



# Framework for computationally-predicted AOPs

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# Objective

## Given:

- **Large numbers of chemicals we know little to nothing about**
- **Multiple 'omics' type studies and screening data**
- **AOPs are useful tools for connecting HTS to regulatory endpoints**

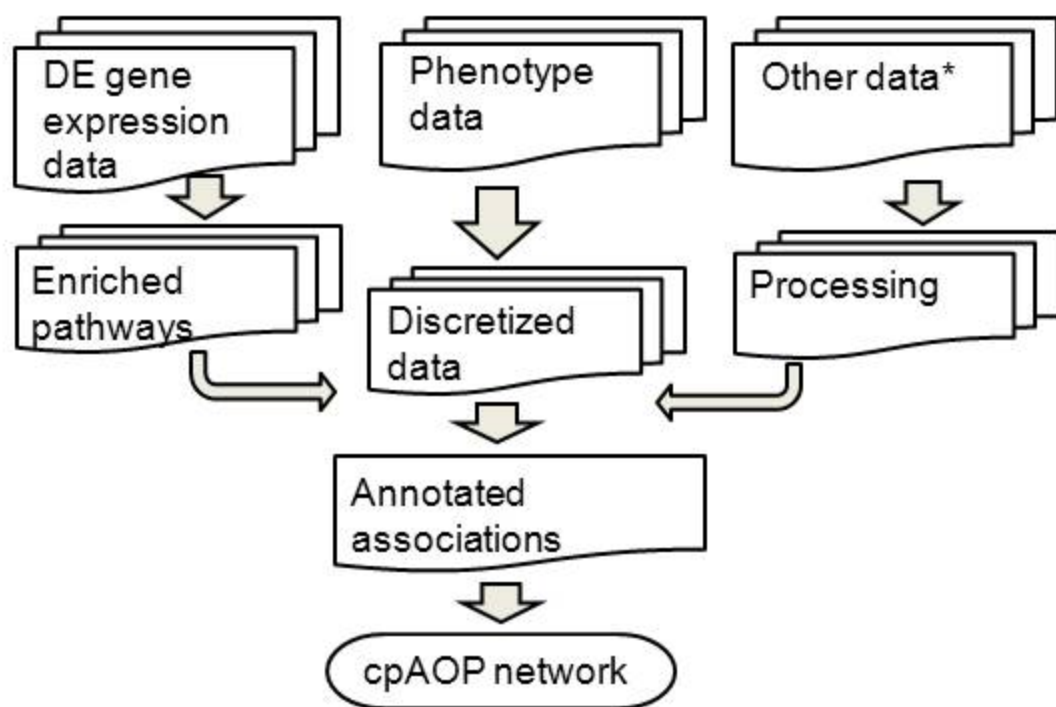
## Can we:

- **Create an approach that can identify 100s of putative AOPs using this data**

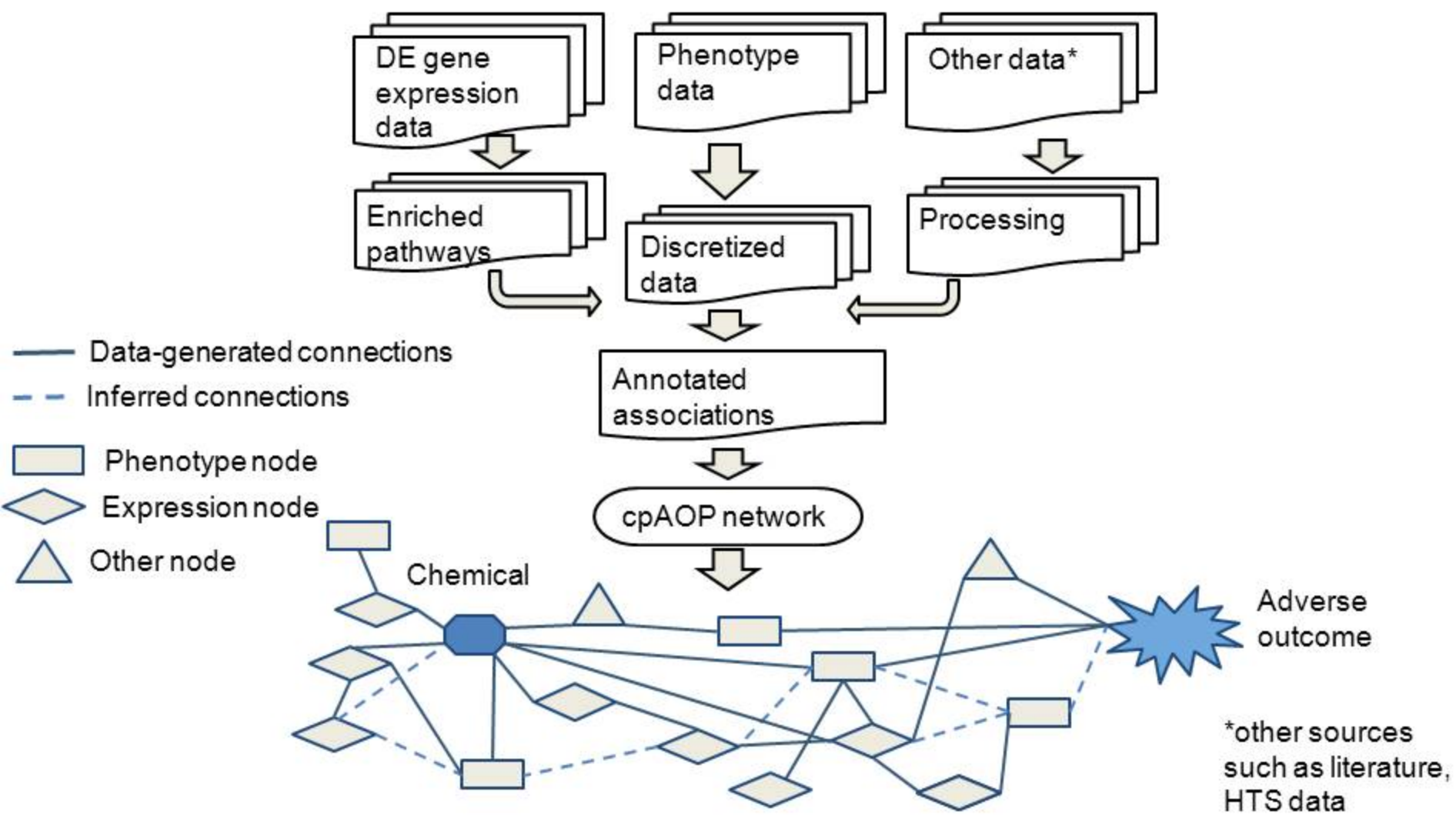


# What do we need?

- **Methods that can deal with**
  - **Sparse, categorical, continuous data**
  - **Missing values and mixed data types**
  - **Lack of “training set” or gold standards**
  - **New data streams - framework for data integration**
- **Outputs that are informative and intuitive to biological domain experts**
  - **This is key for helping evaluate the cpAOPs**



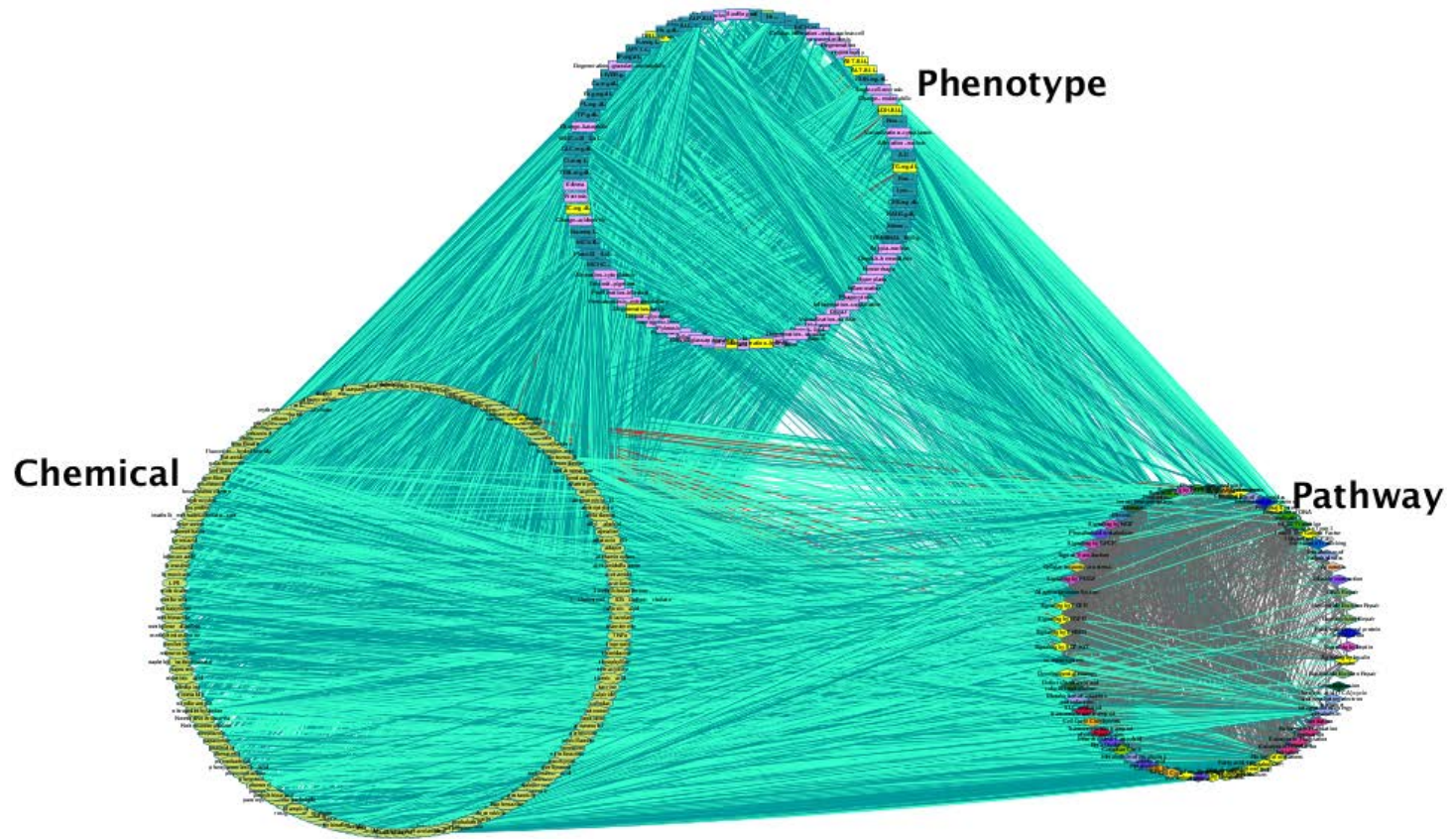
\*other sources  
such as literature,  
HTS data





# Creating a cpAOP network

- **TG GATES data**
  - **Large screen of hundreds of chemicals**
    - **Used only rat liver data**
  - **Includes microarray, clinical chemistry and pathology data**
- **Resulting network has liver-focused cpAOPs**

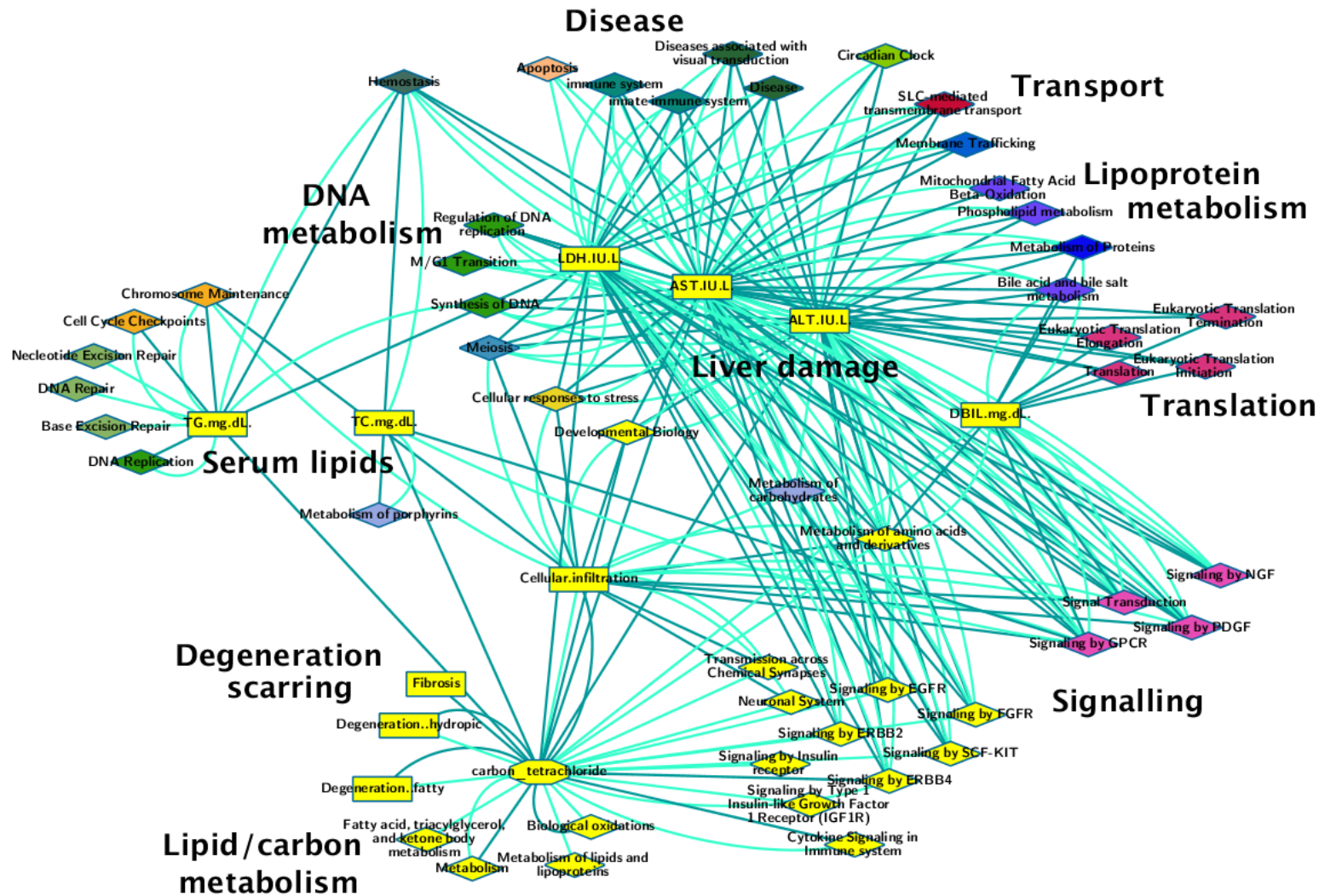


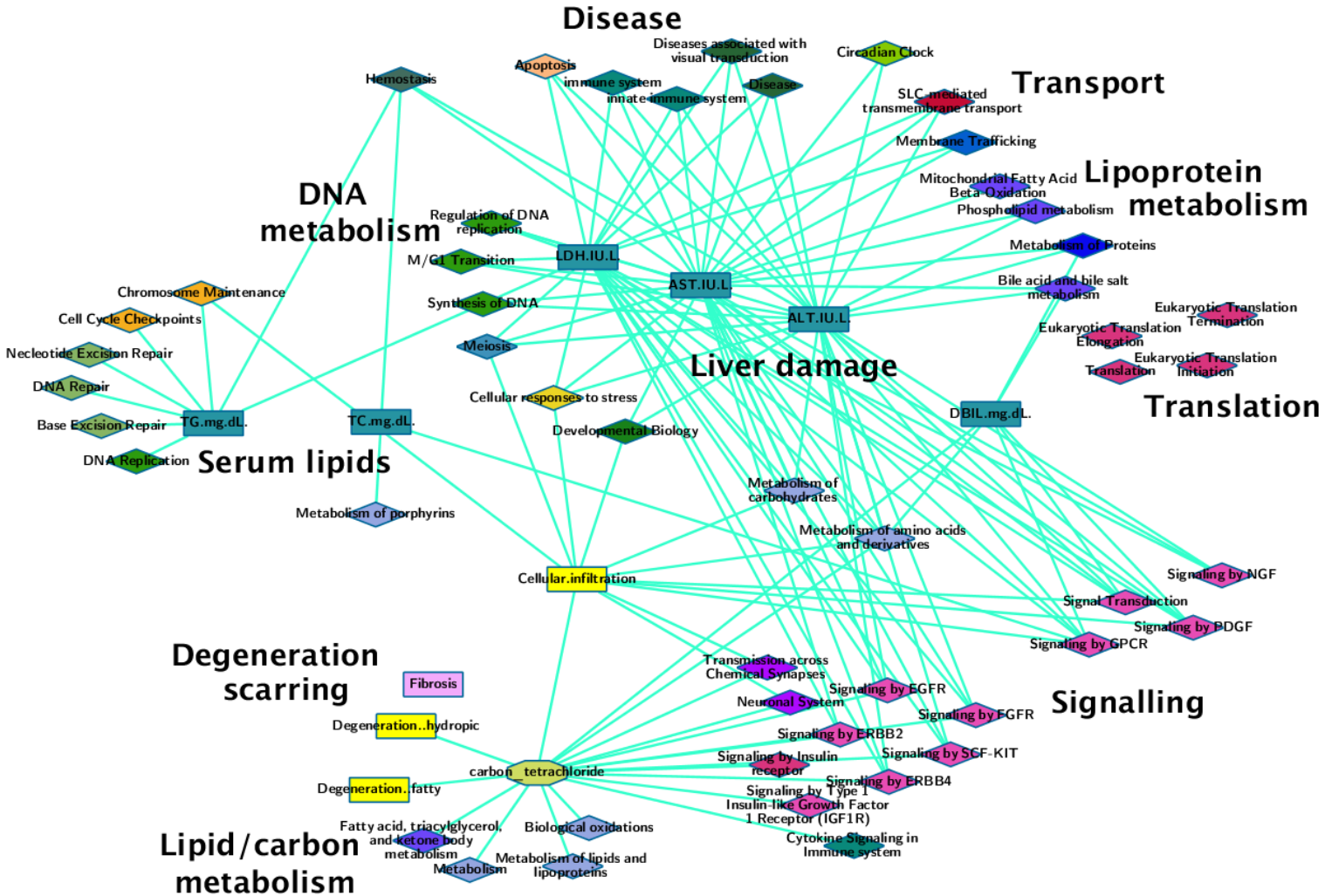


# Carbon tetrachloride example

- **Given:**
  - **Large cpAOP network enriched with liver-specific data**
- **Objective:**
  - **Probe cpAOPnet to find an adverse outcome pathway associated with CCl<sub>4</sub>**







# Data-driven computationally predicted AOP

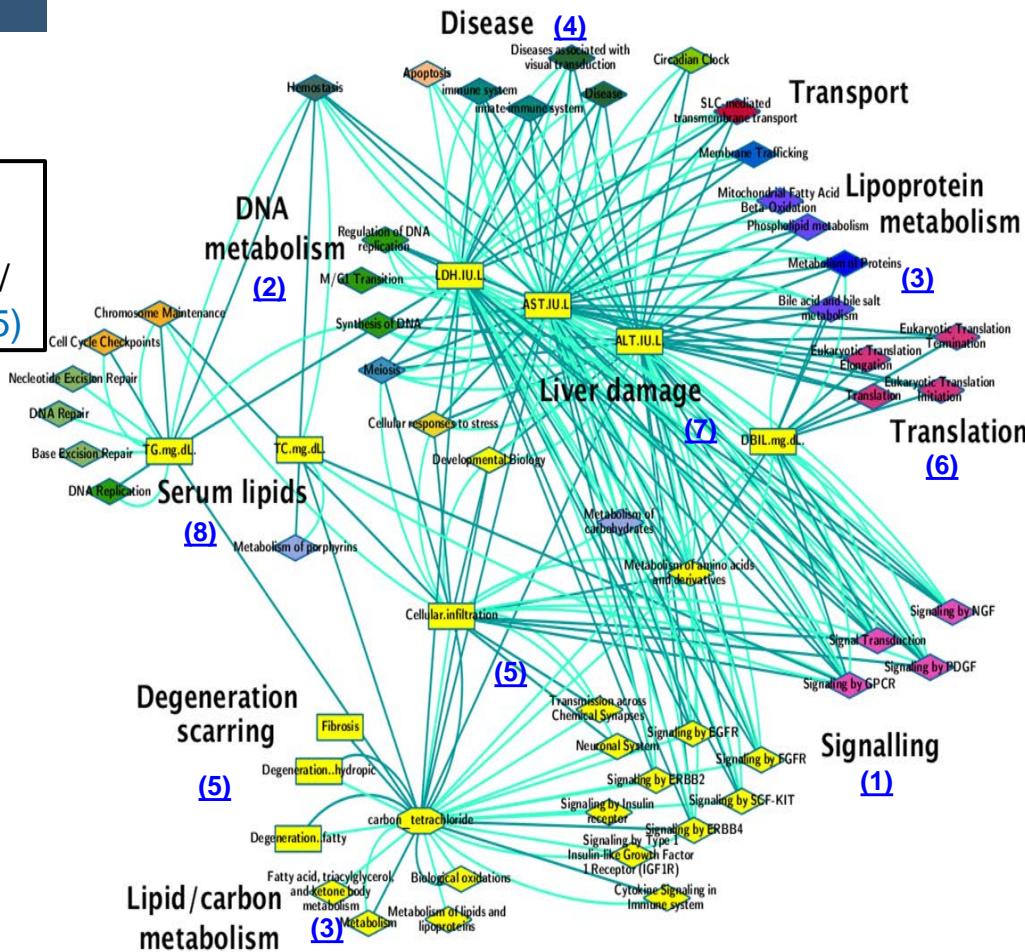
Exposure to CCl<sub>4</sub>

Initial transcription events

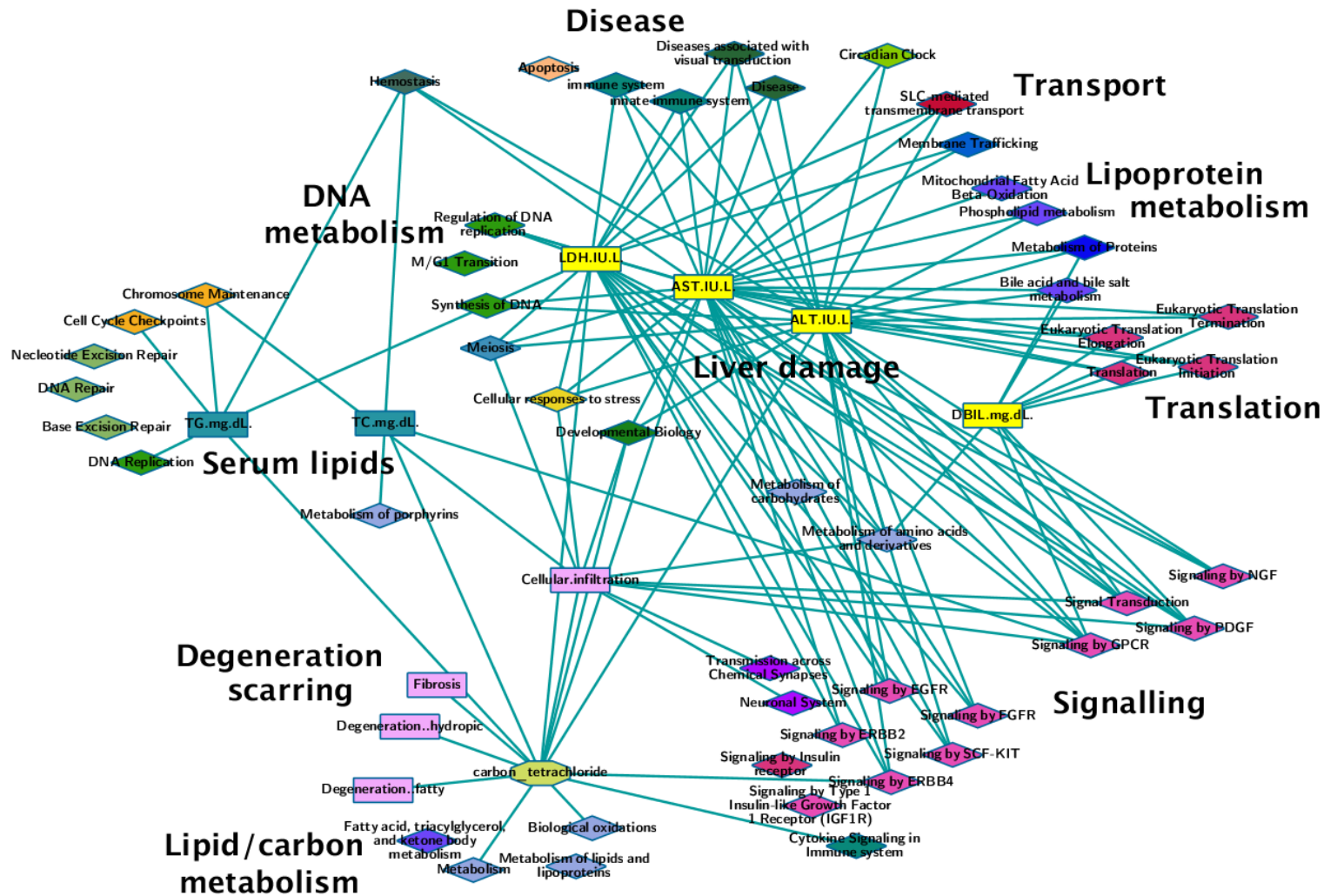
- Cell signaling (1)
- Changes in DNA metabolism (repair, proliferation) (2)
- Lipid metabolism, oxidation (3), disease (4)

Phenotypic events

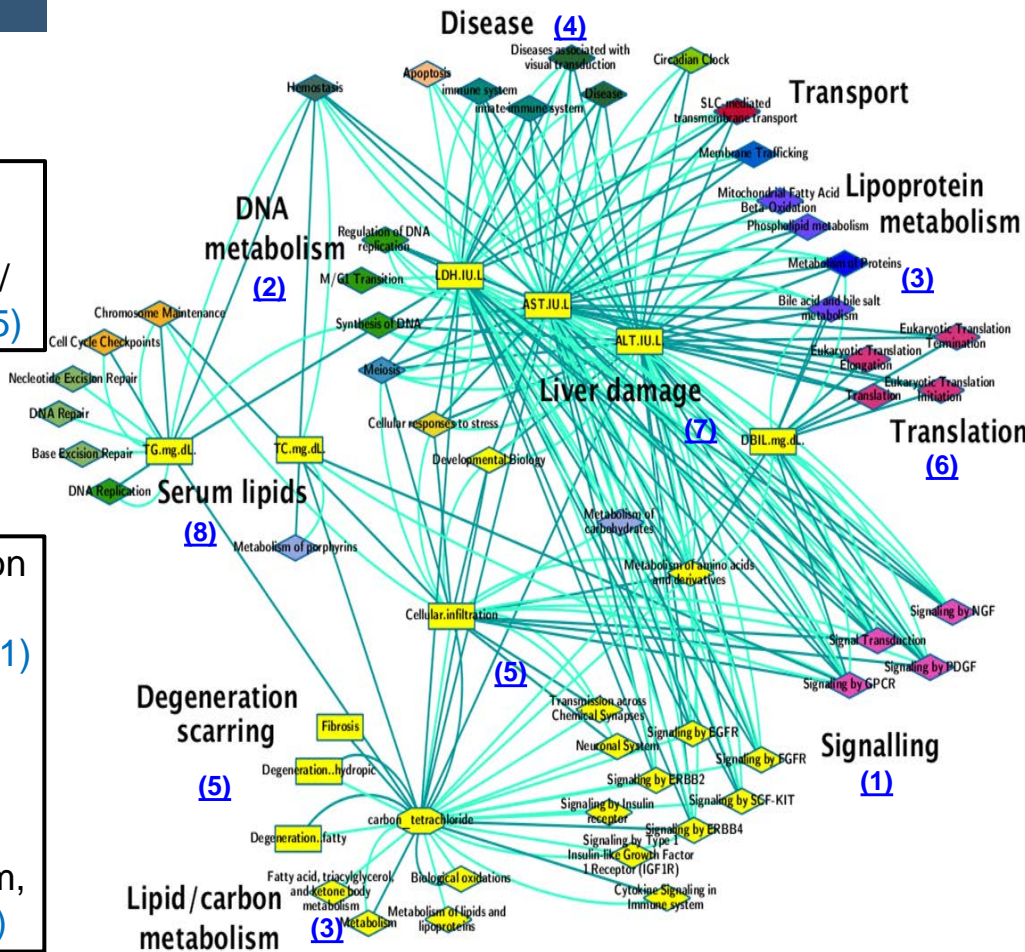
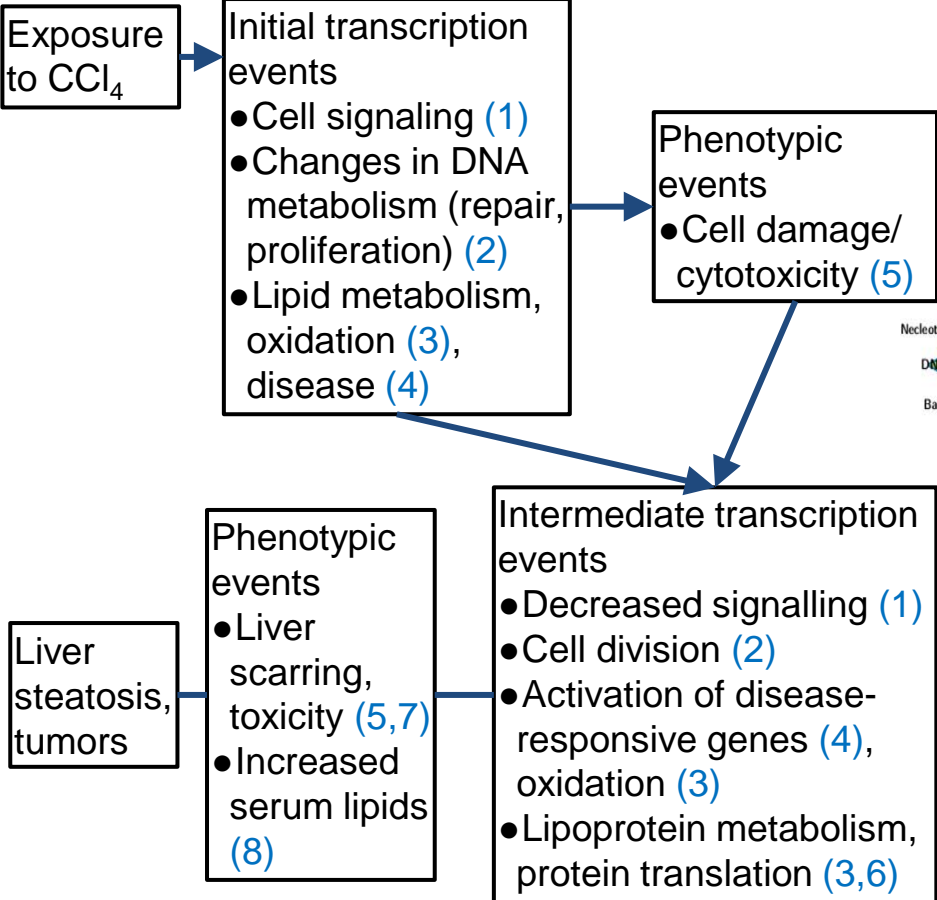
- Cell damage/cytotoxicity (5)



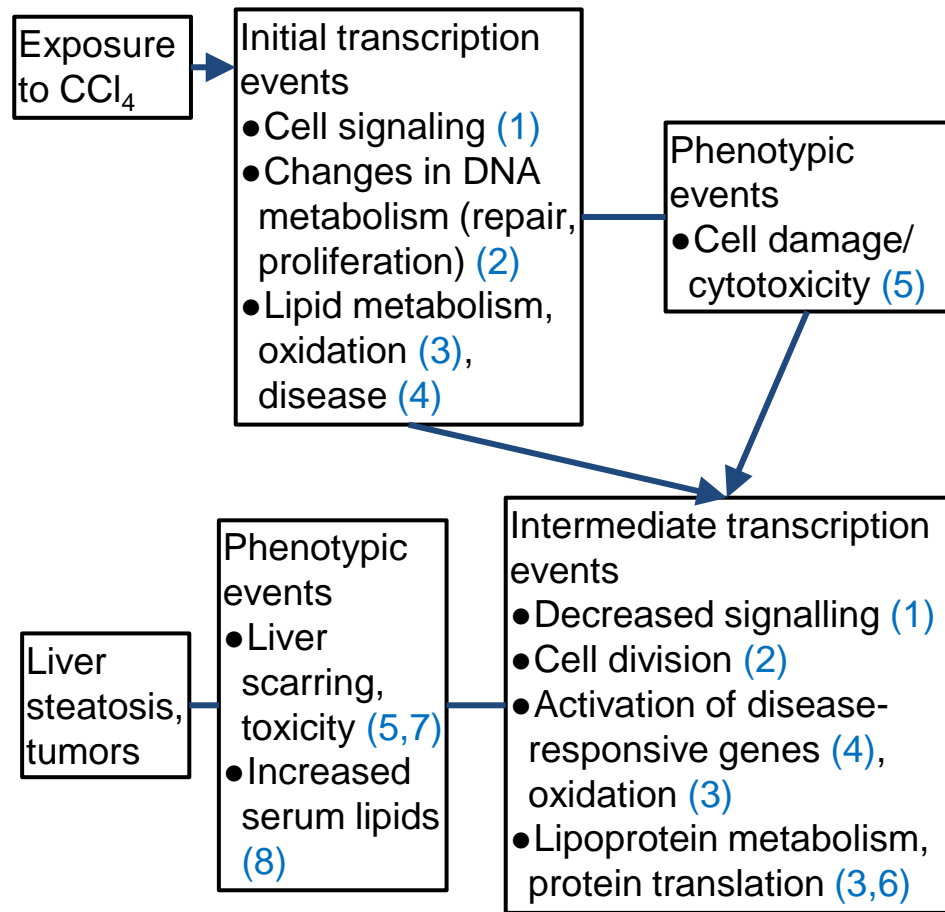




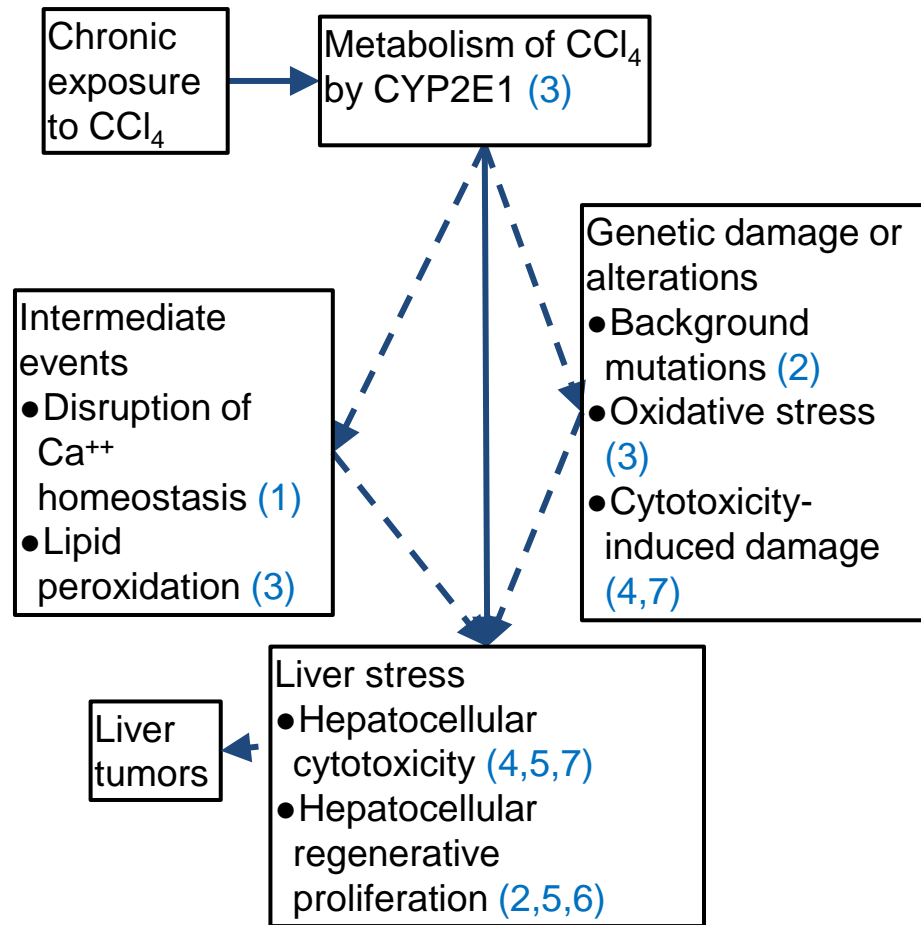
# Data-driven computationally predicted AOP



## Data-driven computationally predicted AOP



## Hypothesized mode of action adapted from EPA CCl<sub>4</sub> IRIS assessment





## Take home

- **Developed a framework for integrating diverse information**
  - **Framework is flexible to data types using edge properties to hold meta data**
- **Demonstrated a (manual) way to extract cpAOPs associated with a chemical from the network**



## Future work

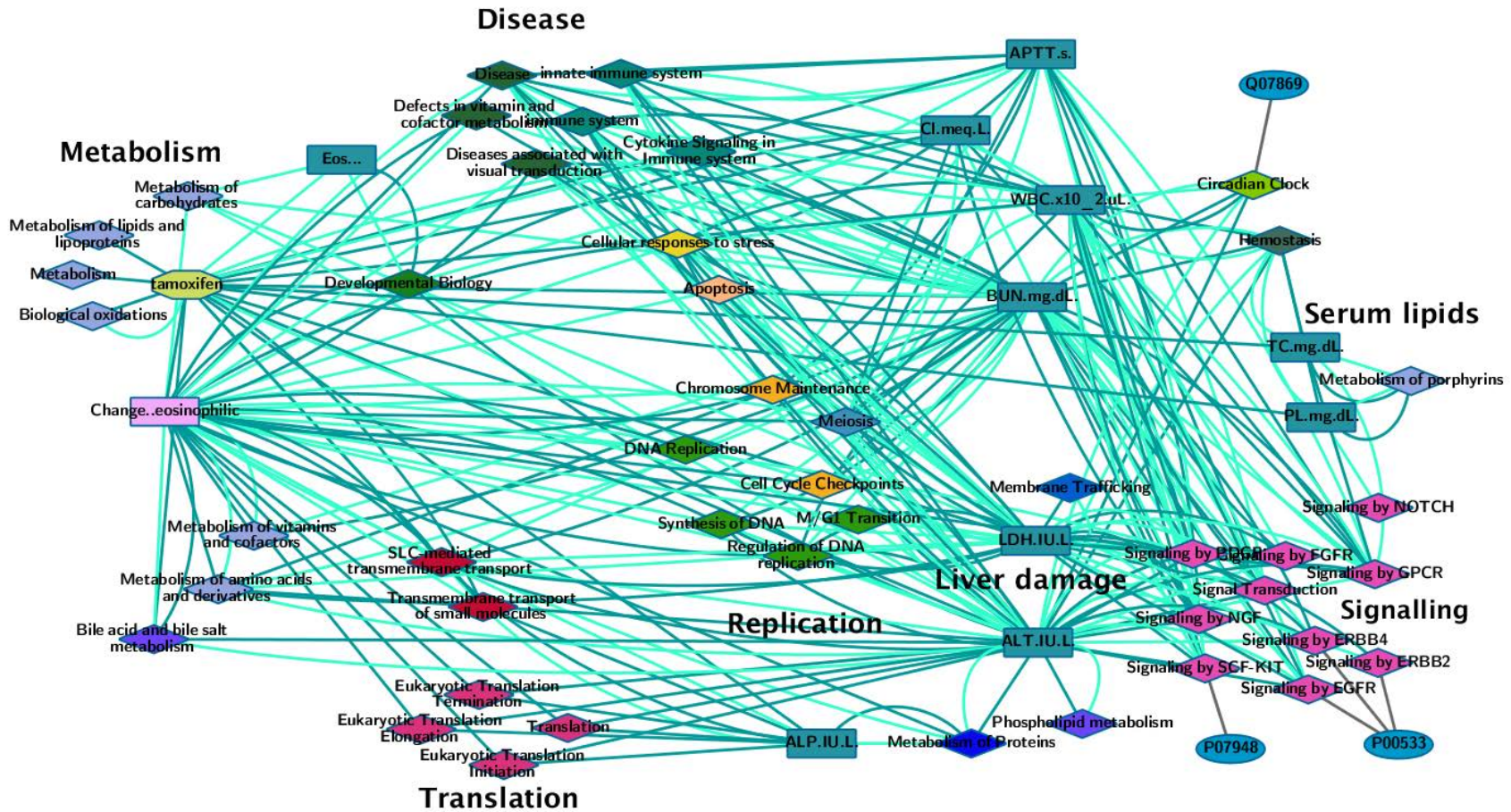
- **Automating the cpAOP identification and ranking**
  - **Engage domain expertise for model refinement**
  - **Generate “straw man” cpAOP to serve as a starting point for curation**
  - **Conform to established AOP definitions**
- **Integrate Tox21-type data**
  - **Challenge is in matching names!!**





# Implications

- **Provide AOPs for more HTS assays - enhanced interpretation**
- **cpAOPs can feed AOP development efforts**
- **Point towards new assay needs**





**Thank you**

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**Noffisat Oki, ORISE**

**Lyle Burgoon, US EPA**