**Report 21:** Human variability: Sources and contribution to differential susceptibility to exposures to environmental agents

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**Brief History:** Risk assessments typically rely on toxicology data derived from single exposures of single highly inbred strains of rodents to predict human risk. Yet we know the variability in both exposure and response among people is enormous, differing based on genetics, ethnicity, socioeconomic factors, health status, lifestage, nutrition, etc. A recent NAS report proposes reversing the presumption that for most exposures and endpoints there is a "safe" level below which no effect will occur, based on the concept that variability across the human population will in many or most cases swamp any safe threshold that may be seen in any individual. Our ability to directly measure genetic variability and our growing understanding of mechanisms that may account for and propagate that variability (e.g., epigenetics) makes it timely to undertake a greater effort to understand sources of variability in addition to genetics in the human population and the influence of such variability in disease incidence and susceptibility, including in specific subpopulations. Such information will aid in improving the ability of risk assessments to accurately characterize human risk.

**Discussion Highlights:**

- Layers of variability:
    - multiple and varied exposures (differ spatially, temporally, socially)
    - differential susceptibility
    - microbiome as newly recognized source of variability
- Need for more and better biomarker sets to reflect the full range of exposures we experience, then work back to identify specific causative agent; need biomarkers that differentiate genetic from epigenetic effects
- Fundamental lack of understanding of the 70% of variability not accounted for by genetics
- Recognition of concept of "exposome" – collective environment and exposures we experience over our lifetimes – and "responsome" – biological changes that ensue from those exposures
- What are major drivers of observed levels of variation
- Research project ideas:
    - Measuring and characterizing variability:
        - Test 20 strains of mice to characterize variation in gene expression
        - Start with agent and close variants (e.g., chemical analogs or class of chemicals such as NTP's study of perfluorinated chemicals); look at variation in response to

members of the class – might that identify a source of variability that can then be looked for across a population with differential susceptibility to that agent?

- Compare transcriptomes derived from 1000 human samples simply to characterize extent of variation beyond genetic
- Do the same with parents of triplets and the children – may have equally high statistical power to tease genetic influence away from other factors

**Recommendations:**

- Need to place greater priority on direct characterization of actual human variability, both generally and as seen in response to specific exposures or environments
    - Use animal studies in conjunction with human studies to provide insights into underlying mechanisms that may explain observed human variability
    - Then seek to identify such mechanisms in humans to better map sources of variability
- Look to mine data being compiled into large integrated databases for insights allowing better characterization of variability
- Seek to develop better sets of biomarkers of exposures and correlate them to types/classes of exposures, and ultimately to specific causative agents. Identify biomarkers that differentiate genetic from epigenetic effects.
- Keep an eye on ethical implications of studying human variability:
    - Avoid “blame the victim” outcomes that identify particularly sensitive individuals as outliers
    - How can studies that seek to correlate differential health status or outcomes in people to underlying differences in exposures or inherent susceptibility be conducted in a manner that doesn’t raise potential for discriminatory actions?

**Discussion Participants:**

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