

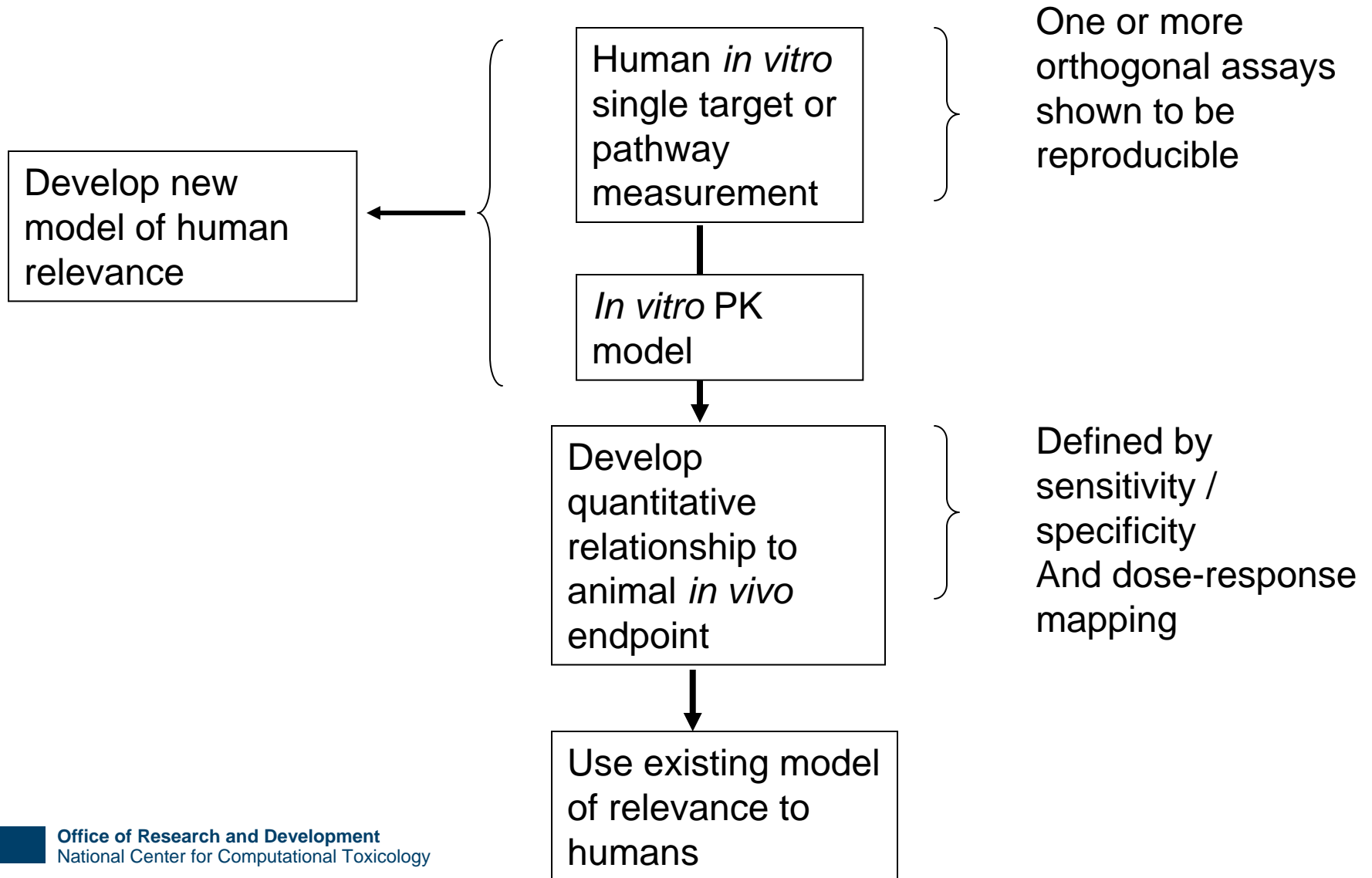
# Screening, Prioritization, Modeling of *In Vivo* Toxicity from *In Vitro* Assays

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



**COMPUTATIONAL  
TOXICOLOGY**

# Alternative Approaches / Pathway Profiling

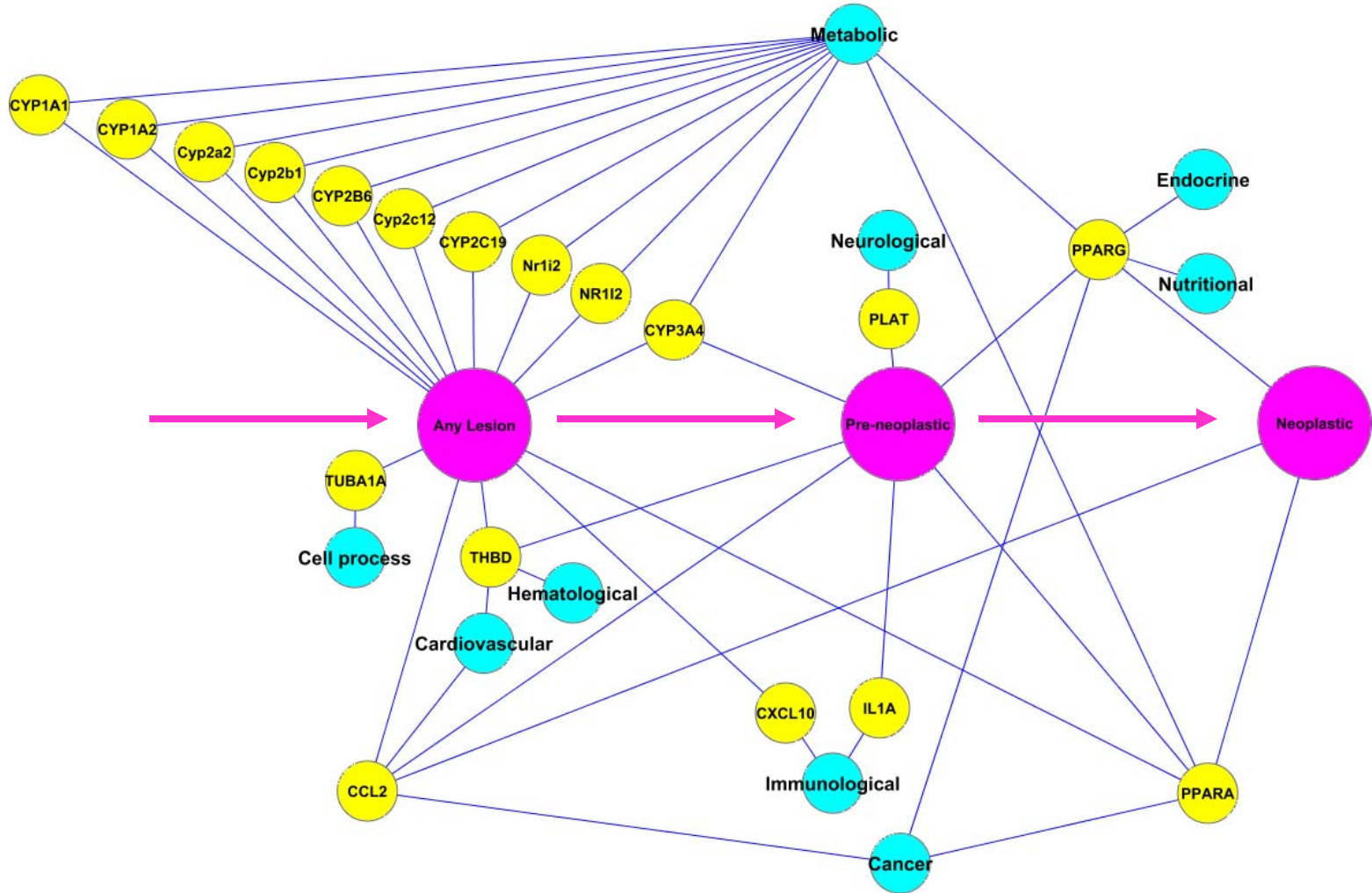


# Key Challenges Of Pathway Profiling

- Find the Toxicity Pathways
  - Hepato vs developmental neurotoxicity
- Obtain HTS Assays for Them
  - Including metabolic capability
- Screen Chemical Libraries
  - Coverage of p-chem properties
- Link Results to *in vivo* Effects
  - Gold standard and dosimetry



# Rat Liver Disease Progression Links



Links Drawn for Univariate Associations with  $p < 0.01$

# Signature Performance – Proliferative Lesions

*In vivo* data

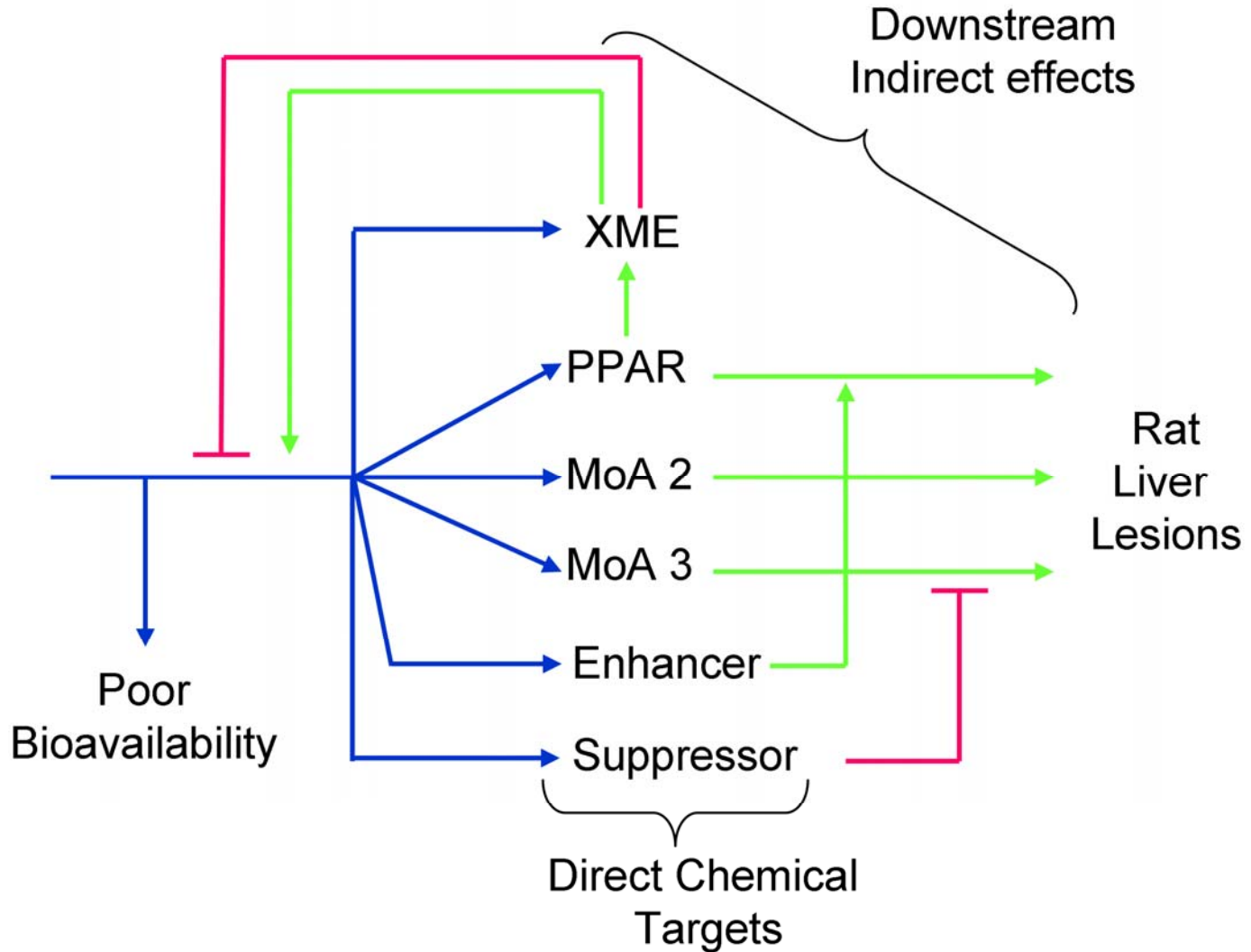
Signature

	+	-
+	31	11
-	30	176

Sensitivity=51%  
Specificity=94%

- 248/309 chemicals had rat data in ToxRefDB (used for model building)
- 8 other chemicals were predicted to be positive
  - PFOA: Causes rat liver adenomas
  - PFOS: Causes rat liver adenomas
  - Diniconazole: rat liver hypertrophy
  - Chlorothalonil: rat liver enlargement, kidney tumors
  - TCMTB: testicular and thyroid adenomas
  - No data for Niclosamide, Methylene bis(thiocyanate), Phenoxyethanol

# Toxicity is Multi-factorial



# Multifactorial Scoring

