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Workshop on Predicting Human Health Effects from Environmental Exposures: Applying Translatable and Accessible Biomarkers of Effect
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Biomarkers of Effect Use in Environmental Health Research and Decision Making: MicroRNAs as an Example

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Presentation outline

1. Biomarker definitions and regulatory drivers for use
   a) Adverse Outcome Pathway (AOP) framework
2. Ideal characteristics of a biomarker of effect
   a) Context of use for regulatory decision making
3. Development of microRNA biomarkers and the road ahead

Biomarker – broad definition

An indicator signaling an event or condition in a biological system or sample and giving a measure of ***exposure***, ***effect***, or ***susceptibility***.

Such an indicator may be a ***measurable*** chemical, biochemical, physiological, behavioral, or other alteration within an organism.

(OECD, Collection of Working Definitions 2012; US National Academy of Sciences report, US NRC, 1989b; WHO International Programme on Chemical Safety, Biomarkers and Risk Assessment: Concepts and Principles 1993)

Drivers for biomarker development and use in toxicology

Higher-throughput, lower cost, and human-relevant toxicity testing

- National Research Council (NRC) - *Toxicity Testing in the 21st Century*
- European Commission - *Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH)*
- US Environmental Protection Agency (US EPA) – *The Next Generation Blueprint for Computational Toxicology*

Predictive toxicology in risk assessment, identification of vulnerable populations

- US EPA - *Frank R. Lautenberg Chemical Safety Act*
- NRC – *Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*

Systems-level integration

- National Academy of Sciences (NAS) **–** *Use of Emerging Science for Environmental Health Decisions*

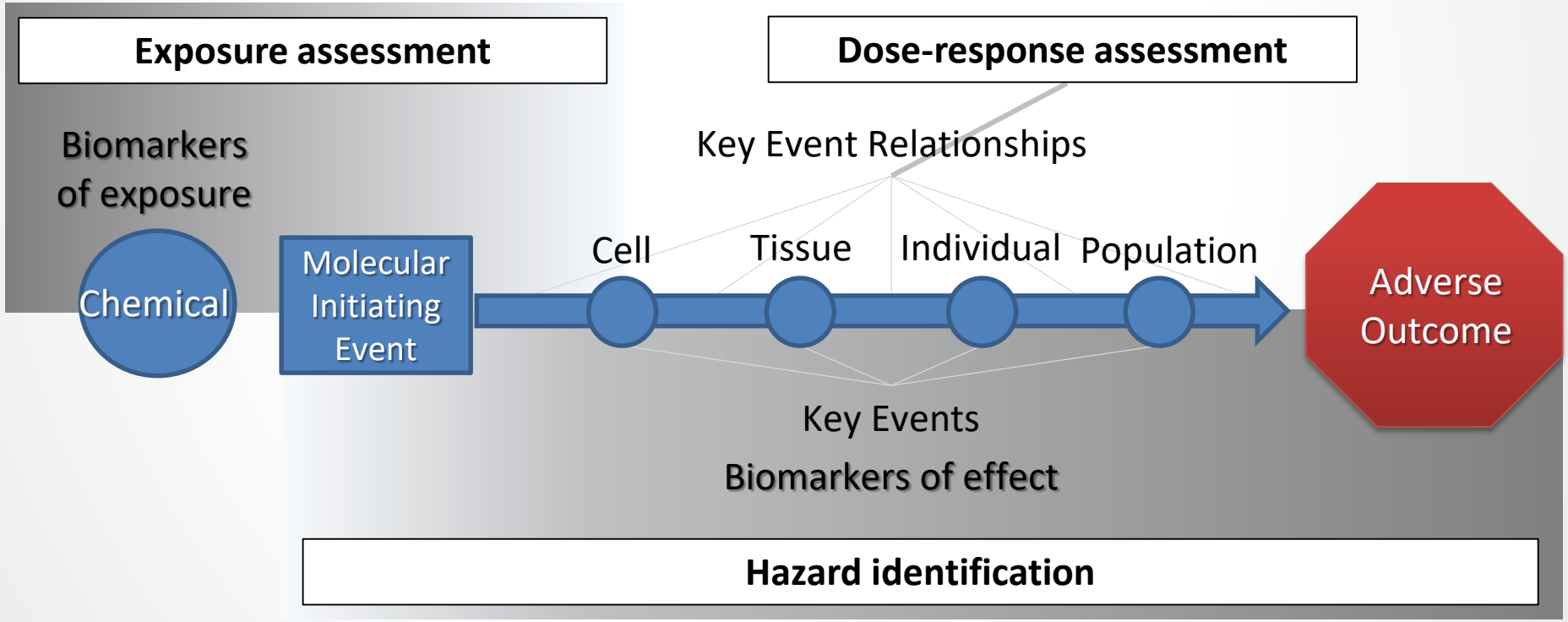
Biomarkers in toxicology

- **Biomarkers of exposure**
  - assess the amount of a chemical that is present within the body
- ***Biomarkers of effect***
  - indicators of a change in biologic function in response to a chemical exposure
- **Biomarkers of susceptibility**
  - factors that may make certain individuals more sensitive to chemical exposure

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/defining-pesticide-biomarkers#table2

Regulatory context considerations

Determining risks to human health due to chemical exposure
Integration of biomarkers



Characteristics of an ideal biomarker

Highly specific biomarker = low false positive rate ← **Specific**

Sensitive → Highly sensitive biomarker = low false negative rate

Early indication of adverse outcome ← **Predictive**

Robust → Rapid, simple, accurate, inexpensive
Large measurement range

Bridge model system to human condition ← **Translatable**

Non-invasive → Present in accessible matrices

modified Table 1 from Etheridge et al., 2011 *Mut Res* PMID: 21402084

Characteristics of an ideal biomarker

Specific

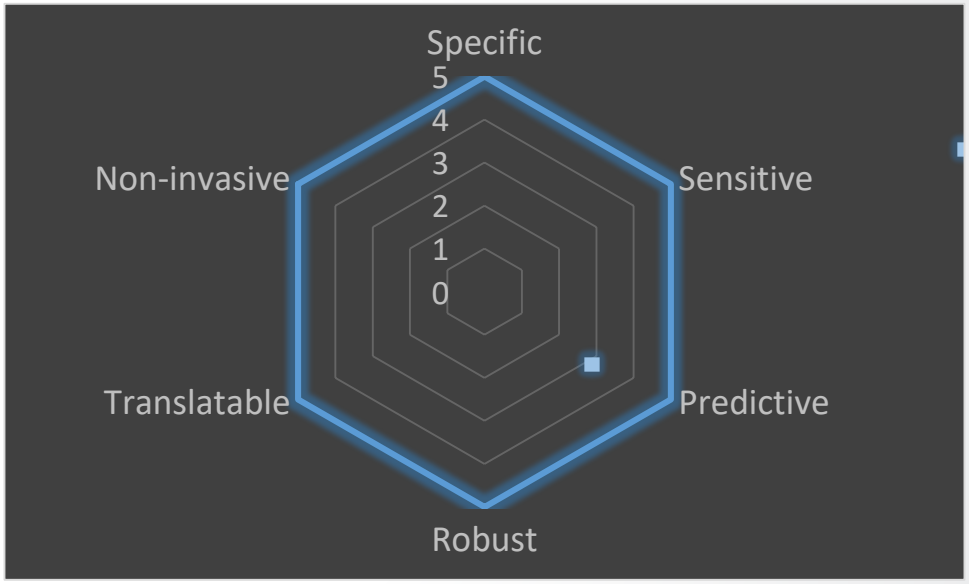
Sensitive

Predictive

Robust

Translatable

Non-invasive

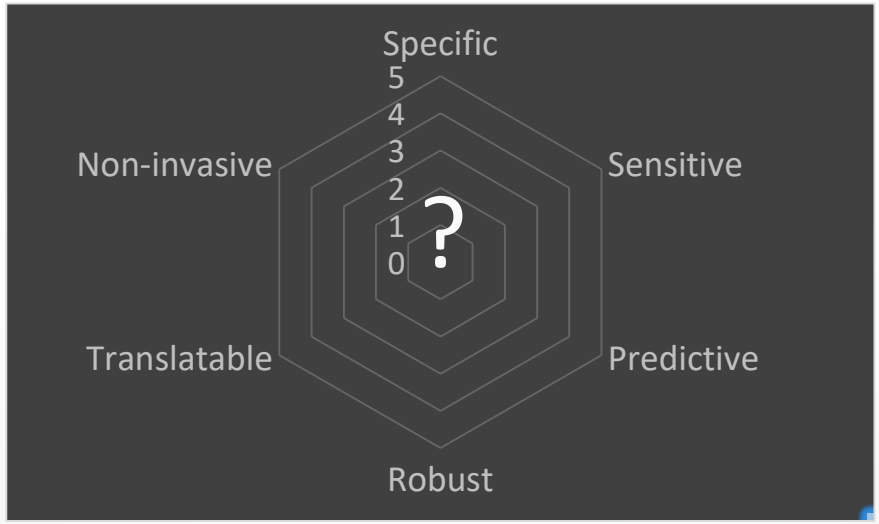


Characteristic importance
5 = most ; 1= least

Regulatory biomarker of effect use

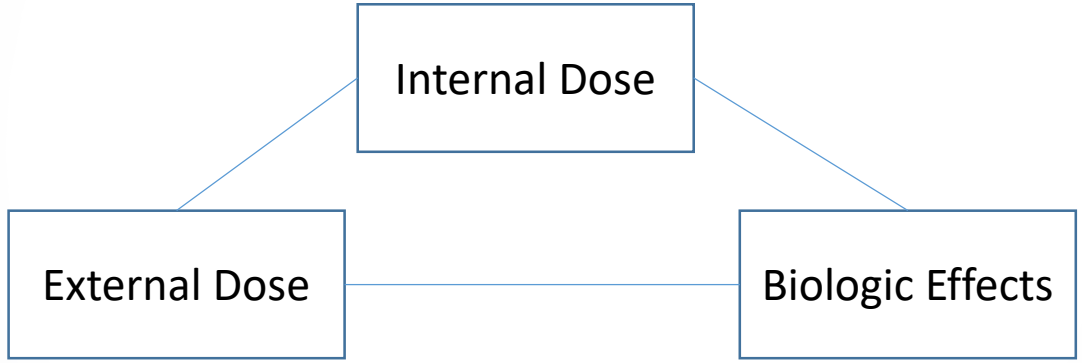
Regulatory context-of-use

- **Biomonitoring** (Exposure)
- **Hazard prioritization** (Hazard ID, Dose response)
- **Hazard identification/weight-of-evidence** (Exposure, Hazard ID, Dose Response)



Contexts of use: Biomonitoring

- Most biomonitoring utilizes **biomarkers of exposure**
- Those most helpful for risk assessment have strong operational relationships of external dose, internal dose and biologic effects



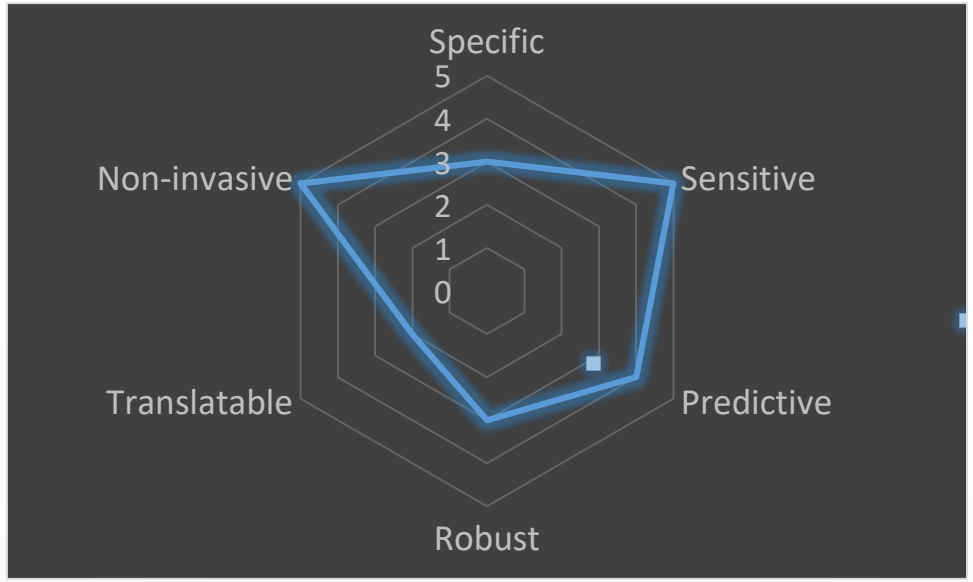
Adapted from Bernard and Lauwerys 1986

- In this context, ***biomarkers of effect*** could be "indirect measures of exposure linked to a biological effect"
  - Genotoxicity biomarkers

Ladeira and Viegas
Biomonitoring 2016

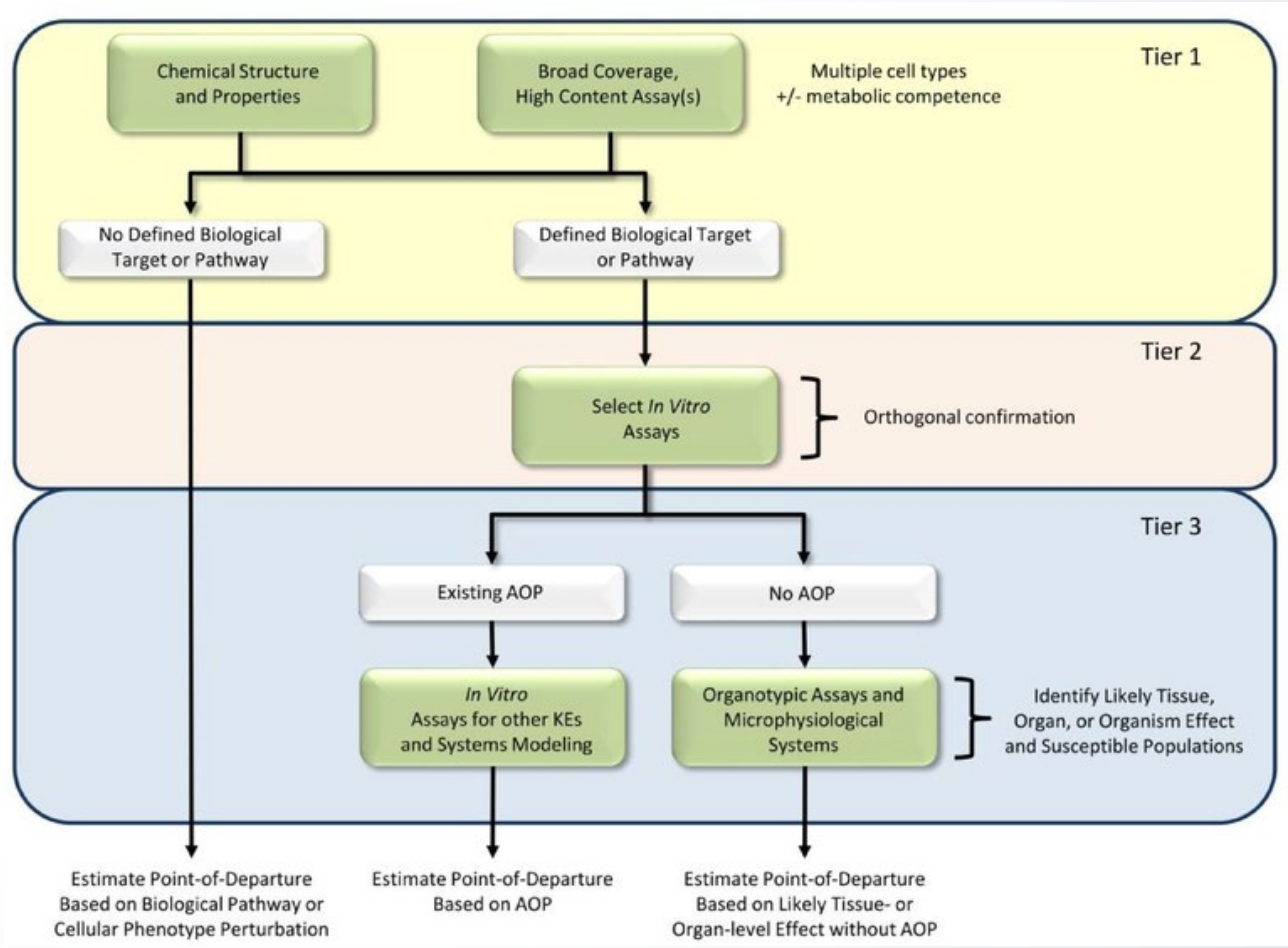
Contexts of use: Biomonitoring

- In the context of biomonitoring, what characteristics do we want for biomarkers of effect?



Contexts of use: Hazard prioritization

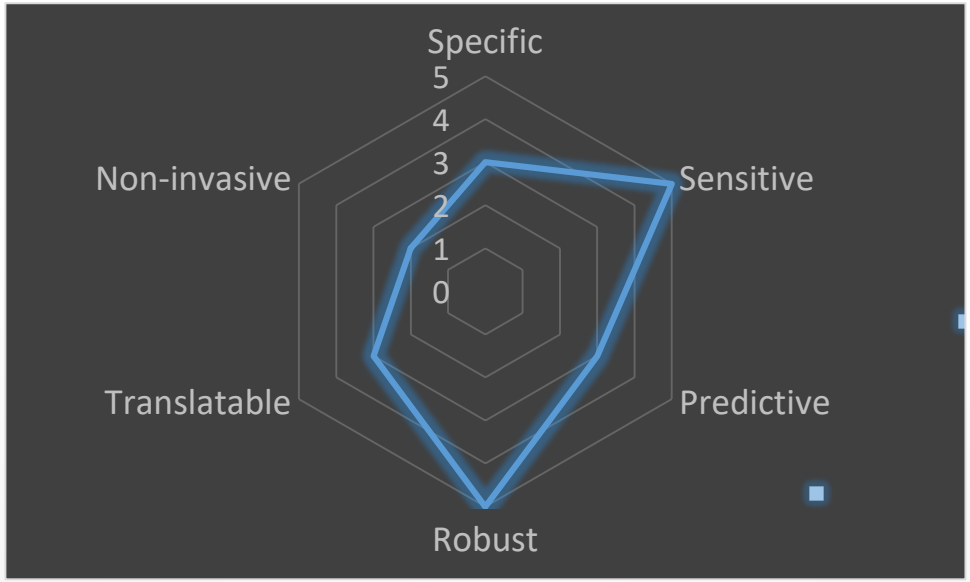
- **"The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency"**
- High-throughput predictive endpoint measurements for thousands of assays
- Current limitations to connect molecular level alterations to more apical adverse outcomes
- Biomarkers of effect are integral for all 3 tiers of testing



Thomas et al. *Tox Sci* 2019

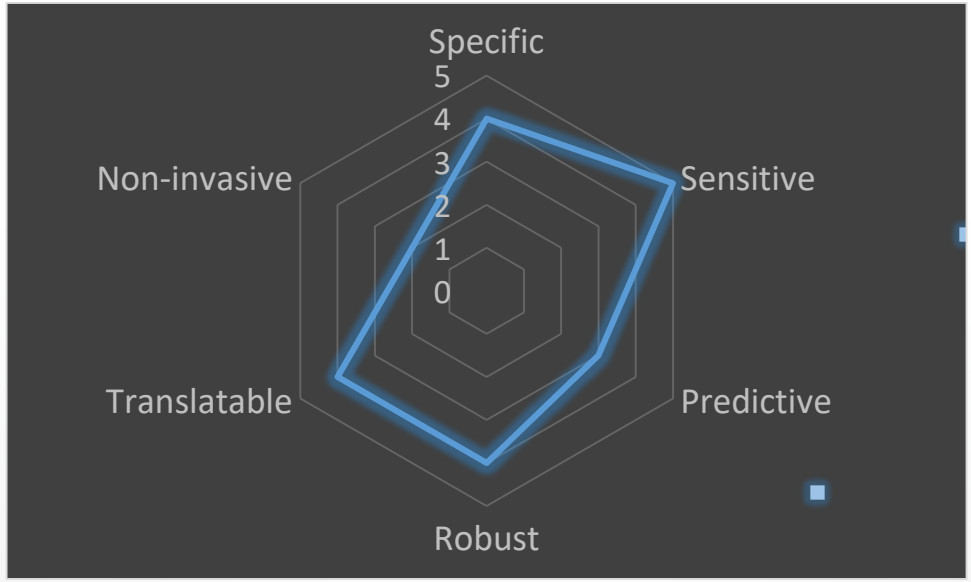
Contexts of use: Hazard prioritization

- In this context, a screening framework is important
  - **Minimize false negatives over false positives** (high sensitivity over high specificity)
  - Quantitative (robust assays)
  - Early change predictive of human adverse outcomes (depending on Tier)



Contexts of use: Weight of Evidence (WoE)

- **Cumulation of evidence to make a regulatory decision**
  - Holistic: suite of biomarkers, multiple models
  - Indicative of human adverse outcome (translatable)
  - Avoid false positives and negatives (sensitive and specific)
  - Clear assessment to define adverse dosage (robust)



Newer technologies and knowledge - newer biomarkers

Epigenetic

Proteomic

Metabolomic

Toxicogenomic

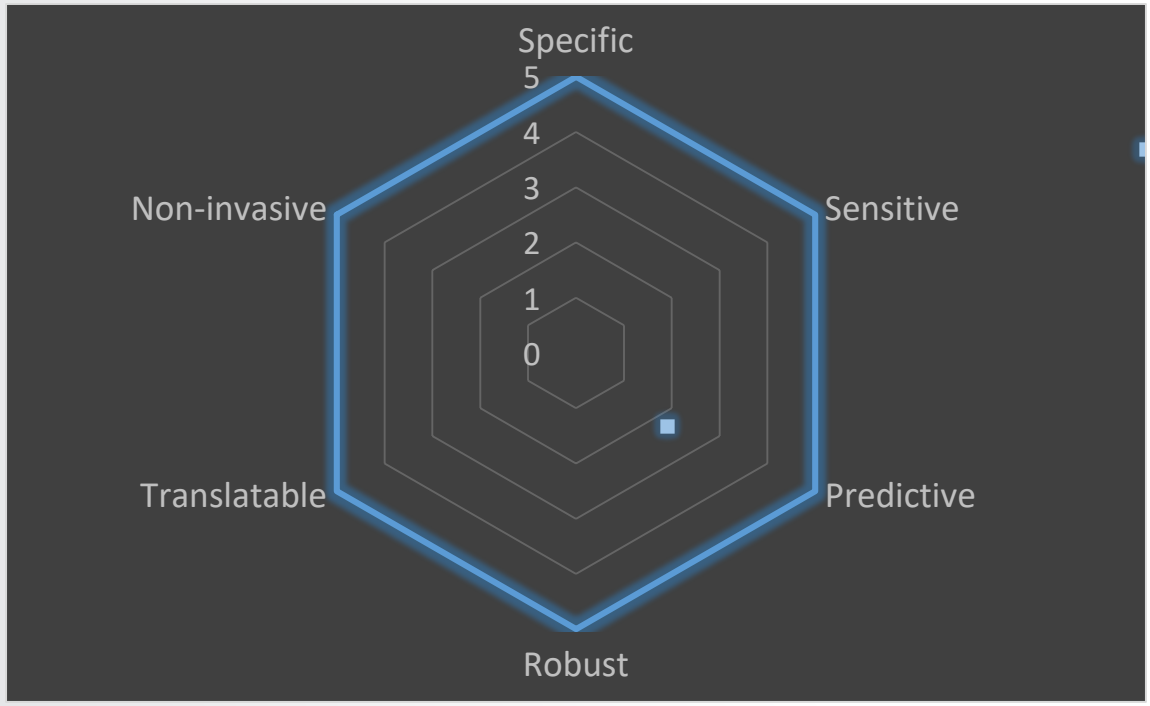
Genotoxic

Tissue toxicity and disease

Inflammation, neurologic, urologic

Computational integration

MicroRNAs – the perfect biomarker?



- Regulatory non-coding RNA
- Tissue specific
- Early and robust alterations
- Many available methods
- Conserved in model species
- Found in biofluids

Roadmap to qualification: kidney microRNA biomarker panel

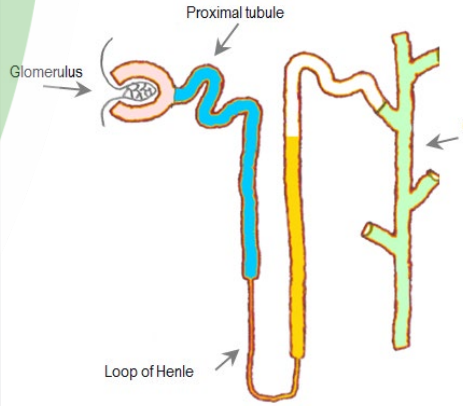
Qualified microRNA biomarker panel

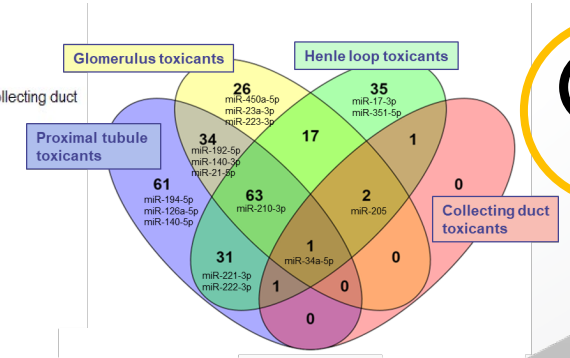
Prepare documents

Validation with reference chemicals

Develop methods and tools urine miRNA

Application to case studies





Finalize kidney miRNA meta analysis and candidate selection

The Health and Environmental Sciences Institute (HESI)

EPA at 50 Progress for a Stronger Future

Summary

- Integrating biomarkers of effect into chemical risk assessment for human health has been a discussion point for decades
- Regulatory drivers to reduce uncertainty, increase relevance, and reduce time/cost for assessment
- Linkages to adverse outcome pathways may aid in development
- The qualities of an ideal biomarker may vary in importance within context of use
- Regulatory use important to fill in gaps of knowledge for weight-of-evidence
- Newer technologies and approaches resulting in recent trend of development
- Highlighting microRNAs as a developing biomarker of effect

Thank you!

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