

# Re-Envisioning Toxicity Assessment @ NTP

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## New DNTP Vision (2019)

“To improve public health through the development of data and knowledge that is *translatable, predictive and timely.*”



Brian R. Berridge, DVM, PhD, DACVP  
Scientific Director, Division of NTP



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Human-Relevant

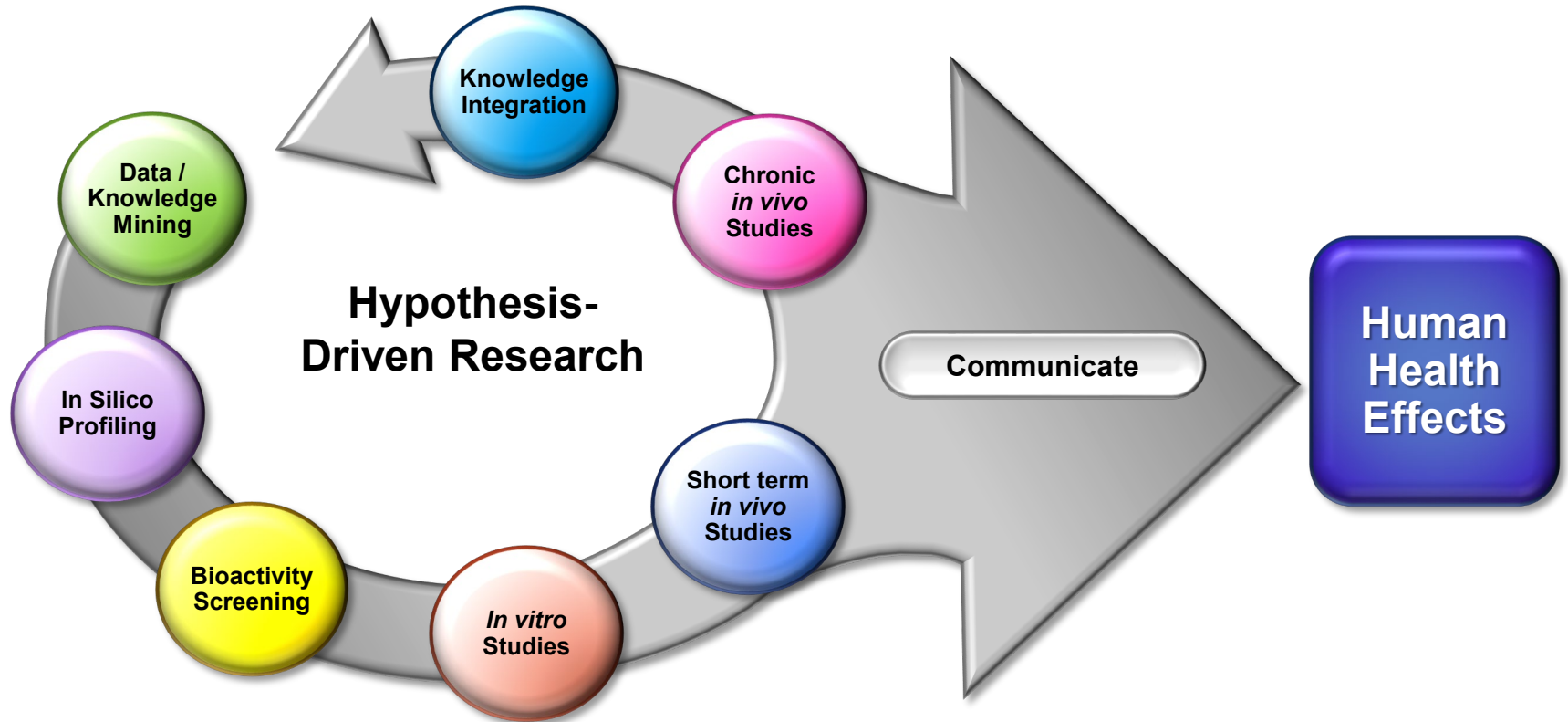
Impactful



Brian R. Berridge, DVM, PhD, DACVP  
Scientific Director, Division of NTP



# Translational Toxicology Pipeline



Applying our capabilities in deliberate, integrated and complementary ways.



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# Types of Programs at NTP

- **Single Agents** – e.g., Arsenic, Benzene
- **Agent Classes** - e.g. PAHs, PFAS



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- **Health Effects Innovation (HEI) areas**



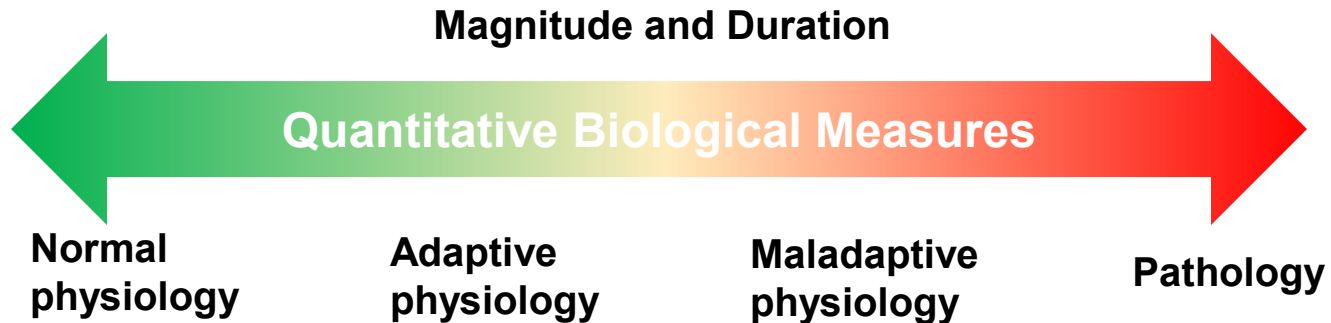
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Move towards a model where deep understanding of human pathobiology informs the evaluation of risk



# Key Challenge – Pathobiology Is Continuum



- Transition from normal to abnormal is generally not binomial.
- Thresholds of biological perturbation that represent ‘toxicity’ are difficult to define and not generally well understood mechanistically.
- Contextualizing those perturbations in a myriad of possible individual susceptibilities is even more difficult.





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# Health Effect Innovation Programs

- Cardiovascular Hazard Assessment in Environmental Toxicology
- Developmental Neurotoxicity Modeling
- Carcinogenicity Assessment



# NTP Congressional Mandate (1978)

*Section 301(b)(4) of the Public Health Service Act, as amended, requires that the Secretary of the Department of Health and Human Services (DHHS) publish an annual report on substance use and abuse. The Report on Carcinogens (RoC) lists:*

- *(A) All substances that are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and to which a significant number of US residents are exposed.*
- *(B) Information concerning the nature of such exposure and the estimated number of persons exposed to such substances*



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**Human Cancer Risk**

**Human-Relevant Exposure**



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**NTP is not obligated to employ any specific approach to assessing carcinogenicity**



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**Does “Chemical X” cause cancer in rats/mice?**



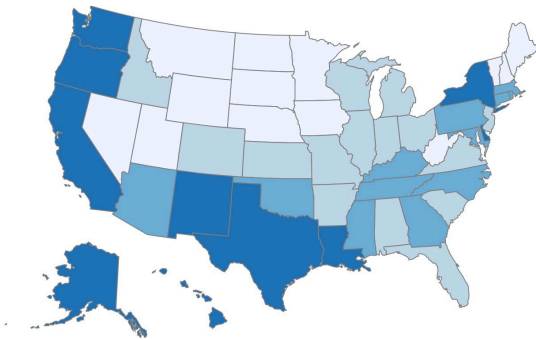
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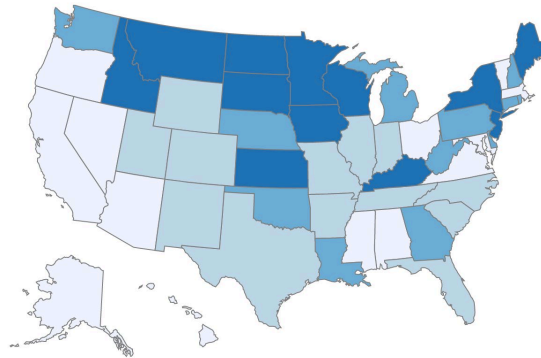
**What environmental factors are contributing to the increase in incidence / mortality of “cancer x” in humans?**

# Cancer Incidence

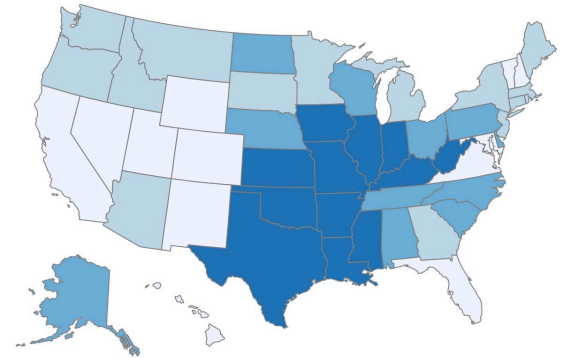
Liver



Leukemia



Kidney



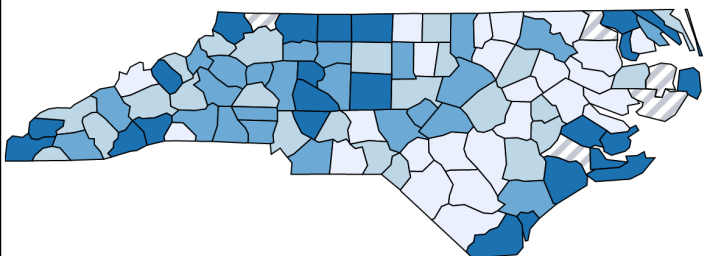
NCI, Surveillance, Epidemiology, and End Results (SEER)



# Cancer Incidence

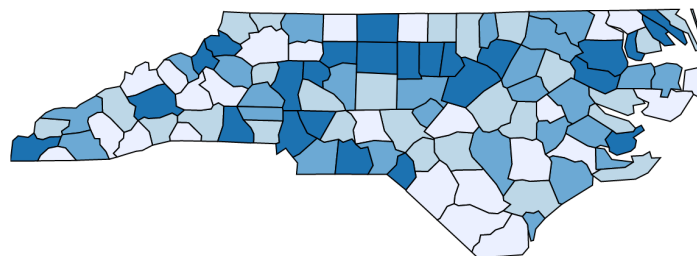
Urinary Bladder, All Ages, All Races/Ethnicities, Male and Female, 2011-2015  
Rate per 100,000 people

 Map  Table  Export



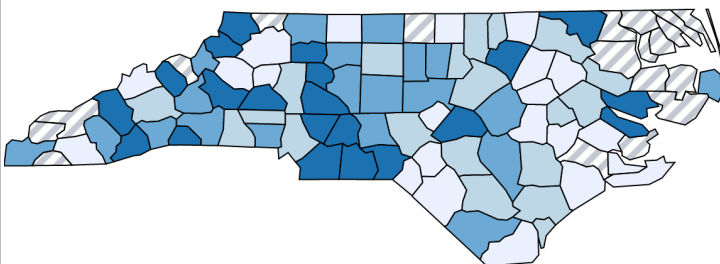
Female Breast, All Ages, All Races/Ethnicities, Female, 2011-2015  
Rate per 100,000 people

 Map  Table  Export



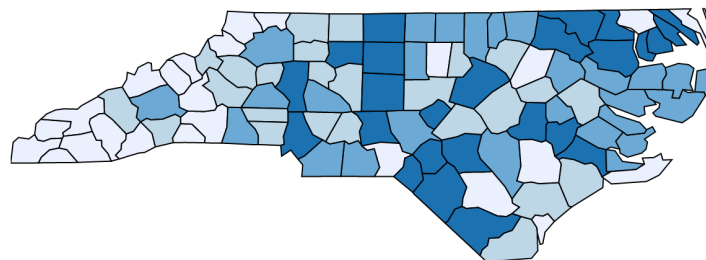
Leukemias, All Ages, All Races/Ethnicities, Male and Female, 2011-2015  
Rate per 100,000 people

 Map  Table  Export



Prostate, All Ages, All Races/Ethnicities, Male, 2011-2015  
Rate per 100,000 people

 Map  Table  Export





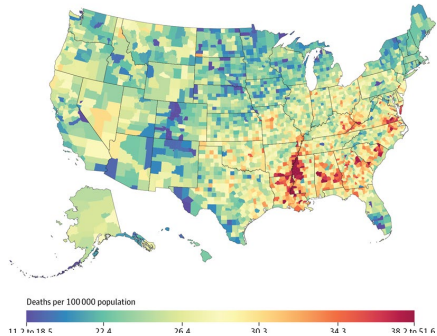


# Cancer Mortality

Mokdad et al. JAMA 2017

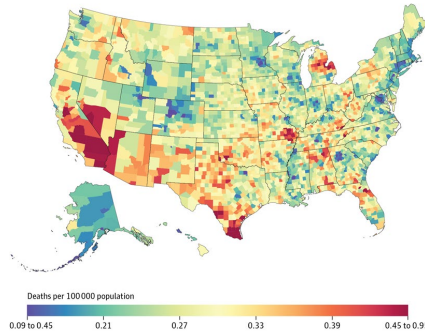
## Breast

A Age-standardized mortality rate from breast cancer (females only), 2014



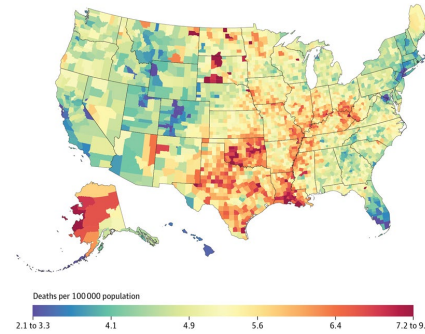
## Testicular

A Age-standardized mortality rate from testicular cancer (males only), 2014



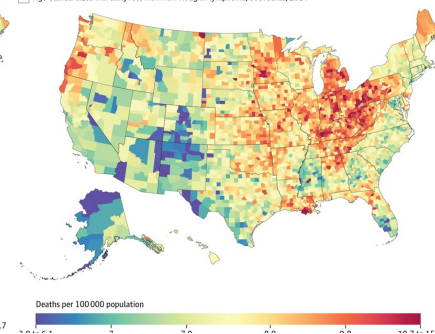
## Lymphoma

A Age-standardized mortality rate from kidney cancer, both sexes, 2014



## Kidney

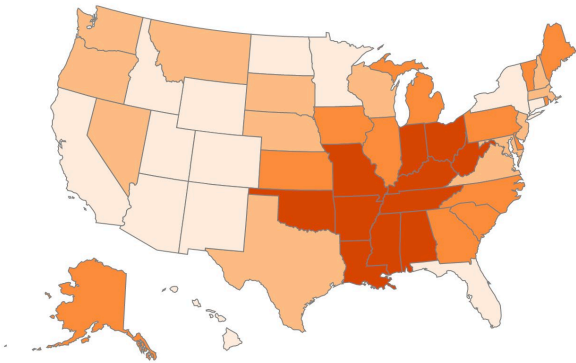
A Age-standardized mortality rate from non-Hodgkin lymphoma, both sexes, 2014



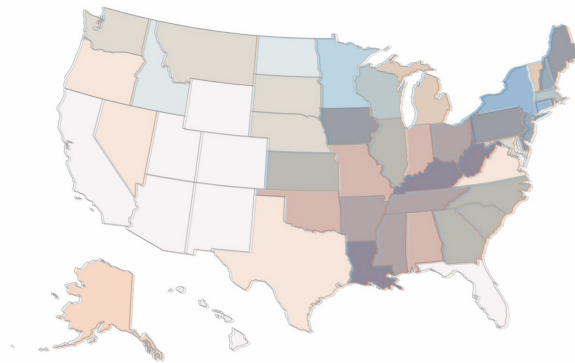
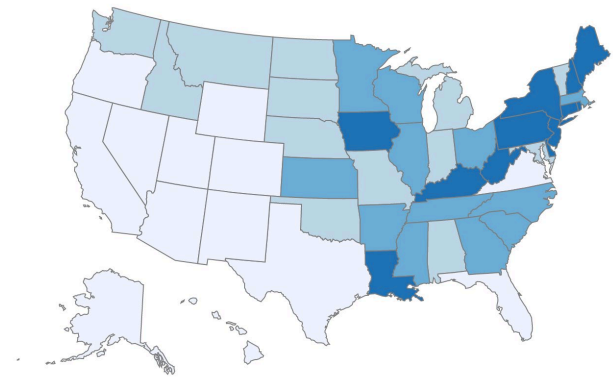


# All Cancers

Mortality



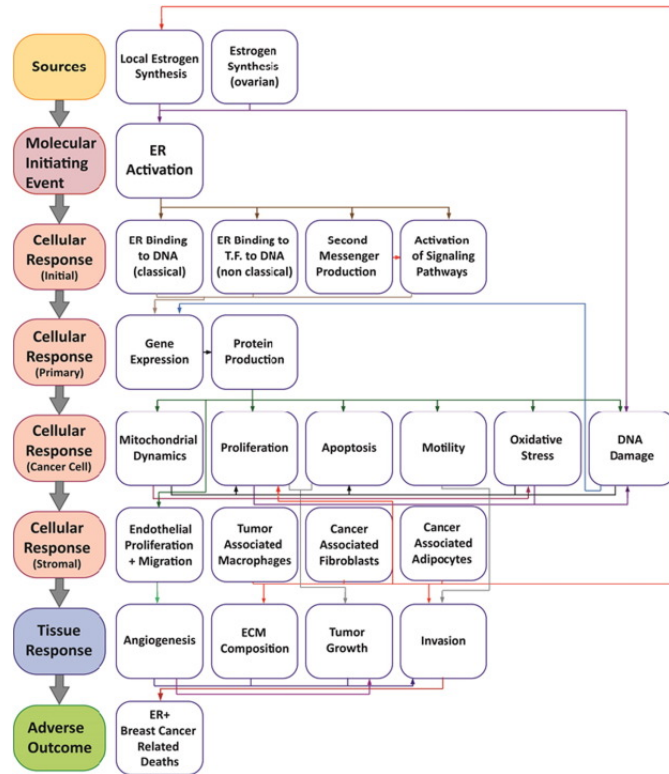
Incidence



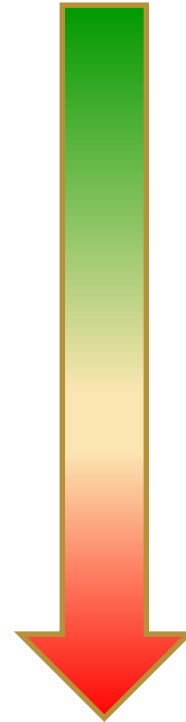
Merged



# ER pathway to breast cancer



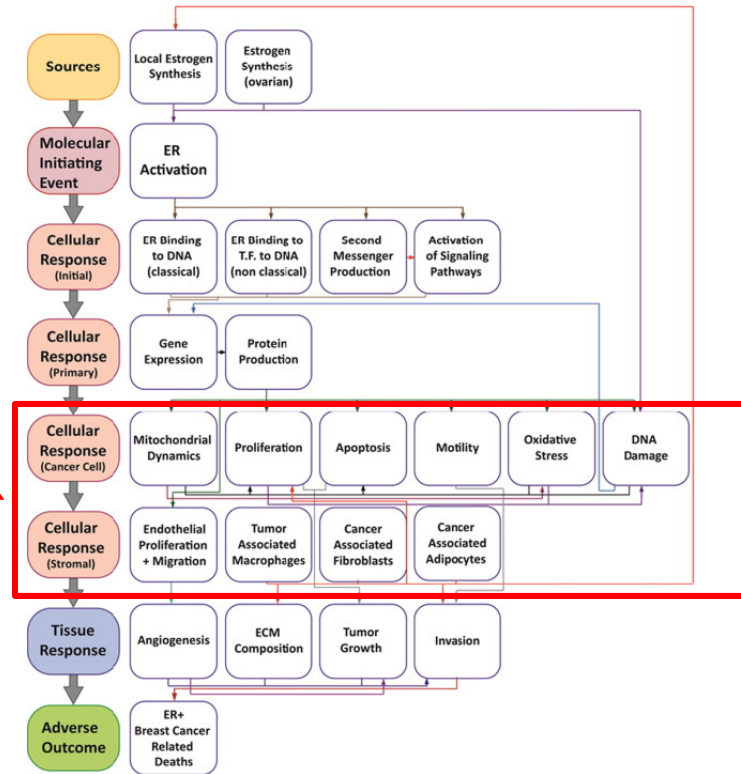
Probabilistic



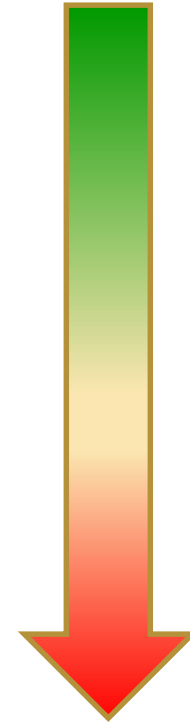


# ER pathway to breast cancer

This is the inflection point we need to model since it represents the bridge between observation and prediction



Probabilistic





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# The Future of Carcinogenicity Assessment @ NTP will be...

- **Human Relevant**
- **Mechanistic**
- **Exposure Driven**



# Problem Formulation





# Problem Formulation





# Problem Formulation





**Thank You!**



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