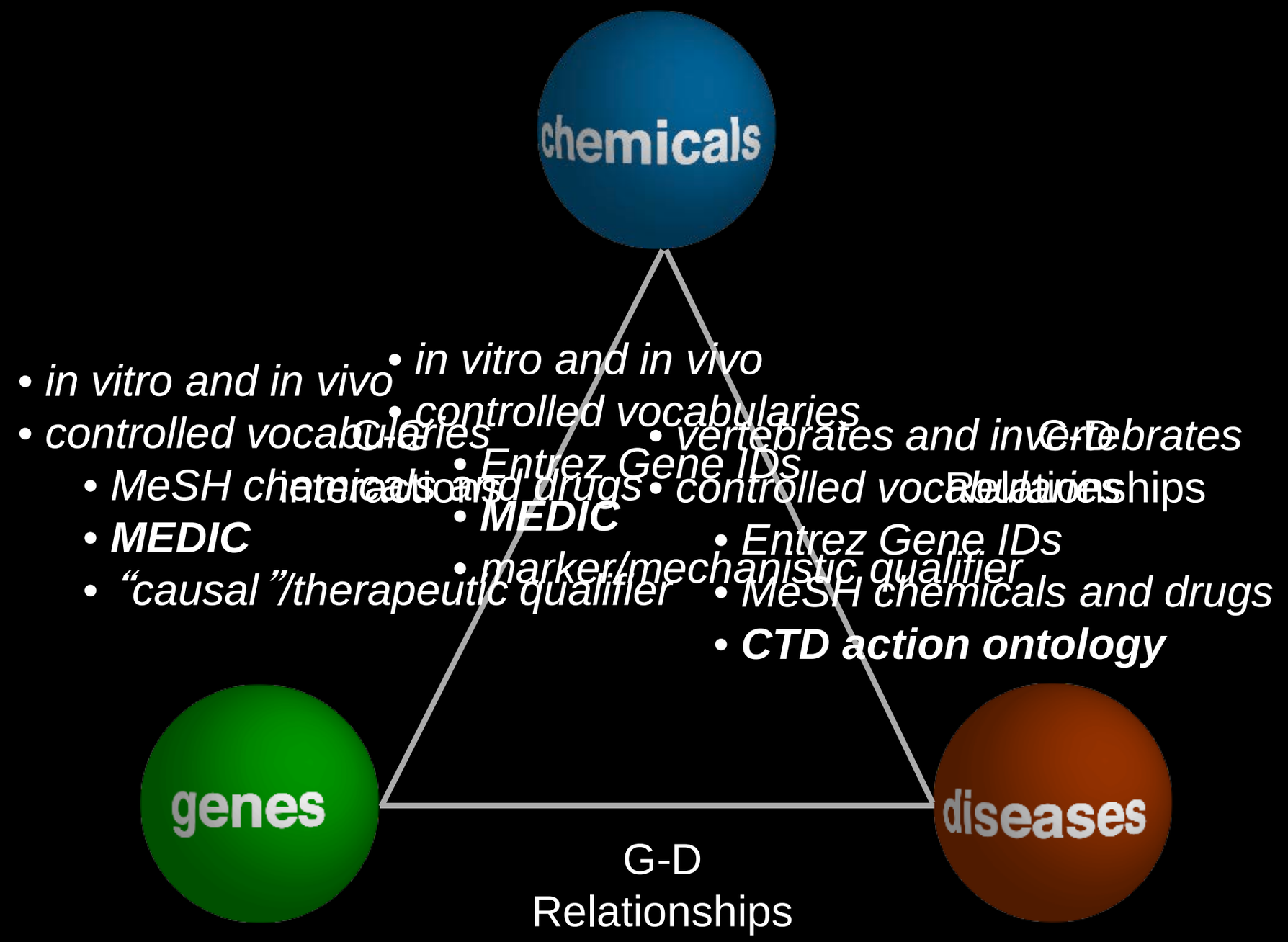
(4-amino-1,4-dihydro-3-(2-pyridyl)-5-thioxo-1,2,4-triazole)copper(II) 2',3,3',4',5-pentachloro-4-hydroxybiphenyl 4-hydroxy-2-nonenal Cadmium Cadmium Chloride cadmium sulfate cobaltiprotoporphyrin cobaltous chloride Copper Copper Sulfate cupric chloride Cisplatin Ethanol Hydrogen Peroxide Iron lead acetate lead nitrate Lipopolysaccharides Mercuric Chloride Mercury Oxygen Streptozocin Tetradecanoylphorbol Acetate Tretinoin vinclozolin

Updated Diseases

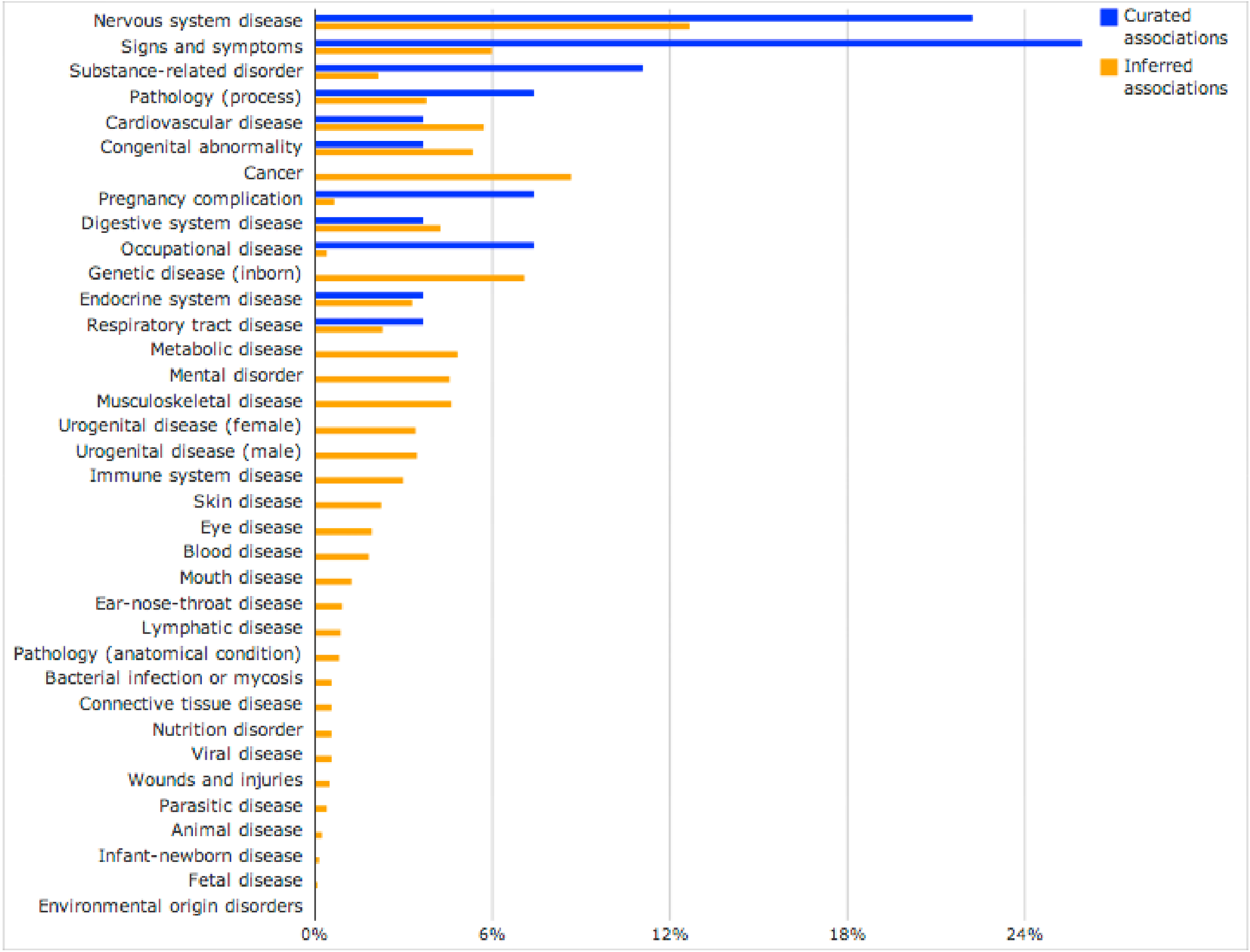
Updated Genes

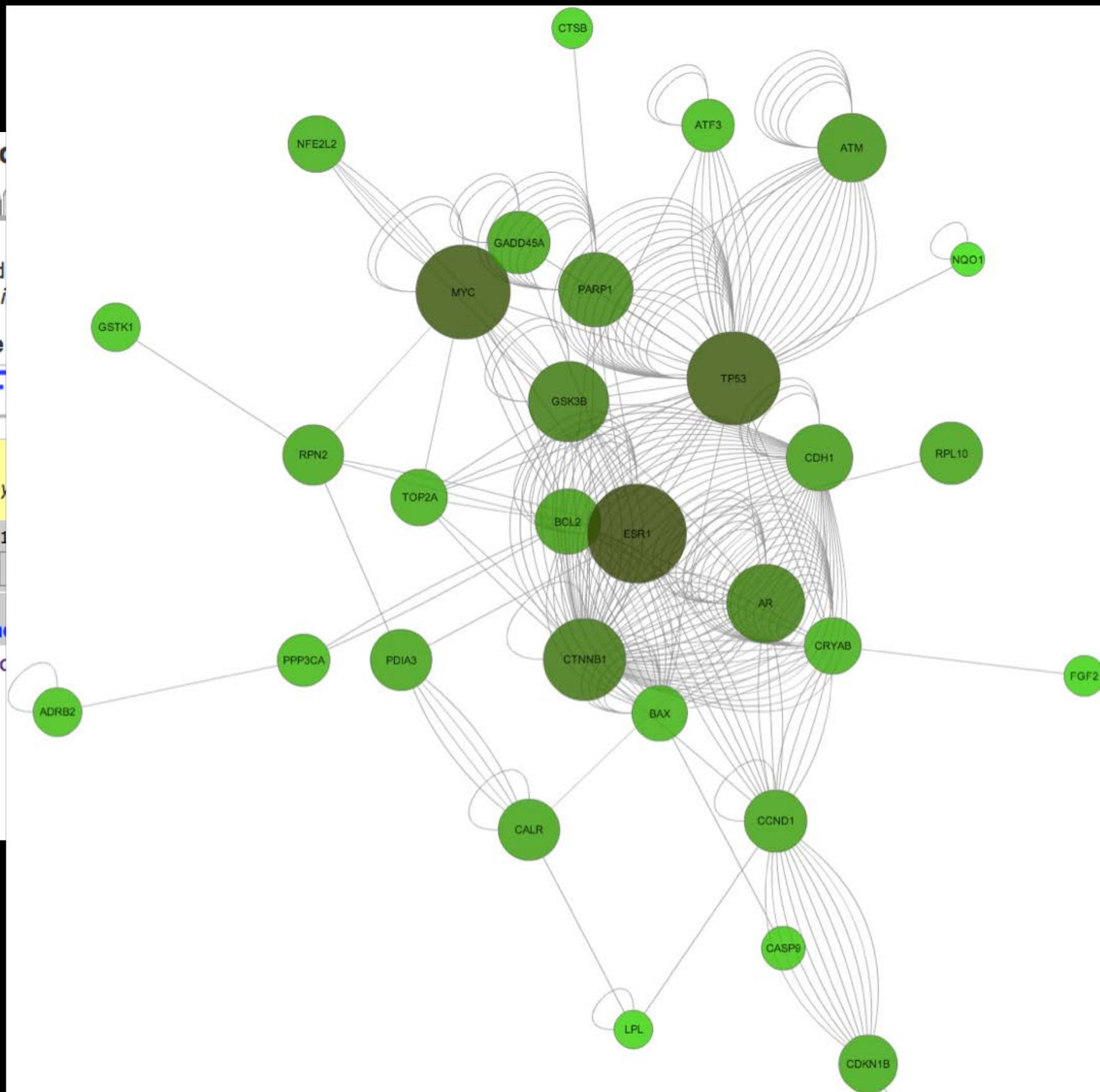
http://ctdbase.org


chemicals
genes
diseases


chemicals
• in vitro and in vivo
• controlled vocabularies
• MeSH chemicals and drugs
• MEDIC
• "causal"/therapeutic qualifier
C-G
Interactions
• in vitro and in vivo
• controlled vocabularies
• Entrez Gene IDs
• MEDIC
• marker/mechanistic qualifier
C-D
Relationships
• vertebrates and invertebrates
• controlled vocabularies
• Entrez Gene IDs
• MeSH chemicals and drugs
• CTD action ontology
genes
diseases
G-D
Relationships

Disease categories [Hide chart]





Chlo

Basics

These d
and/or i

Disease

Filter by

1–50 of 1

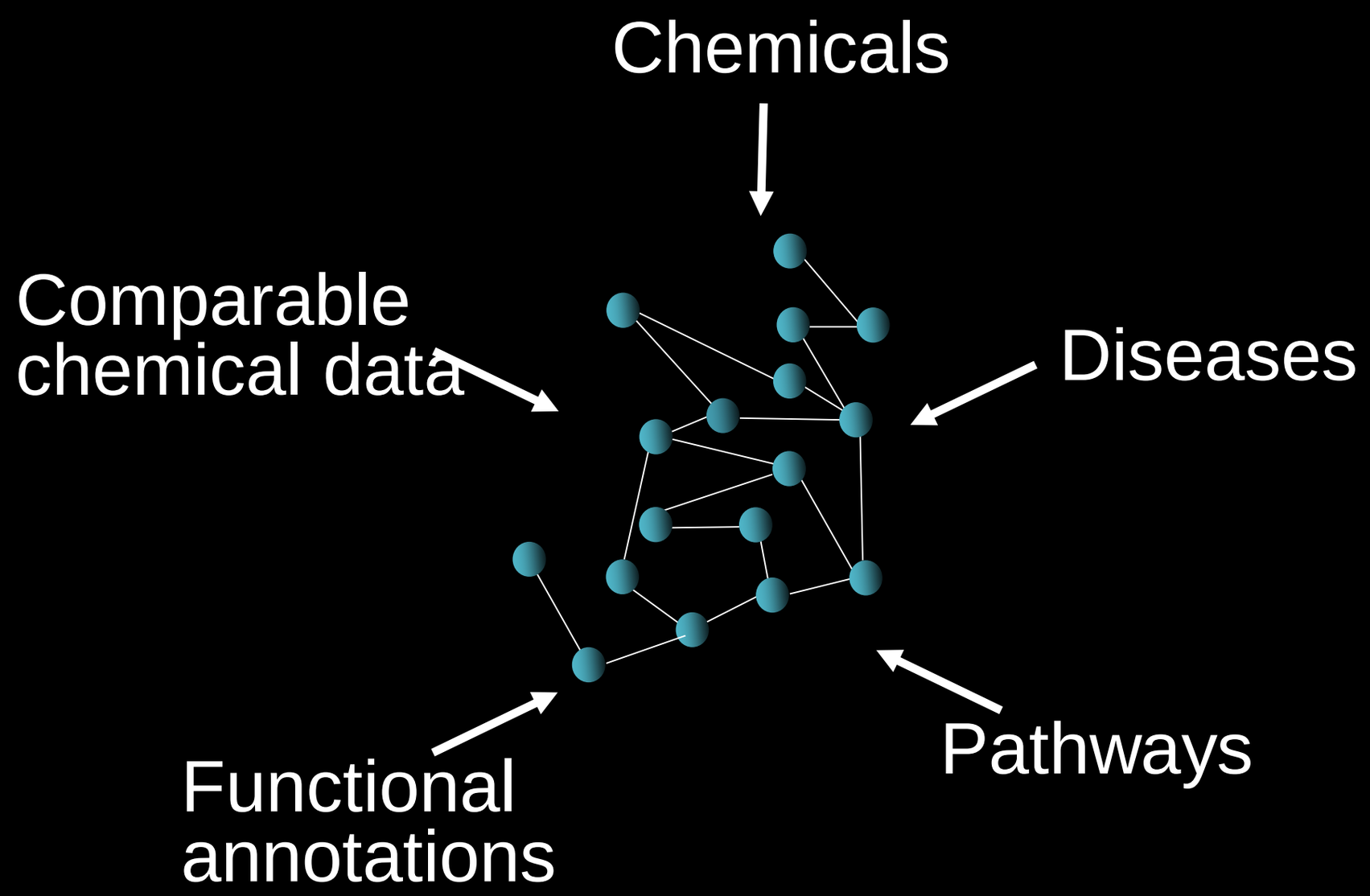
First

	Ch				Inference Score	References
1.	Chlo			X | BCL2 | CALR RYAB | CSRP1 |	49.09	79

echanism and/or T therapeutic)

				e	Annotated Genes
				5e-16	1
				9e-13	
				5e-12	
				2e-11	
				1e-11	
				2e-11	
				9e-11	
				5e-10	
				52e-8	
10.	Thyroid cancer	KEGG:05216	8.74e-10	1.18e-7	
11.	Measles	KEGG:05162	2.27e-9	3.06e-7	

How to best prioritize hypotheses?



Exposure data

- Grounding CTD data in “real-world” exposure data
- Centralizing exposure data
- Integrating exposure information with other biological data

What to capture and how?

Phase I

Initial pilot curation to identify major concepts

Phase II

Model relationships among data concepts

Expand test data set to evaluate extensibility of conceptual model and cross -reference existing ontologies

Iterate data model refinement and curation

Phase III

Full working group evaluation of draft ontology

Phase IV

Disseminate for Public feedback

ExO

Exposure Stressor

Interacts with

Exposure Receptor

Exposure Event

Exposure Outcome

Available on OBOFoundry & BioPortal

Curation-driven ontology development

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	CURATION IDENTIFIERS		STUDY IDENTIFIERS		EXPOSURE STRESSOR			EXPOSURE RECEPTOR			EXPOSURE EVENT				EXPOSURE OUTCOME		SUMMARY
2	4 fields		4 fields		6 fields			15 fields			17 fields				6 fields		2 fields
3	Curator	PMID	Study Title	Collection Years	Stressor Agent	Source	Number Samples	Age	Gender	Race	Methods	Limits of Detection	Assay Value	Event Location	Disease	Phenotype	Comments
4	cmurphy	22264316		1969-1990	Tetrachloroethylene	Dietary	1512	29.3 years	M/F	98.5% White				Cape Cod, MA	Bipolar Disorder		Results provide support for an in
5	cmurphy	22264316		1969-1990	Tetrachloroethylene	Dietary	1512	29.3 years	M/F	98.5% White				Cape Cod, MA	Stress Disorders, Post-Traumatic		Results provide support for an in
6	cmurphy	22264316		1969-1990	Tetrachloroethylene	Dietary	1512	29.3 years	M/F	98.5% White				Cape Cod, MA	Schizophrenia		Results provide support for an in
7																	
8	cmurphy	22239864		2001-2006	Particulate Matter	Environmental			M/F		distance-weighting estimation		13 u/m3	United States			This study generated estimates c
9	cmurphy	22239864		2001-2006	Ozone	Environmental			M/F		distance-weighting estimation		44 ppb	United States			This study generated estimates c
10																	
11	cmurphy	20978189	Agricultural H	1993-2004	Fonofos	occupationa	2,220		M	100% Caucasian	questionnaires			IA, NC, United States	Prostatic Neoplasms		In conclusion, we observed an in
12	cmurphy	20978189	Agricultural H	1993-2004	Coumaphos	occupationa	2,220		M	100% Caucasian	questionnaires			IA, NC, United States	Prostatic Neoplasms		In conclusion, we observed an in
13	cmurphy	20978189	Agricultural H	1993-2004	terbufos	occupationa	2,220		M	100% Caucasian	questionnaires			IA, NC, United States	Prostatic Neoplasms		In conclusion, we observed an in
14	cmurphy	20978189	Agricultural H	1993-2004	Phorate	occupationa	2,220		M	100% Caucasian	questionnaires			IA, NC, United States	Prostatic Neoplasms		In conclusion, we observed an in
15	cmurphy	20978189	Agricultural H	1993-2004	Permethrin	occupationa	2,220		M	100% Caucasian	questionnaires			IA, NC, United States	Prostatic Neoplasms		In conclusion, we observed an in
16																	
17	cmurphy	22251442	NHANES III	1988-1994	dimethyl phosphate	Dietary	192		M/F		GC-MS	0.5 u/L	2.07 u/L	United States			Human exposure to organophos
18	cmurphy	22251442	NHANES III	1988-1994	dimethyl phosphate	Dietary	192		M/F		GC-MS	0.5 u/L	13.4 u/L	United States			Human exposure to organophos
19	cmurphy	22251442	NHANES III	1988-1994	dimethyl phosphate	Dietary	192		M/F		GC-MS	0.5 u/L	2.14 u/g creatinine	United States			Human exposure to organophos
20	cmurphy	22251442	NHANES III	1988-1994	dimethyl phosphate	Dietary	192		M/F		GC-MS	0.5 u/L	25.2 u/g creatinin	United States			Human exposure to organophos
21	cmurphy	22251442	NHANES 199	1999-2000	dimethyl phosphate	Dietary	814		M/F		GC-MS	0.58 u/L	0.68 u/L	United States			Human exposure to organophos
22	cmurphy	22251442	NHANES 199	1999-2000	dimethyl phosphate	Dietary	814		M/F		GC-MS	0.58 u/L	9.7 u/L	United States			Human exposure to organophos
23	cmurphy	22251442	NHANES 199	1999-2000	dimethyl phosphate	Dietary	814		M/F		GC-MS	0.58 u/L	0.76 u/g creatinin	United States			Human exposure to organophos
24	cmurphy	22251442	NHANES 199	1999-2000	dimethyl phosphate	Dietary	814		M/F		GC-MS	0.58 u/L	14.6 u/g creatinine	United States			Human exposure to organophos
25	cmurphy	22251442	NHANES 199	2001-2002	dimethyl phosphate	Dietary	1,121		M/F		GC-MS	0.5 u/L	11.5 u/L	United States			Human exposure to organophos

- Status
  - ~50 data points captured
  - ~3,000 priority articles: 600 curated, 16,000 exposure statements, 300 unique chemicals, 100 diseases

Mattingly CJ, McKone TE, Callahan MA, Blake JA, Hubal EA. Environ Sci Technol. 2012; 46(6):3046

Shin HM et al., (2011) PMID: 21813367

"Serum perfluorooctanoic acid concentrations predicted by linked exposure and absorption, distribution, metabolism, and excretion models correlated well with observed 2005-2006 human serum concentrations for C8 Health Project participants."

STRESSOR
perfluorooctanoic acid

RECEPTOR
Study participants

EVENT
Medium: Serum
Biomarker: perfluorooctanoic acid
Location: Ohio, United States; West Virginia, United States

OUTCOME

DETAILS

perfluorooctanoic acid	24.300	parts per billion	median
perfluorooctanoic acid	40.000	parts per billion	median
perfluorooctanoic acid	25.800	parts per billion	median
perfluorooctanoic acid	37.500	parts per billion	median
perfluorooctanoic acid	36.600	parts per billion	median
perfluorooctanoic acid	15.300	parts per billion	median
perfluorooctanoic acid	23.000	parts per billion	median
perfluorooctanoic acid	27.500	parts per billion	median
perfluorooctanoic acid	28.900	parts per billion	median

Query flexibility

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ctd™ Giving insight into how chemicals affect our health.

Comparative Toxicogenomics Database

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Chemicals | Name, CAS RN, ID | Search

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Exposure Studies Query

Reference (PMID)

Collection Years

First Author

Study Title: ANY, Agricultural Health Study, CHAMACOS, NHANES, Etc.

Search free text for Refs and Study titles, search CV terms for stressors, receptors, events, and outcomes

Stressor Attributes

Stressor Agent: equals Permethrin

Stressor Source: Environmental, Residential, Occupational, Dietary, Commercial Product, Medicinal

Receptor Attributes

Type: group

Age: equals years

Gender: M/F

Race: Caucasian, African-American, Hispanic, Asian, Indian, Mexican-American

Smoker status: Smoker

Exposure Event Details

Detection frequency: greater than

Country: equals

Outcome Details

Disease: equals

GO-BP: contains

Search

Clear

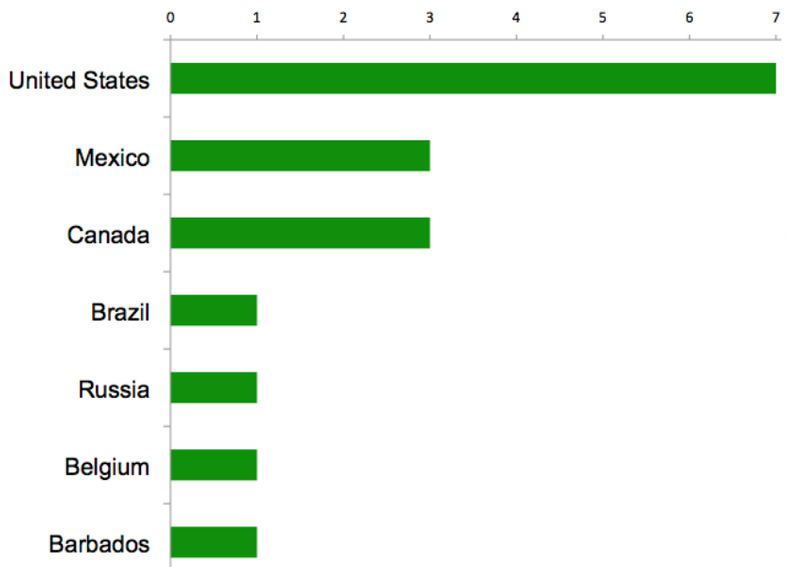
Integrated results

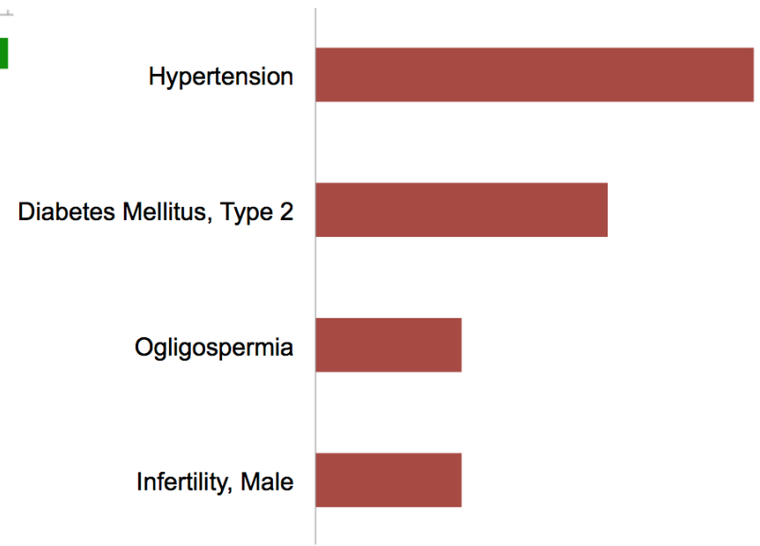
sition we studied.

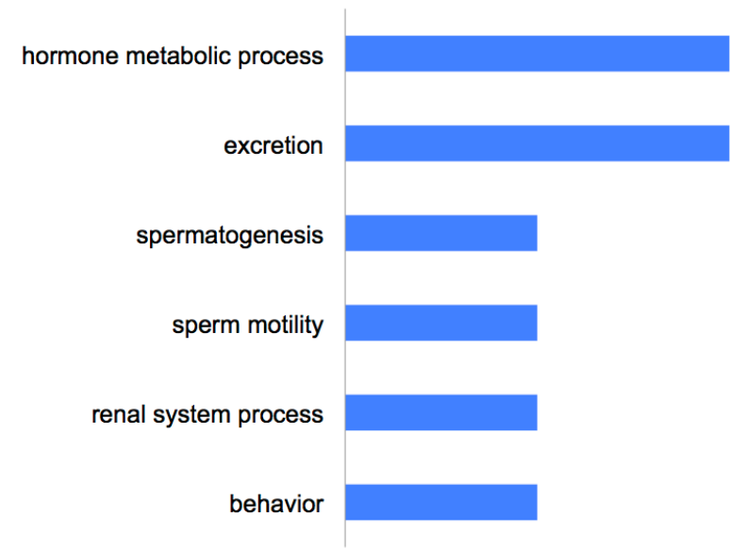
Pesticides

Basics | Gene Interactions | Genes | Diseases | Comps | Pathways | GO | References | Exposure Studies | Exposure Levels

+ Exposure Summary







+ Exposure Studies

Stressor	Receptor	Country	Medium	Biomarkers	Outcome	Author Summary	Details
Pesticides	school children | adults	Russia	Serum | Nails | Indoor Air	Hexachlorobenzene | beta-hexachlorocyclohexane | Dichlorodiphenyl Dichloroethylene | Cadmium | HAVCR1	Growth Disorders | regulation of blood presssure | Cardiovascular diseases	*Serum organochlorine pesticides concentrations measured at 8-9 years of age were associated with reduced growth, particularly reduced body mass index, during the peripubertal period, which may affect attainment of optimal adult body mass and height.*	Burns JS, et al. (2012)
Arsenicals		United States | Canada | Mexico	Urine	dimethyl phosphate | O,O-diethyl dithiophosphate | diethyl phosphate | O,O-dimethyl phosphorothionate | Defoliants, Chemical		*Our data indicate that the most vulnerable segments of our population-children and older adults-have higher exposures to organophosphorus pesticides than other population segments. However, according to dialkylphosphate urinary metabolite data, exposures to organophosphorus pesticides have declined during the last six years at both the median and 95th percentile levels.*	Barr DB, et al. (2011)

bisphenol A

Basics | Gene Interactions | Genes | Diseases | Comps | Pathways | GO | References | Exposure Studies | Exposure Levels

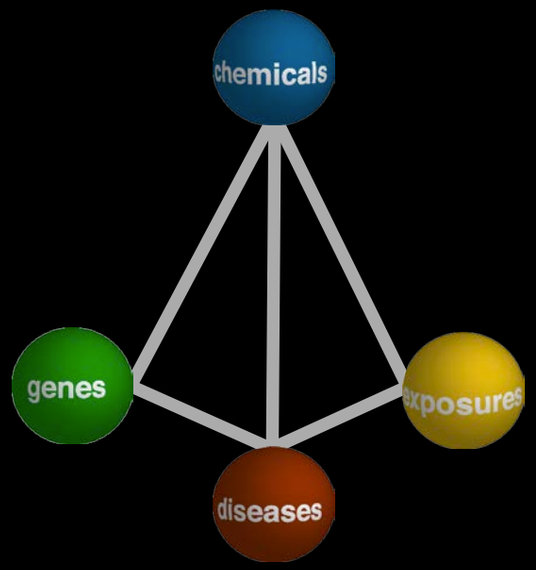
DETAILS

Stressor	Medium	Biomarker	Level	Units	Measurement description	Details
bisphenol A	urine	bisphenol A	1.340	nanograms per milliliter	mean	Nahar, et al. (2012)
Air Pollution	serum	bisphenol A	> 0.700	nanograms per milliliter	median	Nahar, et al. (2012)
Vehicle Emissions	plasma	bisphenol A	< 12.000	nanograms per milliliter	maximum	Nahar, et al. (2012)
bisphenol A	urine	bisphenol A	3.300	micrograms per gram creatinine	median	Madeup et al., (2010)
bisphenol A	urine	bisphenol A, disodium salt A	2.000	micrograms per gram creatinine	median	Madeup et al., (2010)
Estradiol	urine	bisphenol A, disodium salt A	2.600	micrograms per gram creatinine	median	Madeup et al., (2010)
bisphenol A	urine	bisphenol A	0.840	nanograms per milliliter	geometric mean	Madeup et al., (2010)
bisphenol A	urine	TPEN	1.240	parts per million	mean	Sgabjar et al. (2009)
bisphenol A	urine	TPEN	1.000	parts per million	median	Sgabjar et al. (2009)
bisphenol A	urine	TPEN	< 6.200	parts per million	maximum	Sgabjar et al. (2009)
bisphenol A	urine	TPEN	0.790	parts per million	geometric mean	Sgabjar et al. (2009)
bisphenol A	urine	bisphenol A	0.600	nanograms per milliliter	median	Woodruff, et al (2001)
bisphenol A	urine	bisphenol A	12.000	nanograms per milliliter	maximum	Woodruff, et al (2001)
bisphenol A	urine	aluminum-bisphenol A	0.890	nanograms per milliliter	geometric mean	Woodruff, et al (2001)
bisphenol A	urine	bisphenol A	2.830	nanograms per milliliter	mean	Woodruff, et al (2001)
bisphenol A	urine	bisphenol A	2.600	nanograms per milliliter	median	Woodruff, et al (2001)
bisphenol A	urine	bisphenol A	16.100	nanograms per milliliter	maximum	Woodruff, et al (2001)
bisphenol A	urine	bisphenol A	1.960	nanograms per milliliter	geometric mean	You, et al (2007)
bisphenol A	urine	bisphenol A	1.750	nanograms per milliliter	mean	You, et al (2007)
bisphenol A	urine	bisphenol A	1.020	nanograms per milliliter	median	You, et al (2007)
bisphenol A	urine	bisphenol A	10.800	nanograms per milliliter	maximum	You, et al (2007)
bisphenol A	urine	bisphenol A	1.000	nanograms per milliliter	geometric mean	You, et al (2007)
bisphen		A	2.130	nanograms per milliliter	mean	You, et al (2007)
bispher		A	1.020	nanograms per milliliter	median	Cantonwine, et al (2010)
bispher		A	10.800	nanograms per milliliter	maximum	Cantonwine, et al (2010)
bispher		A			mean	Galloway, et al (2009)
bispher		A				Galloway, et al (2009)
bispher		A				Galloway, et al (2009)

data displayed if chemical or its descendant is in the “Stressor” **<u>or</u>** “Biomarker” column

STRESSOR		RECEPTOR	EVENT			OUTCOME	AUTHOR SUMMARY	REFERENCE
Agent	Source	Description	Country	Medium	Biomarker(s) assayed	Phenotype		
bisphenol A	commercial product	grumpy old men	Brazil	Serum	Hexachlorobenzene | beta-hexachlorocyclohexane | Dichlorodiphenyl Dichloroethylene	Alopecia	Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat	Burns JS, et al. (2012)
resveratrol	commercial product		United States | Brazil | Mexico	Urine	dimethyl phosphate | O,O-diethyl dithiophosphate | diethyl phosphate | O,O-dimethyl phosphorothionate		Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat	Barr DB, et al. (2011)
TCDD		kittens	Brazil	Urine	Cadmium | HAVCR1	Kidney Diseases	Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco	Pennemans, et al. (2011)

Acknowledgements



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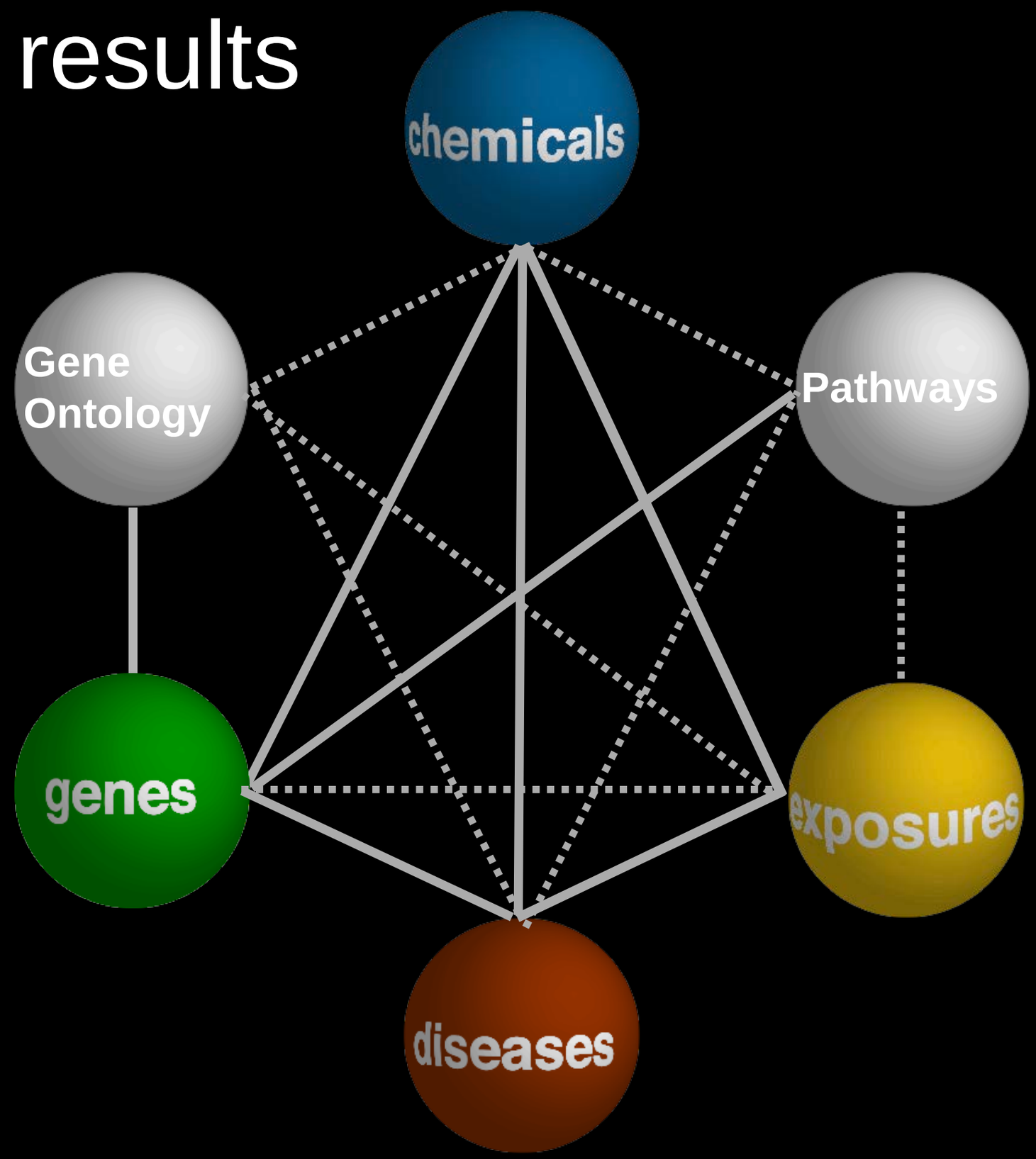
Funding:

NIEHS (curation)

ACC (ExO development)

Curated Chemicals	12,985
Curated Genes	32,464
Curated Diseases	6,354
Chemical-Gene Interactions	869,902
Unique Chemicals	10,150
Unique Genes	31,344
Unique Organisms	492
Curated Gene-Disease Relationship	27,397
Curated Chemical-Disease Relationships	186,986

>300 manuscripts using CTD data
>30 public databases incorporating CTD data

Integrated results